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Clinical Study Protocol

INCB 24360-204 / NCT02327078

(CA209)

A Phase 1/2 Study of the Safety, Tolerability, and Efficacy of Epacadostat Administered in Combination With Nivolumab in Select Advanced Cancers

Product:	**Epacadostat and Nivolumab**
IND Number:	**122945**
EudraCT Number:	**2016-002423-29**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803 (In collaboration with Bristol-Myers Squibb)**
Date of Protocol:	**15 AUG 2014**
Date of Amendment 1:	**01 OCT 2014**
Date of Amendment 2:	**03 APR 2015**
Date of Amendment 3:	**16 JUL 2015**
Date of Amendment 4:	**12 FEB 2016**
Date of Amendment 5:	**13 JUL 2016**
Date of Amendment 6:	**05 JUL 2017**
Date of Amendment (Version) 7:	**29 SEP 2017**
Date of Amendment (Version) 8:	**31 MAY 2018**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312, and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

The information in this document is confidential. No part of this information may be duplicated, referenced, or transmitted in any form or by any means (electronic, mechanical, photocopy, recording, or otherwise) without the prior written consent of Incyte Corporation.

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochures for nivolumab and epacadostat. I have read the INCB 24360-204 Protocol Amendment 8 (Version 8 dated 31 MAY 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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SYNOPSIS

Name of Investigational Products: Nivolumab and epacadostat	
Title of Study: A Phase 1/2 Study of the Safety, Tolerability and Efficacy of Epacadostat Administered in Combination With Nivolumab in Select Advanced Cancers	
Protocol Number: INCB 24360-204	**Study Phase:** 1/2

Primary Objectives:

Phase 1

- **Part 1 Safety:** To assess the safety and tolerability of epacadostat orally in combination with nivolumab, and to identify dose-limiting toxicities (DLTs) and the recommended Phase 2 dose (RP2D) of the combination immunotherapy, in subjects with select advanced (metastatic and/or unresectable) cancers (solid tumors and B-cell non-Hodgkin lymphoma [NHL] or Hodgkin lymphoma [HL]).
- **Part 2 Safety:** To assess the safety and tolerability and to determine a maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD) of epacadostat in combination with nivolumab and chemotherapy in subjects with advanced or metastatic squamous cell carcinoma of head and neck (SCCHN) and in subjects with advanced or metastatic non–small cell lung cancer (NSCLC).

Phase 2

- **Efficacy:**
  - To assess objective response rate (ORR) and progression-free survival (PFS) at 6 months in subjects with select solid tumors or subjects with diffuse large B-cell lymphoma (DLBCL).
  - To assess overall survival (OS) at 9 months for subjects with glioblastoma.

Secondary Objectives:

Phase 1

- **Part 1 Efficacy:** To assess the preliminary antitumor activity of the combination of epacadostat and nivolumab in subjects with select advanced solid tumors, B-cell NHL or HL, or glioblastoma by assessing ORR.
- **Part 2 Efficacy:** To explore the preliminary efficacy of epacadostat administered in combination with nivolumab and chemotherapy in subjects with advanced or metastatic SCCHN and advanced or metastatic NSCLC by assessing ORR, duration of response (DOR), and PFS.

Phase 2

- **Efficacy:**
  - To assess the preliminary antitumor activity of the combination of epacadostat and nivolumab in subjects with select advanced solid tumors and DLBCL by assessing DOR and duration of disease control.
  - To evaluate OS in subjects with select solid tumors and DLBCL.
  - To evaluate ORR, PFS, DOR, and duration of disease control for subjects with glioblastoma.
- **Safety:**
  - To assess the safety and tolerability of epacadostat twice daily (BID) orally when given in combination with nivolumab 240 mg every 2 weeks.
  - To assess the safety and tolerability of epacadostat BID orally when given in combination with nivolumab 480 mg every 4 weeks.

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Primary Endpoints:

Phase 1

- **Safety:** In Part 1 and Part 2 of Phase 1 of the study, all subjects who receive at least 1 dose of epacadostat or nivolumab will be assessed for safety by monitoring the frequency and severity of adverse events (AEs), serious adverse events (SAEs), and deaths.

Phase 2

- **Efficacy:**
  - The ORR and PFS at 6 months will be assessed based on RECIST v1.1 criteria for subjects with select solid tumors or Cheson criteria for subjects with DLBCL.
  - OS will be assessed at 9 months for subjects with glioblastoma as determined by death due to any cause.

Secondary Endpoints:

Phase 1

- **Part 1 Efficacy:** ORR will be assessed per RECIST v1.1 and modified RECIST for subjects with select advanced solid tumors, Cheson and modified Cheson criteria for B-cell NHL or HL, and Response Assessment in Neuro-Oncology (RANO) and modified RANO criteria for glioblastoma.
- **Part 2 Efficacy:** ORR, DOR, and PFS will be assessed per RECIST v1.1 and modified RECIST for subjects with advanced or metastatic SCCHN and advanced or metastatic NSCLC treated with epacadostat in combination with nivolumab and chemotherapy.

Phase 2

- **Efficacy:** The DOR and duration of disease control will be assessed based on RECIST v1.1 criteria and modified RECIST for select solid tumors, Cheson and modified Cheson criteria for DLBCL, or RANO and modified RANO criteria for subjects with glioblastoma. OS will be evaluated for solid tumors and DLBCL cohorts. ORR and PFS will be assessed for glioblastoma per modified RANO.
- **Safety:** All subjects who receive at least 1 dose of epacadostat or nivolumab will be assessed for safety by monitoring the frequency and severity of AEs, SAEs, and deaths.

[redacted]

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Overall Study Design:

This is a Phase 1/2 open-label study that will be conducted in 2 phases. Phase 1 of the study will consist of 2 parts (Part 1 and Part 2). Part 1 of Phase 1 will consist of a standard dose-escalation design to determine the MTD or PAD of epacadostat when coadministered with nivolumab (defined as combination immunotherapy) in subjects with select advanced solid tumors and lymphomas, including melanoma (MEL), NSCLC, colorectal cancer (CRC), SCCHN, ovarian cancer, glioblastoma, and B-cell NHL or HL. The study design is shown in Figure A1 and Figure A2 below.

Part 2 of Phase 1 will evaluate the preliminary safety of epacadostat in combination with nivolumab and several chemotherapy regimens (defined as combination chemo-immunotherapy) in subjects with SCCHN and NSCLC by using a dose de-escalation design. The starting dose of epacadostat in Part 2 will be the RP2D of epacadostat selected for the use of combination immunotherapy in Part 1. Initial dose-finding cohorts in Part 2 will be expanded to safety expansion cohorts and will further evaluate tolerated dose(s) of epacadostat when given in combination with nivolumab and chemotherapy regimens (see Figure A2).

Phase 2 of the study will include 9 expansion cohorts in tumor types tested in Phase 1 Part 1 (except DLBCL will be the only lymphoma permitted) with a) historically high activity under nivolumab monotherapy, and b) with historically low activity with nivolumab monotherapy. In Phase 2 of the study, nivolumab will be administered at 240 mg intravenously (IV) every 2 weeks or 480 mg IV every 4 weeks for specific tumor types as described in Figure A1.

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Figure A1: Study Design for Combination Immunotherapy Cohorts (Phase 1 Part 1 and Phase 2)

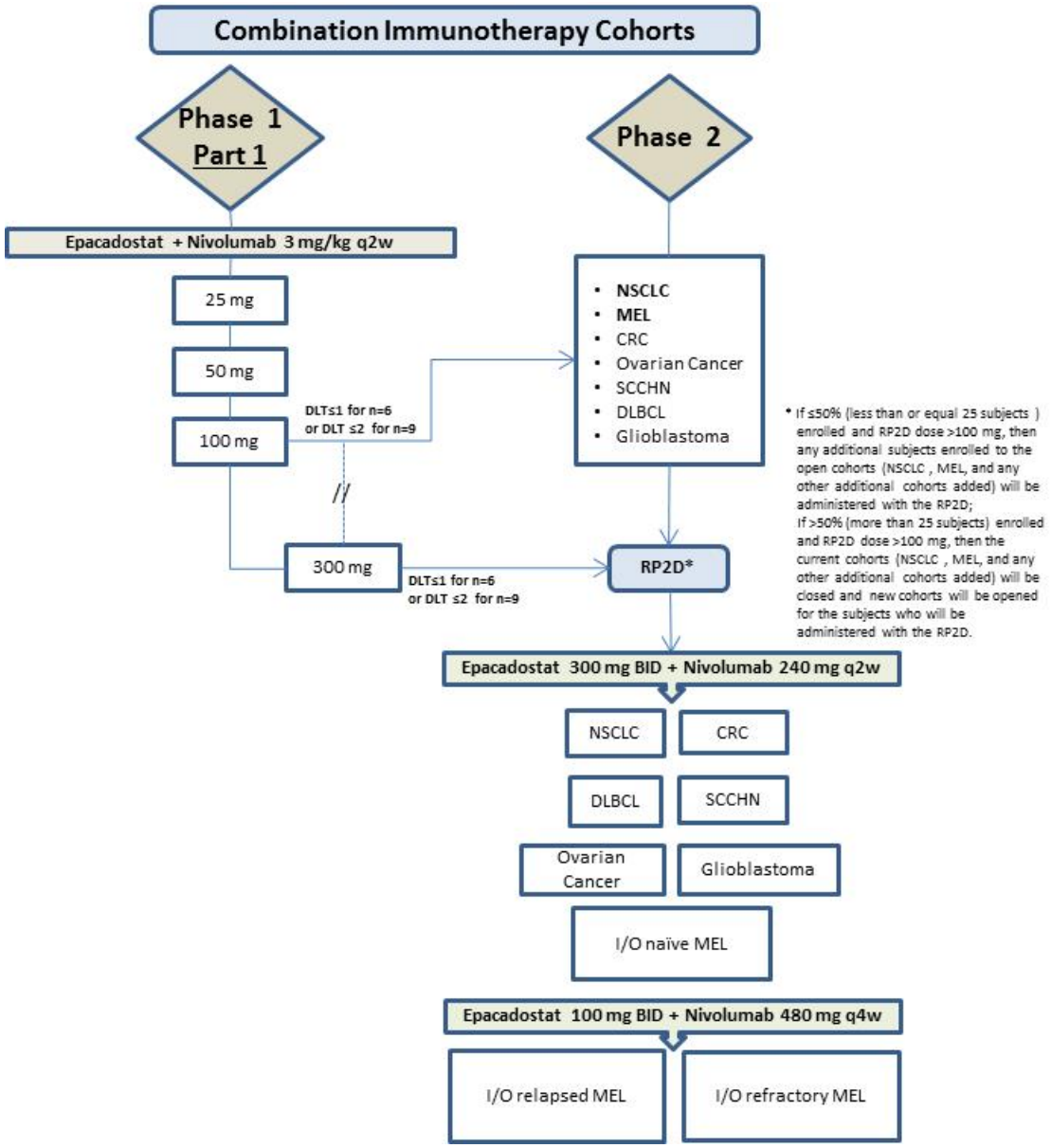

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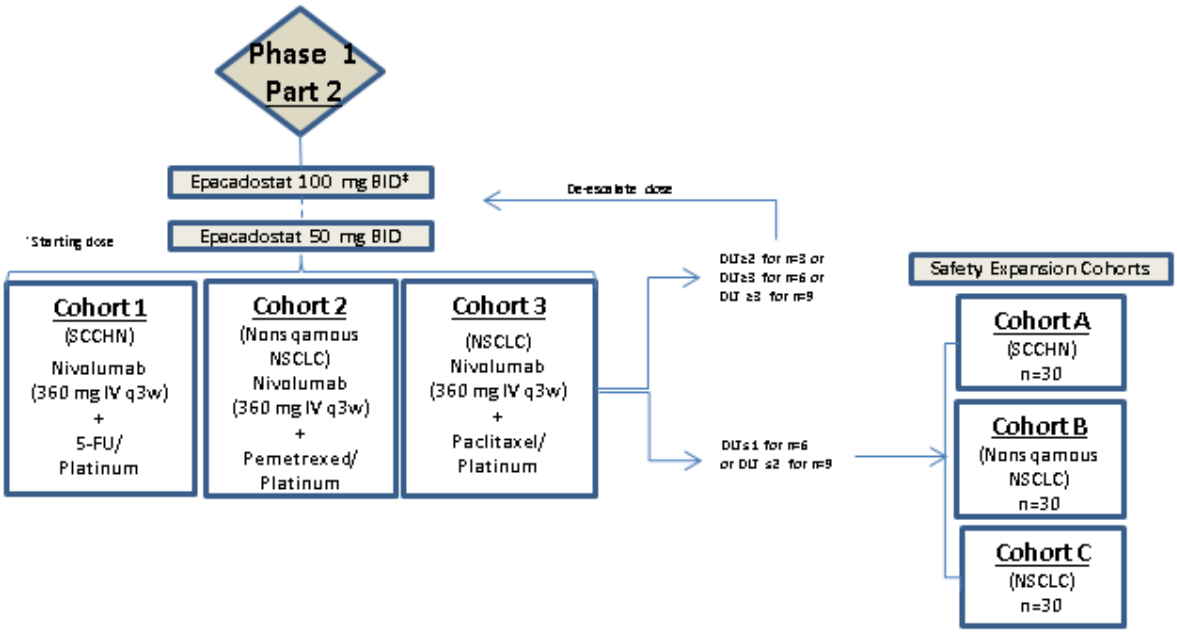
Figure A2: Study Design for Combination Chemo-Immunotherapy Cohorts (Part 2 of Phase 1 Only)



Phase 1 Dose-Finding and Safety Expansion (Part 1 and Part 2)

In Part 1, for combination immunotherapy cohorts, a 3 + 3 + 3 standard dose-escalation design will be used to assess the safety of epacadostat when given in combination with nivolumab.

In Part 2, for combination chemo-immunotherapy cohorts, a (3 + 3) + 3 dose de-escalation study design will be used to evaluate the safety of epacadostat when administered in combination with nivolumab and chemotherapy regimen. Part 2 will be initiated after Phase 1 Part 1 of the study is completed and the Phase 2 dose of epacadostat for the combination immunotherapy is determined.

Combination Immunotherapy Cohorts (Part 1)

The starting dose of epacadostat when given in combination with nivolumab (3 mg/kg IV every 2 weeks, Q2W) is 25 mg BID continuous daily dose administration. The epacadostat dose regimens during dose escalation in combination immunotherapy cohorts are provided in Table A1.

The BID continuous administration cohorts will be tested first. If epacadostat 50 mg BID continuous daily administration is determined as tolerable, the investigators and sponsor may agree to only evaluate continuous daily administration. However, if epacadostat 50 mg BID exceeds the MTD, an every-other-week administration schedule of epacadostat administered BID may be tested. If a dose is determined safe for both schedules, a safety expansion cohort may be opened for each dose regimen to include approximately 9 subjects in each cohort before selecting the schedule to move to Phase 2. If at least 50 mg BID continuous or every other week cannot be combined safely with nivolumab 3 mg/kg, other alternative dose schedules (ie, other intermittent administration) of epacadostat may be tested, if needed, following the review of available safety data at the Dose Escalation/Cohort Review meetings. If an alternate schedule is tested and determined to be safe, re-escalation of epacadostat according to Table A1 will proceed with nivolumab 3 mg/kg every 2 weeks.

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Table A1: Dose Regimens in Combination Immunotherapy Cohorts During Dose Escalation (Part 1)

Dose Level Number	Total Subjects (N)[a]	Epacadostat (Oral)	Nivolumab/BMS-936558 (IV; Once Every 2 Weeks)
1	Approximately 3-9	25 mg BID	3 mg/kg
2a	Approximately 3-9	50 mg BID	3 mg/kg
2b	Approximately 3-9	50 mg BID every other week	3 mg/kg
3a	Approximately 3-9	100 mg BID	3 mg/kg
3b	Approximately 3-9	100 mg BID every other week	3 mg/kg
4a	Approximately 3-9	300 mg BID[b]	3 mg/kg
4b	Approximately 3-9	300 mg BID every other week[b]	3 mg/kg
Total	Approximately 21-63		

[a] Approximately 3 to 9 subjects will be enrolled during dose escalation. Additional subjects may be added to any dose level after determining the preliminary safety at that dose level for a minimum of 6 and maximum of 9 evaluable subjects per dose level. Dose level numbers marked "a" and "b" may occur in parallel. Oral administration of epacadostat BID will occur on a daily basis unless indicated by the weekly alternating schedule of BID each day for 1 week followed by no doses for the following week. Nivolumab administration will be 3 mg/kg IV every 2 weeks.

[b] If 300 mg BID is not tolerated, an intermediate dose of 200 mg BID may be tested on either a continuous schedule or every-other-week schedule (see above for RP2D decision process).

The DLT observation period will last for 6 weeks (42 days). Three subjects will be treated initially at each dose level. If 0 DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects experience a DLT, that cohort will be expanded to 6 subjects. If 1 of 6 subjects experiences a DLT, a new cohort of 3 subjects will be treated at the next higher dose level. If 2 of 6 DLT subjects experience a DLT, that cohort will be expanded to 9 subjects. If ≥ 2/3, 3/6, or 3/9 subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD.

If epacadostat 100 mg BID is deemed tolerable, up to 6 additional subjects (for a minimum of 6 evaluable subjects) will be enrolled to confirm the safety of the dose in combination with nivolumab. If 1 of 6 or < 3 of 9 subjects experience DLTs, the Phase 2 MEL and NSCLC expansion cohorts will open with epacadostat 100 mg BID in combination with nivolumab. The 300 mg BID dose in Phase 1 will be tested in parallel to the Phase 2 MEL and NSCLC cohorts opening. Additional Phase 2 cohorts in other tumor types may also be opened to test epacadostat 100 mg BID if it is deemed pharmacologically active and safe based on available data from Phase 1 cohorts.

Note: Up to 6 additional subjects may be enrolled into each cohort for a total of up to 9 evaluable subjects to further explore safety [redacted] objectives (original 3-9 subjects from dose escalation plus additional subjects required to have a total cohort size of 9).

If epacadostat 300 mg BID is deemed tolerable, up to 6 additional subjects (for a minimum of 6 subjects) will be enrolled before opening Phase 2 to further confirm the safety of the dose in combination with nivolumab. If 1 of 6 or < 3 of 9 subjects experience DLTs, the remaining Phase 2 cohorts may be opened with 300 mg BID as the RP2D after reviewing the emerging data from Phase 2 cohorts testing 100 mg BID.

If 300 mg BID is tested and not tolerated, an intermediate dose of 200 mg BID may be tested on either a continuous schedule or every-other-week schedule or 100 mg BID may be selected as the RP2D. The RP2D decision for the remaining Phase 2 cohorts will be made based on the available data from ongoing Phase 2 cohorts administered 100 mg BID. If an MTD is not determined based on the data from Phase 1 and ongoing Phase 2 cohorts, then the remaining Phase 2 cohorts may be opened at a PAD of epacadostat (eg, 100 mg BID).

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Phase 2 Dose Selection for Combination Immunotherapy (Part 1 of Phase 1)

If 100 mg BID of epacadostat is determined as safe and tolerable in Phase 1 Part 1, Phase 2 of the study may begin to enroll in the I/O-naive MEL and NSCLC cohorts in parallel with the Part 1 evaluation of epacadostat at 300 mg BID. If 300 mg BID is then selected as the Phase 2 dose (RP2D), and either I/O-naive MEL or NSCLC cohort enrolls < 50% of total cohort (≤ 25 subjects) at 100 mg BID up to RP2D decision, then any additional subjects in that specific cohort being enrolled will be treated with epacadostat 300 mg BID at the sponsor's discretion, in lieu of opening new cohorts of I/O-naive MEL and NSCLC with 300 mg BID. The same rule will apply to any additional Phase 2 tumor cohorts (ie, CRC, ovarian cancer, etc) that may be opened with epacadostat 100 mg BID before RP2D selection. (Note: Additional I/O-relapsed and I/O-refractory MEL cohorts will be opened at 100 mg BID).

Combination Chemo-Immunotherapy Cohorts (Part 2 of Phase 1)

The starting dose of epacadostat when given in combination with nivolumab (360 mg IV every 3 weeks, Q3W) and chemotherapy will be 100 mg BID continuous daily dose administration, which is one dose level less than what was determined to be tolerable in Part 1 of Phase 1 and provides an adequate safety margin. Part 2 of Phase 1 will consist of 3 tumor cohorts (1 SCCHN cohort, and 2 NSCLC cohorts) that will enroll in parallel. A minimum of 6 evaluable subjects will be enrolled in each tumor cohort at epacadostat 100 mg BID, and each cohort will be observed for 42 days for DLTs.

In a tumor cohort the following rules will be applied to determine dose or dose de-escalation:

- If ≤ 1 of 6 evaluable subjects has a DLT, then 100 mg BID will be used in a safety expansion cohort (Cohort A, B, or C) for that specific tumor type.
- If 2 of 6 evaluable subjects have a DLT, 3 additional subjects will be enrolled in the same cohort (Cohort 1, 2, or 3). If there are no additional DLTs (≤ 2 DLTs occurred in a total of 9 evaluable subjects), then a safety expansion cohort (Cohort A or B or C) will start to enroll in that specific dose level.
- If ≥ 2/3, 3/6, or ≥ 3/9 evaluable subjects have DLTs within a specific tumor cohort, epacadostat will be de-escalated to 1 lower dose level, 50 mg BID, and that tumor cohort will enroll 6 subjects to test this dose level as described above.
- **Note:** If different MTDs are determined for the 2 NSCLC cohorts (combination chemo-immunotherapy), 3 to 6 additional subjects may be enrolled in each NSCLC cohort to further evaluate the safety profile before dose selection for safety expansion.

The doses of epacadostat to be evaluated and scenarios for de-escalation are summarized in Table A2.

Table A2: Epacadostat Dose De-Escalation Scenarios for Combination Chemo-Immunotherapy Cohorts in Part 2

Combination Chemo-Immunotherapy Cohort	Epacadostat Dose
Dose Level 1 **(starting dose)**	**100 mg BID**[a]
Dose Level -1	50 mg BID

[a] If epacadostat 100 mg BID is not tolerated within a specific cohort, the dose of epacadostat will be de-escalated to 50 mg BID for evaluation. Alternate doses may be evaluated at the sponsor discretion [redacted] and safety results.

Epacadostat dose regimens in combination chemo-immunotherapy cohorts by tumor types are provided in Table A3.

Once 100 mg BID or 50 mg BID of epacadostat in combination chemo-immunotherapy cohorts is determined as the MTD or PAD, each of the tumor cohorts will be expanded for safety evaluation at that dose level of epacadostat. Each of the safety expansion cohorts with combination chemo-immunotherapy will enroll up to 30 evaluable subjects.

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Table A3: Summary of Treatment Regimens for Each Possible Epacadostat Dose-Finding Scenario for Combination Chemo-Immunotherapy Cohorts in Part 2

Tumor Types[a]	Cohort[b]	Total Subjects, N	Epacadostat (Oral)	Nivolumab (IV, Once Every 3 Weeks)	Chemotherapy Regimen
SCCHN	1	~6-9	100 mg BID	360 mg	Cisplatin (100 mg/m^2 IV Q3W for up to 6 cycles) or Carboplatin AUC 5 IV Q3W for up to 6 cycles 5-FU (1000 mg/m^2 continuous IV for 4 days Q3W for up to 6 cycles, on Day 1 of each cycle starting C1D1)
	1a	~6-9	50 mg BID	360 mg	Same as above
Nonsquamous NSCLC	2	~6-9	100 mg BID	360 mg	Pemetrexed (500 mg/m^2 IV Q3W for up to 6 cycles but no less than 4 cycles, on D1of each cycle starting C1D1) Carboplatin (AUC 5 IV Q3W up to 6 cycles but no less than 4 cycles, on Day 1 of each cycle starting C1D1) or Cisplatin (100 mg/m^2 IV Q3W up to 6 cycles but no less than 4 cycles)
	2a	~6-9	50 mg BID	360 mg	Same as above
NSCLC	3	~6-9	100 mg BID	360 mg	Paclitaxel (200 mg/m^2 IV Q3W for up to 6 cycles but no less than 4 cycles, on Day 1 of each cycle starting C1D1) Carboplatin (AUC 6 IV Q3W up to 6 cycles but no less than 4 cycles, on Day 1 of each cycle starting C1D1) or Cisplatin (100 mg/m^2 IV Q3W up to 6 cycles but no less than 4 cycles)
	3a	~6-9	50 mg BID	360 mg	Same as above
Total		~18-54			

[a] Cohort 1, Cohort 2, and Cohort 3 will enroll in parallel.
[b] If Cohort 1, Cohort 2, Cohort 3 with epacadostat 100 mg BID proves intolerable, then Cohort 1a, Cohort 2a, or Cohort 3a may be evaluated with epacadostat 50 mg BID. If the epacadostat 100 mg BID is determined to be safe and tolerable at a specific tumor type, then the safety expansion cohort for that specific tumor type will enroll at 100 mg BID. Alternative doses of epacadostat may be investigated at the sponsor discretion.

In Phase 1, no intrasubject dose escalation is allowed. In Phase 1 Part 1, additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects if discontinuations or dose interruptions or reductions occur that result in a subject being nonevaluable for DLTs. In Phase 1 Part 2, additional subjects will be enrolled in a cohort to achieve the minimum of 6 evaluable subjects. In both Part 1 and Part 2, subjects who withdraw from the study during the DLT period for reasons other than a DLT may be replaced within the same dose level.

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For the purpose of making decisions on dose of epacadostat from a safety perspective, subjects will be considered evaluable if they meet 1 of the following criteria:

- In Part 1, in the combination immunotherapy cohorts, subjects must have received at least 2 out of the 3 scheduled nivolumab doses of 3 mg/kg through the 6-week (42-day) DLT observation period (only if the 1 missed dose was secondary to nonmedical reasons) and must have received at least 75% of the cohort-specified dose of epacadostat during the DLT observation period.
- In Part 2, in combination chemo-immunotherapy cohorts, subjects must have received 2 doses of nivolumab and chemotherapy regimen and must have received at least 75% of the cohort-specified dose of epacadostat in during the 42 day DLT observation period.
- In addition, subjects with dose delays during the 42-day DLT observation period of > 1 week for non-DLT events will be considered not evaluable for making decisions on dose escalation or dose de-escalation and should be replaced.

Dose escalation in Part 1 or dose de-escalation in Part 2 of epacadostat will be based on the number of dose limiting toxicities (DLTs) experienced during the DLT observation period. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor.

Phase 2 Combination Immunotherapy Cohort Expansions

The purpose of the cohort expansions in Phase 2 is to gather additional safety, tolerability, preliminary efficacy, [redacted] information regarding the combination of epacadostat and nivolumab. Once the safety profile of active doses is characterized and the RP2D has been defined, the cohort expansions will be initiated at the RP2D. However, the I/O-naive MEL and NSCLC cohorts may be opened using epacadostat 100 mg BID in parallel to testing 300 mg BID if the 100 mg BID dose of epacadostat is deemed tolerable in Phase 1 Part 1. Treatment doses in the cohort expansion groups will not exceed the MTD. Nine expansion cohorts in Phase 2 will be restricted to the same tumor types tested in Phase 1 Part 1 (except DLBCL will be the only lymphoma permitted in Phase 2), and Phase 2 will also include a cohort for glioblastoma. The NSCLC and I/O-naive MEL cohorts, which have demonstrated activity with nivolumab monotherapy and are in Phase 3 evaluation in these indications, will be used to assess increased activity of the combination. In Phase 2, there will be 2 additional MEL cohorts to explore the activity of combination immunotherapy; one cohort will enroll subjects who relapsed on or after anti–programmed death receptor-1(PD-1)/PD-L1 therapy (I/O relapsed) and the other cohort will enroll subjects who were refractory to prior anti–PD-1/PD-L1 therapy (I/O refractory) (for I/O relapsed MEL cohort and I/O refractory MEL cohort definitions, see eligibility section below). Subjects who are enrolled in these 2 new MEL cohorts will be administered nivolumab 480 mg IV every 4 weeks whereas, subjects who are enrolled in I/O-naive MEL, NSCLC, CRC, SCCHN, ovarian cancer, DLBCL and glioblastoma cohorts will be administered nivolumab 240 mg IV every 2 weeks. Subjects enrolled in I/O MEL cohorts will be administered epacadostat 100 mg BID; however, if there is no or minimal activity in tumor responses in these cohorts, alternative doses of epacadostat may be explored at the sponsor discretion. The CRC, SCCHN, ovarian cancer, DLBCL, and glioblastoma cohorts will explore activity of the combination in tumors with preliminary, unknown, or historically low responses to nivolumab monotherapy. Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If the cumulative incidence of Grade 3 or Grade 4 study treatment-related AEs exceeds 40% after enrolling the first 6 subjects in any of these cohorts, the findings will be reviewed and further enrollment will be interrupted until the sponsor(s), investigators, and regulatory authorities, if applicable, have determined the appropriate course of action. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level of epacadostat.

In each of the NSCLC and I/O-naive MEL cohorts, approximately 50 subjects will be enrolled to allow for a more precise estimate of the ORR in these tumors where activity for nivolumab as monotherapy has been established. The sample size for the I/O-relapsed MEL, I/O-refractory MEL, CRC, ovarian, SCCHN, and DLBCL cohorts will be approximately 25 subjects each. The sample size for the glioblastoma cohort will be approximately 28 (Table A4).

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Table A4: Tumor Types Eligible for Combination Immunotherapy Cohort Expansion

Tumor Type	No. of Subjects to be Enrolled (Phase 2 Only)
NSCLC	50
I/O-naive MEL	50
I/O-relapsed MEL	25
I/O-refractory MEL	25
CRC	25
Ovarian cancer	25
SCCHN	25
DLBCL	25
Glioblastoma	28
Totals	~278

Dose-Limiting Toxicity: For the purpose of guiding dose escalation, DLTs will be defined separately and will be determined based on the incidence, intensity, and duration of AEs that occur within the first 42 days (6 weeks) after the initiation of epacadostat dosing. Adverse events will be graded according to the National Cancer Institute (NCI) CTCAE v4.

For all subjects enrolled in Part 1 and Part 2 of Phase 1 and in Phase 2, participation has following main periods:

Screening: Up to 28 days.

Treatment: The treatment period with the combination immunotherapy (nivolumab + epacadostat) will continue every 56 days and with the combination chemo-immunotherapy (nivolumab + epacadostat + chemotherapy) will continue every 21 days as long as the subjects are receiving benefit from treatment and have not met any criteria for study withdrawal.

End of Treatment (EOT): + 5 days of withdrawal from study treatment.

Safety Follow-Up: Safety follow-up visits will occur at 30 and 100 days after EOT (or after the last dose of study drug if the EOT visit was not performed).

Combination Immunotherapy and Chemo-Immunotherapy, Regimen, and Mode of Administration:

Epacadostat is an investigational agent and will be self-administered BID orally without regard to food and continued BID continuous or every other week during the 8-week cycle for an every-2-week dose schedule of nivolumab in combination immunotherapy cohorts. In combination chemo-immunotherapy cohorts, epacadostat will be administered BID continuously during 21-day cycle (3 weeks) for as long as subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal. Intrasubject dose escalation of epacadostat is not permitted.

The RP2D defined during Phase 1 will be used for Phase 2. (Note: Subjects enrolled into I/O-refractory and I/O-relapsed MEL cohorts in Phase 2 will be administered epacadostat 100 mg BID). Intrasubject dose escalation of epacadostat is not allowed. All BID doses will be taken morning and evening, approximately 12 hours apart. If a dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual time.

Nivolumab will be administered 3 mg/kg as a 60-minute infusion every 2 weeks on Days 1, 15, 29, and 43 of each 8-week cycle of study therapy in Phase 1 Part 1. In Phase 1 Part 2, for the combination chemo-immunotherapy cohorts, the dose of nivolumab will be 360 mg as a 30-minute infusion every 3 weeks on Day 1 of each 21-day cycle.

In the Phase 2 dose expansion of the combination immunotherapy cohorts, the dose of nivolumab will be 240 mg as a 30-minute infusion every 2 weeks on Days 1, 15, 29, and 43 of each 8-week cycle.

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For I/O-relapsed and I/O-refractory MEL cohorts in Phase 2, the dose of nivolumab will be 480 mg as a 30-minute infusion every 4 weeks on Day 1 and Day 29 of each 8-week cycle. Subjects will continue to receive nivolumab for up to 2 years as long as the subject is deriving benefit and have not met any protocol-defined criteria for study treatment withdrawal. Intrasubject dose escalation of nivolumab is not permitted. Nivolumab doses and schedules are summarized in Table A5.

Table A5: Nivolumab Doses and Schedules in Phase 1 and Phase 2

Study Phases and Cohorts	Phase 1		Phase 2	
	Part 1 – dose finding for combination immunotherapy cohorts	**Part 2** – dose finding for combination chemo-immunotherapy cohorts and safety expansion cohorts	Select tumor cohorts for combination immunotherapy	I/O-relapsed and I/O-refractory MEL cohorts
Nivolumab (Dose, schedule, infusion duration, cycle length)	3 mg/kg, Q2W 60 min IV 8-week cycle	360 mg, Q3W 30 min IV 21-day cycle	240 mg, Q2W 30 min IV 8-week cycle	480 mg Q4W 30 min IV 8-week cycle

Paclitaxel/Platinum (Carboplatin or Cisplatin) will be administered on Day 1 of each 21-day cycle for a minimum of 4 cycles and up to 6 cycles. Subjects will receive paclitaxel 200 mg/m^2 IV over 3 hours (± 15 min) with either AUC 6 carboplatin or 100 cisplatin mg/m^2 IV over 30 minutes (± 5 min). Premedications include the following: 1) dexamethasone 20 mg PO 12 hours and 6 hours before or dexamethasone 16 mg to 20 mg IV 30 minutes before, 2) chlorphenamine 10 mg IV 30 minutes before, and 3) ranitidine 50 mg IV 30 minutes before paclitaxel administration. Premedications may be adjusted based on institutional guidelines, study investigator practice, or availability of similar medications on the investigative site's formulary. Subjects may receive prophylactic G-CSF support after completion of Cycle 1.

Pemetrexed/Platinum (Carboplatin or Cisplatin) will be administered on Day 1 of each 21-day cycle for a minimum of 4 cycles and up to 6 cycles. Subjects will receive pemetrexed 500 mg/m^2 IV over 10 minutes (± 5 min) with either AUC 5 carboplatin or 100 mg/m^2 cisplatin IV over 30 minutes (± 5 min). Pemetrexed may continue as maintenance therapy after 6 cycles as long as the subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal. Premedications include the following: 1) dexamethasone 4 mg orally (PO) BID (or equivalent) taken the day before, the day of, and the day after pemetrexed administration; 2) folic acid 400 µg to 1000 µg PO once daily beginning 7 days before first dose of pemetrexed and continued through the full course of therapy and for 21 days after the last dose of pemetrexed; and 3) vitamin B_{12} 1 mg intramuscularly 1 week before the first dose of pemetrexed and every 3 cycles thereafter. Premedications may be adjusted based on institutional guidelines, study investigator practice, or availability of similar medications on the investigative site's formulary. Subjects may receive prophylactic G-CSF support after the completion of Cycle 1.

5-Fluorouracil (5-FU) and Platinum (cisplatin or carboplatin) will be administered beginning on Day 1 of each 21-day cycle for up to 6 cycles. 5-FU will be administered on Day 1 of each cycle. Subjects will receive 100 mg/m^2 cisplatin IV over 30 minutes (± 5 min) or carboplatin AUC 5 IV over 30 minutes (± 5 min) followed by 5-FU 1000 mg/m^2 per day as continuous IV infusion over 4 days. Premedications, including corticosteroids, may be given based on institutional guidelines, study investigator practice, or availability of similar medications on the investigative site's formulary. Subjects may receive prophylactic granulocyte-colony stimulating factor (G-CSF) support after completion of Cycle 1.

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Duration of Participation: Subject participation is continuous 8-week cycles in the combination immunotherapy cohorts or 21-day cycles in the combination chemo-immunotherapy cohorts. Subjects may continue on epacadostat and/or nivolumab for up to 2 years as long as they are receiving benefit and do not meet other treatment withdrawal criteria.

Study Population:

Subjects with Stage IIIB, Stage IV, or recurrent NSCLC; unresectable or Stage IV MEL; recurrent (unresectable) or metastatic CRC; recurrent (unresectable) or metastatic SCCHN; International Federation of Gynecology and Obstetrics (FIGO) Stage Ic, II, III, or IV recurrent ovarian cancer (unresectable); B-cell NHL or HL; and relapsed or refractory glioblastoma after standard-of-care therapy may enroll. Subjects with select cancers must have had disease progression on treatment or intolerance to treatment, or subjects who have refused currently approved treatment may enroll with medical monitor approval (except for subjects with MEL, who may be enrolled as initial treatment for their advanced cancer).

Key Inclusion Criteria:

- Male or female subjects, age 18 years or older.
- Subjects with histologically or cytologically confirmed NSCLC, MEL, CRC, SCCHN, ovarian cancer, recurrent B-cell NHL or HL, or glioblastoma.
- Subjects with Stage IIIB, Stage IV, or recurrent NSCLC; unresectable or Stage IV MEL; recurrent (unresectable) or metastatic CRC; recurrent (unresectable) or metastatic SCCHN; FIGO Stage Ic, II, III, or IV recurrent ovarian cancer (unresectable); relapsed or refractory B-cell NHL or HL (including relapsed or refractory DLBCL); or relapsed or refractory glioblastoma and meet the following tumor-specific criteria:
  - Subjects with Stage IIIB, Stage IV, or recurrent NSCLC:
    - **For all NSCLC subjects (Phase 1 and Phase 2):**
      - Subjects with nonsquamous NSCLC must be screened for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) fusion oncogene status.
      - Tumors with driver mutations (EGFR mutation–positive or ALK fusion oncogene–positive) previously treated with an approved tyrosine kinase inhibitor (TKI) must have progressed on or been intolerant to the TKI therapy. (Note: For subjects with driver mutations and treated with a prior TKI therapy, up to 2 additional lines of therapy that include a TKI therapy are permitted.)
      - Maintenance or switch maintenance therapy after first line chemotherapy is acceptable.
      - Malignancy must be deemed unresectable.
    - **For combination immunotherapy cohorts (Part 1 of Phase 1 and Phase 2),** subjects with nonsquamous, squamous, or adenosquamous NSCLC, or NSCLC NOS histology who have received <u>up to 1 prior systemic regimen</u> for Stage IIIB, Stage IV, or recurrent NSCLC. Prior systemic regimen must have contained a platinum-based therapy (at least 2 cycles with or without bevacizumab).
      - Subjects ineligible for platinum-based therapy who have received alternative chemotherapy regimens or are intolerant of platinum-based therapy may enroll with medical monitor approval.
      - Subjects who completed and progressed on a platinum-containing regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy within the 6 months before screening would be counted as having received 1 prior platinum-containing regimen and, therefore, would not require re-treatment with a platinum-containing regimen for advanced or metastatic disease.

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- **For combination chemo-immunotherapy cohorts (Part 2 of Phase 1 only),** subjects with nonsquamous or squamous NSCLC must have no more than 1 prior line of therapy for Stage IIIB, Stage IV, or recurrent NSCLC.
  - Subjects must not have received previous platinum-based doublet chemotherapy for Stage IIIB, Stage IV, or recurrent NSCLC.
  - Subjects who completed a platinum-based chemotherapy doublet regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible for combination chemo-immunotherapy only. If progression occurred < 6 months after completing therapy, the subject will not be eligible.
  - In the dose-finding cohorts, subjects may have received a prior TKI for tumors with any driver mutation (EGFR mutation positive or ALK fusion oncogene positive).
  - In the safety expansion cohorts, subjects must not have any prior therapy for advanced or metastatic disease, except TKI for driver mutations.

– Subjects with unresectable or Stage IV MEL. **Note:** There will be 3 MEL cohorts in Phase 2, which will include I/O-naive, I/O-relapsed, and I/O-refractory cohorts as defined below:
- For all MEL subjects **(Phase 1 and Phase 2):**
  - Documentation of V600E-activating BRAF mutation status or consent to BRAF V600E mutation testing during the screening period. Testing should be performed in a Clinical Laboratory Improvement Amendments–certified laboratory. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criteria for BRAF mutation testing.
  - No nitrosoureas (eg, carmustine or lomustine) within the past 6 weeks and during study treatment.
  - Must not have any prior ocular toxicity on any prior therapy, including immune checkpoint inhibitors.
  - No more than 2 prior lines of therapy for advanced/metastatic disease, only 1 of which can be a prior anti–PD-1/PD-L1 therapy with or without anti–cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) therapy. Prior anti–CTLA-4 monotherapy is not permitted.
  - Must not have ocular melanoma.
- For subjects with advanced or metastatic **I/O-naive MEL (Part 1 of Phase 1 and Phase 2):**
  - Subjects must be treatment-naive or have received only 1 prior treatment for advanced or metastatic disease, including targeted therapy.
  - Subjects must not have received any prior anti–PD-1/PD-L1 therapy.
    Note: Anti–CTLA-4 given as in the adjuvant setting or as first-line treatment for advanced or metastatic disease will be permitted. These subjects must have discontinued anti–CTLA-4 therapy at least 12 weeks before first dose of epacadostat.
- For subjects with advanced or metastatic MEL who were relapsed on or after the previous anti–PD-1/PD-L1 therapy following an initial response to PD-1 pathway–targeted therapy **(I/O-relapsed MEL; Phase 2 only):**
  - **Relapsed** is defined as having a best response CR, partial response (PR), or stable disease with a subsequent confirmed radiographic progression per RECIST v1.1 on or after anti–PD-1/PD-L1 therapy with or without anti–CTLA-4 therapy.
    Note: Disease progression may be confirmed based on study investigator's certification at screening assessment).
  - If with known BRAF mutations, subjects may have had prior BRAF/MEK inhibitors following the last anti–PD-1/PD-L1 therapy (with or without anti–CTLA-4 therapy).
  - No more than 2 prior lines of therapy for advanced/metastatic disease, only 1 of which can be a prior anti–PD-1/PD-L1 therapy, with or without anti–CTLA-4 therapy. Prior anti–CTLA-4 monotherapy is not permitted.

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- For subjects with advanced or metastatic MEL who were refractory to previous anti–PD-1/PD-L1 therapy **(I/O-refractory MEL; Phase 2 only):**
  - **Refractory** is defined as having a best response of confirmed radiographic progression per RECIST v1.1 to a prior anti-PD–1/PD-L1 therapy with or without anti–CTLA-4 therapy. **Note:** Disease progression may be confirmed based on study investigator's certification at screening assessment.
  - If with known BRAF mutations, may have had prior BRAF/MEK inhibitors following the last anti–PD-1/PD-L1 therapy (with or without anti–CTLA-4 therapy).
  - No more than 2 prior lines of therapy for advanced/metastatic disease, only 1 of which can be a prior anti–PD-1/PD-L1 therapy, with or without anti–CTLA-4 therapy. Prior anti–CTLA-4 monotherapy is not permitted.

– Subjects with recurrent (unresectable) or metastatic CRC:
  - Histologically or cytologically confirmed adenocarcinoma of the colon or rectum.
  - Prior treatment: Previous treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti–vascular endothelial growth factor (VEGF) therapy (if no contraindication); and, if KRAS wild type and no contraindication, an anti-EGFR therapy and progressed following the last administration of approved therapy.
  - Subjects who have discontinued treatment due to unacceptable toxicity may enroll.

– Subjects with recurrent (unresectable) or metastatic SCCHN:
  - Histologically confirmed metastatic or recurrent squamous cell carcinoma not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy). Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and salivary gland or nonsquamous histologies will be excluded.
  - For combination immunotherapy cohorts in Phase 1 Part 1 and Phase 2: No more than 2 prior systemic regimens for advanced disease. Prior systemic regimens must include a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Subjects who relapsed within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
  - For combination chemo-immunotherapy cohorts in Phase 1 Part 2: Subjects must not have received a previous platinum-based chemotherapy for recurrent or metastatic SCCHN. **Note:** Subjects who completed a platinum based chemotherapy as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing the therapy, the subject will not be eligible.
  - Documentation of human papillomavirus status (eg, p16-status) of tumor.

– Subjects with FIGO Stage Ic, Stage II, Stage III, Stage IV, recurrent, or persistent (unresectable) histologically confirmed epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube carcinoma:
  - Subjects must have received a platinum-taxane–based regimen as frontline therapy.
  - Subjects who received maintenance paclitaxel, bevacizumab, or alternative maintenance therapy (eg, vaccines) are eligible for enrollment provided they have discontinued therapy at least 4 weeks for prior taxane and at least 8 weeks for bevacizumab, or they have received medical monitor approval for time lapse from alternative maintenance therapy before enrollment and recovered from toxicities to less than Grade 2.
  - Borderline, low malignant potential epithelial carcinoma per histopathology is excluded.

– Subjects with relapsed or recurrent B-cell NHL or HL (including relapsed or refractory DLBCL, excluding Burkitt's lymphoma and precursor B-lymphoblastic leukemia/lymphoma):
  - Prior allogeneic stem-cell transplantation is excluded.
  - Not a candidate for curative therapy or hematopoietic stem cell transplantation (due to disease burden, fitness, or preference).

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  - Subjects must have relapsed or have had refractory DLBCL specifically for Phase 2 but may have any B-cell NHL or HL as noted above for Phase 1 dose escalation.
  - Subjects with HL: must be brentuximab vedotin refractory or intolerant.
- Subjects with histologically confirmed diagnosis of relapsed or refractory glioblastoma:
  - Previous first-line treatment with at least radiotherapy and temozolomide.
  - Documented first recurrence of glioblastoma by diagnostic biopsy or contrast enhanced magnetic resonance imaging (MRI) per RANO criteria.

    Note: Relapse is defined as progression following initial line of therapy (ie, radiation ± chemotherapy). If the participant had a surgical resection for relapsed disease and no antitumor therapy was instituted for up to 12 weeks, this is considered 1 relapse or recurrence.
  - MRI within 14 days before start of study drug. MRIs should include vascular imaging when possible. Corticosteroid dose must be stable or decreasing for at least 5 days before the scan. If steroids are added or the steroid dose is increased between the date of the screening MRI and the start of treatment, a new baseline MRI is required.
  - An interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either 1) histopathologic confirmation of recurrence of tumor or 2) new enhancement on MRI outside of the radiotherapy treatment field.
  - An interval of ≥ 21 days and full recovery (ie, no ongoing safety issues) from surgical resection before enrollment.

- Presence of measurable disease per RECIST v1.1 for solid tumors or Response Criteria for Lymphoma (Cheson et al 2007) B-cell NHL (including DLBCL) or HL. For subjects with glioblastoma, presence of measurable disease is not required.
- ECOG performance status 0 to 1.
- Fresh baseline tumor biopsies (defined as a biopsy specimen taken since completion of the most recent prior systemic regimen) are required for all cohorts except glioblastoma. For I/O-relapsed MEL and I/O-refractory MEL cohorts (Phase 2) as well as all combination chemo-immunotherapy cohorts (Part 2 of Phase 1), biopsies will be confirmed to contain adequate tumor tissue by a local pathology review. If a subject has inaccessible lesions, such as in ovarian cancer, the subject may be enrolled with medical monitor approval. In this case, submission of archived tumor tissue may be acceptable.

  For archived tumor tissue, a formalin fixed paraffin-embedded tumor tissue block is preferred. If a block is not available, a minimum of 20 unstained freshly cut slides may be submitted to the testing laboratory as specified in the Laboratory Manual.

  Note: Unstained slides must have been prepared from a formalin fixed paraffin-embedded block obtained within 6 months before screening).
- Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal as defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test at screening. All female (and male as appropriate for Protocol) subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy (or fathering children), with at least 99% certainty, from screening through 150 days after the last dose of epacadostat. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.

Key Exclusion Criteria:

- Laboratory and medical history parameters not within Protocol-defined range unless directly resulting from the bone marrow infiltration of the underlying malignancy. All screening laboratory tests should be performed within 7 days of the first dose of epacadostat (Cycle 1 Day 1) and must be independent of hematopoietic growth factor support:
  - Absolute neutrophil count < 1.5×10^9/L (in no case < 1.0×10^9/L).

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- Platelets < 100 × 10^9/L (in no case < 50 × 10^9/L).
- Hemoglobin < 9 g/dL or ≤ 5.6 mmol/L (transfusion is acceptable to meet this criterion).
- Serum creatinine ≥ 1.5 × institutional upper limit of normal (ULN), or measured or calculated creatinine clearance (CrCl) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.
- Aspartate aminotransferase, alanine aminotransferase > 2.5 × ULN OR ≥ 5 × ULN for subjects with liver metastases.
- Total bilirubin ≥ 1.5 × ULN or conjugated (direct) bilirubin ≥ ULN (need only be tested if total bilirubin exceeds ULN). If an institutional ULN for conjugated bilirubin is not available, then conjugated bilirubin should be < 40% of total bilirubin to be considered eligible.
- International normalized ratio (INR) or prothrombin time (PT) > 1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants.
- Activated partial thromboplastin time (aPTT) > 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.

• Current pregnancy or breastfeeding.
• Participation in any other study in which receipt of an investigational study drug occurred within 28 days or 5 half-lives (whichever is longer) before Cycle 1 Day 1. For investigational agents with long half-lives (eg, 5 days), enrollment before the fifth half-life requires medical monitor approval.
• Subjects who have received prior immune checkpoint inhibitors (eg, anti–CTLA-4, anti–PD-1, anti–PD-L1, and any other antibody or drug specifically targeting T-cell costimulation) or an IDO inhibitor (except as required for I/O-relapsed and I/O-refractory MEL cohorts [Phase 2], see inclusion criteria above). Subjects who have received experimental vaccines or other immune therapies should be discussed with the medical monitor to confirm eligibility.
• Any prior immune-related adverse events (irAEs) must have resolved to ≤ Grade 1 before first dose of epacadostat and nivolumab (Cycle 1 Day 1). Any ≥ Grade 3 irAEs (except lymphopenia or asymptomatic amylase/lipase elevations) from prior immunotherapies, including CTLA-4 treatment, are excluded.
  Note: Subjects with history of ≥ Grade 3 endocrinopathies must be discussed with the medical monitor to determine eligibility.
• Subjects who are receiving an immunologically based treatment for any reason, including chronic use of systemic steroid or prednisone equivalent at doses ≥ 10 mg/day within 7 days before the first dose of epacadostat and nivolumab (Cycle 1 Day 1). Use of inhaled or topical steroids or systemic corticosteroids < 10 mg is permitted.
  Note: There are some exceptions in use of systemic corticosteroids or physiological replacement doses of steroids for subjects with glioblastoma)
• Subjects who have received any anticancer medication in the 21 days before Cycle 1 Day 1 or has any unresolved toxicity greater than Grade 1 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity, alopecia, and fatigue.
• Prior monoclonal antibody within 4 weeks before starting Cycle 1 Day 1 or not recovered (≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier. Exception to this rule would be use of denosumab.
• Untreated central nervous system (CNS) metastases or CNS metastases that have progressed (eg, evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases or cerebral edema). Subjects with previously treated and clinically stable CNS metastases (without evidence of radiographic progression shown by imaging at least 28 days before Cycle 1 Day 1) and off all corticosteroids for at least 2 weeks before Cycle 1 Day 1 are eligible.

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- Subjects with any active or inactive autoimmune process (eg, rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, inflammatory bowel disease) or who are receiving systemic therapy for an autoimmune or inflammatory disease.
  - Exceptions include subjects with vitiligo, hypothyroidism stable on hormone replacement, controlled asthma, Type I diabetes, Graves' disease, Hashimoto's disease, or with medical monitor approval.
- Evidence of interstitial lung disease or active, noninfectious pneumonitis including symptomatic and/or pneumonitis requiring treatment.
- Subjects who have had prior radiotherapy within 2 weeks of Cycle 1 Day 1. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week wash out is permitted for palliative radiation to non-CNS disease with medical monitor approval.
- Any history of serotonin syndrome (SS) after receiving 1 or more serotonergic drugs.
- History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is > 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.
- History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Known allergy or reaction to any component of epacadostat, nivolumab, 5-FU, cisplatin, carboplatin, paclitaxel, pemetrexed, or their formulation components or mannitol.
- Exclusion criteria for subjects enrolled with glioblastoma:
  - More than 1 recurrence of glioblastoma.
  - Presence of extracranial metastatic or leptomeningeal disease.
  - Diagnosis of secondary glioblastoma (ie, glioblastomas that progress from low-grade diffuse astrocytoma or anaplastic astrocytoma).
  - Previous radiation therapy with anything other than standard therapy (ie, focally directed radiation).
  - Subjects requiring escalating (within 7 days of Cycle 1 Day 1) or chronic supraphysiologic doses (to be more than 2 mg of Decadron® or biologic equivalent per day) of corticosteroids for control of their disease.
  - Treatment with carmustine wafer except when administered as first-line treatment and at least 6 months before Cycle 1 Day 1.
  - Evidence of > Grade 1 CNS hemorrhage on the baseline MRI.
  - History or evidence upon physical/neurological examination of CNS disease (eg, seizures) unrelated to cancer unless adequately controlled by medication or potentially interfering with Protocol treatment.
  - Subjects unable (due to existent medical condition, eg, pacemaker or implantable cardioverter defibrillator device) or unwilling to have a head contrast-enhanced MRI.
  - History of intracranial abscess within 6 months before enrollment.
  - Prior VEGF or VEGF-receptor directed therapy (ie, bevacizumab).
- Use of any prohibited medication.
- Has a known history of or is positive for hepatitis B (HBsAg reactive) or has active hepatitis C (HCV RNA). Note: Testing must be performed to determine eligibility.
  - HBV DNA must be undetectable and HBsAg negative at screening visit.

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- Hepatitis C Ab testing is allowed for screening purposes in countries where HCV RNA is not part of SOC. In these cases, HCV antibody positive participants will be excluded.
- Participants who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening visit. (Includes serology testing shown in the laboratory analytes.)

• Subjects with bleeding associated with tumors that invade or are adjacent to major blood vessels, as shown unequivocally by imaging studies, or history of bleeding related to disease under study within 3 months of Cycle 1 Day 1.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site on Day 1 of every cycle (CXD1) and at designated timepoints within each cycle, as noted in the Schedule of Assessments. Safety assessments will include laboratory assessments, vital sign collection, ECGs, and physical examinations. Adverse events will be assessed continuously during the study and for 100 days after the last dose of combination treatment. Adverse events will be coded using the most current version of MedDRA at Protocol initiation and reviewed for potential significance and importance. Subjects should be followed until all treatment related AEs have recovered to baseline or are deemed irreversible by the investigator. Both AEs and laboratory tests will be graded using the NCI CTCAE v4.

Efficacy measures will be assessed 8 and 16 weeks after the start of treatment for subjects in the combination chemo-immunotherapy cohorts (Phase 1 Part 2) and then every 12 weeks thereafter. All other subjects (Phase 1 Part 1 and Phase 2) will have efficacy assessments every 12 weeks. All subjects will continue to have efficacy assessments until the end of treatment; no efficacy assessments are required during the safety follow-up period. Tumor responses will be derived for appropriate populations of subjects as defined by RECIST v1.1 for solid tumors, Cheson criteria for lymphoma, or RANO criteria for subjects with glioblastoma based on recorded tumor measurements as well as based on investigator assessment of response.

The decision to treat a subject with additional cycles of study therapy will be based on tumor assessment (evaluation completed before the first dose in the next cycle): 1) radiographic progression, 2) clinical deterioration suggesting that no further benefit from treatment is likely, 3) intolerability to therapy, 4) the subject meets criteria for discontinuation of study therapy, or 5) the subject has received 2 years of nivolumab therapy.

Subjects will enter the safety follow-up period upon discontinuation of treatment.

[redacted]

Planned Number of Subjects:

Up to approximately 485 subjects may be enrolled in the overall study. There will be approximately up to 207 subjects enrolled in the Phase 1, which will include subjects enrolled in both dose escalation in combination immunotherapy cohorts as well as in combination chemo-immunotherapy cohorts and combination chemo-immunotherapy safety expansion cohorts. In Phase 2, there will be up to approximately 278 subjects enrolled.

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Principal Coordinating Investigator: TBD

Statistical Methods:

Selection of Sample Size

Phase 1 (Part 1 and Part 2): Dose Finding and Safety Expansion: For Part 1 of Phase 1 dose-escalation of combination immunotherapy cohorts, the sample size at each dose depends on the number of observed toxicities (3 + 3 + 3 design) during DLT observation period. Between 3 and 9 subjects are expected to be treated during dose escalation in each cohort.

For Part 2 of Phase 1 dose finding (dose de-escalation) of combination chemo-immunotherapy cohorts, the sample size at each dose also depends on the number of observed toxicities during DLT observation period. Between 6 and 9 subjects are expected to be treated in each individual cohort. For safety expansion cohorts of combination chemo-immunotherapy, up to 30 subjects will be enrolled in each tumor /combination chemo-immunotherapy specific cohorts.

Phase 2 Cohort Expansion: During cohort expansion, approximately 25 subjects are expected to be enrolled in each of the 4 low historic response expansion cohorts (CRC, SCCHN, ovarian cancer, and DLBCL) and in the 2 MEL cohorts (I/O relapsed and I/O refractory). Approximately 50 subjects are expected in each of the 2 higher historic ORR cohorts (NSCLC and I/O-naive MEL). For these cohorts, ORR and PFS will be analyzed as dual primary endpoints. The sample size yields a power of 80% to detect either an increase in ORR by 17% to 26% from historical response rate of each tumor type, or a PFS rate at 6 months increased by 17% to 22% from historical survival probability. This assumes a 1-sided alpha of 2.5% (based on Bonferroni adjustment due to dual primary endpoints for each independent cohort), 10% lost to follow-up, enrollment period of 6 to 10 months (depends on cohort), and 6 to 10 months of follow-up (depends on cohort) after last subject enrolled. Twenty-eight subjects are expected to be enrolled in the glioblastoma cohort. This yields a power of 80% to detect an OS rate at 9 months of 25% increase (Ha) from historical survival probability (H0). This assumes a 1-sided alpha of 5%, 10% lost to follow-up, enrollment period of 4 months, and 9 months of follow-up after last subject enrolled.

Statistical Analysis:

Primary Analyses:

Phase 1 (Part 1 and Part 2) and Phase 2: Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. DLTs will be summarized for each cohort. Dose exposure and density will be calculated for Phase 1. AEs will be coded by MedDRA, and incidences will be tabulated by preferred term and system organ class for all events, related events, and events ≥ Grade 3. Severity of AEs will be based on the CTCAE scale. Quantitative safety variables and their changes from baseline (laboratory, vital signs) will be summarized with descriptive statistics. Clinically significant abnormal values will be flagged and tabulated based on predefined criteria.

Phase 2: The proportion of subjects with objective response (ORR) will be tabulated by tumor type (cohort). The PFS and OS will be analyzed by the Kaplan-Meier method. The PFS/OS rate and the corresponding confidence interval using log-log transformation will be provided by tumor type (cohort) at 6 months for PFS and 9 months for OS.

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Safety Monitoring Committee: Due to the complexity of combination chemo-immunotherapy cohorts, a Safety Monitoring Committee (SMC) will review safety data at regular intervals throughout Phase 1 Part 2. Details regarding SMC membership, roles and responsibilities of the committee will be specified in the SMC charter.

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TABLE OF CONTENTS

SYNOPSIS 3
LIST OF ABBREVIATIONS 33
1. INTRODUCTION 37
1.1. Pharmaceutical and Therapeutic Background 37
1.1.1. Inhibition of PD-1 as a Target for Cancer 37
1.1.2. Inhibition of Indoleamine 2,3-Dioxygenase as a Target for Cancer 39
1.1.3. Combined Immune Checkpoint Inhibition 40
1.1.4. Rationale for Studying Immunotherapy in Advanced or Metastatic Cancers 42
1.1.5. Overview of 5-Fluorouracil and Cisplatin in Squamous Cell Carcinoma of Head and Neck 44
1.1.6. Overview of Platinum-Based Doublet Chemotherapy Compared With Immunotherapy in Squamous and Nonsquamous Non–Small Cell Lung Cancer 44
1.2. Study Rationale 46
1.2.1. Rationale for Combining PD-1 Inhibitor and IDO1 Inhibitor [redacted] 46
1.2.2. Rationale for Combining PD-1 Inhibitor and IDO1 Inhibitor With Chemotherapy [redacted] 47
1.2.3. Preclinical and Clinical Study Data for Epacadostat and Nivolumab 49
1.3. Potential Risks and Benefits of the Treatment Regimen 49
[redacted] 49
1.3.2. Risks From Nivolumab 50
1.3.3. Risks for the Combination of Epacadostat and Nivolumab 50
1.3.4. Risks From 5-Fluorouracil/Platinum (Cisplatin or Carboplatin) 50
1.3.5. Risks From Paclitaxel/Carboplatin 51
1.3.6. Risks From Paclitaxel/Cisplatin 51
1.3.7. Risks From Pemetrexed/Carboplatin 51
1.3.8. Risks From Pemetrexed/Cisplatin 52
1.3.9. Risks From Combining an IDO Inhibitor With Chemotherapy 52
1.3.10. Risks From Combining a PD-1 Inhibitor With Chemotherapy 52
1.4. Justification for Treatment Regimens 52
1.4.1. Rationale for 2-Year Duration of Treatment 55

Printed on: , ; Printed by: .

2. STUDY OBJECTIVES AND PURPOSE 56
2.1. Primary Objectives 56
2.1.1. Phase 1 56
2.1.2. Phase 2 56
2.2. Secondary Objectives 56
2.2.1. Phase 1 56
2.2.2. Phase 2 56
[redacted] 57
3. SUBJECT ELIGIBILITY 58
3.1. Study Population 58
3.2. Subject Inclusion Criteria 58
3.3. Subject Exclusion Criteria 63
4. INVESTIGATIONAL PLAN 67
4.1. Overall Study Design 67
4.1.1. Phase 1 Dose-Finding and Safety Expansion (Part 1 and Part 2) 69
4.1.1.1. Combination Immunotherapy Cohorts (Part 1) 69
4.1.1.2. Combination Chemo-Immunotherapy Cohorts (Part 2 of Phase 1) 71
4.1.2. Phase 2 Combination Immunotherapy Cohort Expansions 74
4.2. Study Endpoints 76
4.2.1. Primary Endpoint 76
4.2.1.1. Phase 1 76
4.2.1.2. Phase 2 76
4.2.2. Secondary Endpoints 76
4.2.2.1. Phase 1 76
4.2.2.2. Phase 2 76
[redacted] 77
4.3. Measures Taken to Avoid Bias 77
4.4. Number of Subjects 77
4.5. Study Termination 78
5. TREATMENT OF SUBJECTS 78
5.1. Administration of Study Drugs 78
5.1.1. Epacadostat 78
5.1.2. Nivolumab 78

Printed on: , ; Printed by: .

5.1.2.1. Timing of Dose Administration of Nivolumab 79
5.2. Background Therapies 80
5.2.1. Paclitaxel/Platinum (Carboplatin or Cisplatin)....80
5.2.1.1. Description and Administration....80
5.2.1.2. Supply, Packaging, and Labeling 80
5.2.2. Pemetrexed/Platinum (Carboplatin or Cisplatin)....80
5.2.2.1. Description and Administration....80
5.2.2.2. Supply, Packaging, and Labeling 81
5.2.3. Platinum (Carboplatin or Cisplatin)/5-Fluorouracil 81
5.2.3.1. Description and Administration....81
5.2.3.2. Supply, Packaging, and Labeling 82
5.3. Treatment Compliance....82
5.4. Randomization and Blinding 82
5.5. Duration of Treatment and Subject Participation 82
5.6. Rationale for Dose Modifications....83
5.6.1. Definition of Dose-Limiting Toxicities 83
5.6.1.1. Procedures for Cohort Review and Dose Escalation 84
5.6.1.2. Follow-Up for Dose-Limiting Toxicities....84
5.7. Dose Modification of Study Drugs....85
5.7.1. Planned Dose Modifications....85
5.7.2. Criteria and Procedures for Interruption....85
5.7.3. Procedures for Subjects Exhibiting Immune-Related Adverse Events 89
5.7.3.1. Procedures and Guidelines for Pneumonitis....91
5.7.3.2. Procedures and Guidance for Enterocolitis 91
5.7.3.3. Procedures and Guidance for Hepatitis 92
5.7.3.4. Procedures for Immune-Mediated Dermatitis 93
5.7.3.5. Procedures for Immune-Mediated Neuropathies....94
5.7.3.6. Procedures for Immune-Mediated Endocrinopathies 95
5.7.3.7. Procedures for Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations....96
5.7.4. Procedures for Subjects Exhibiting Serotonin Syndrome 97
5.8. Criteria for Permanent Discontinuation of Study Drug(s)....98
5.9. Study Completion 99

Printed on: , ; Printed by: .

5.9.1. Study Completion Criteria 99
5.9.2. Withdrawal Procedures 100
5.10. Beginning and End of the Study 100
5.11. Concomitant Medications and Measures 100
5.11.1. Acceptable Concomitant Medications 100
5.11.2. Supportive Care Guidelines 101
5.11.3. Management of Infusion Reactions From Nivolumab 101
5.12. Restricted Medications and Measures 103
5.13. Prohibited Medications and Measures 103
6. STUDY ASSESSMENTS 104
6.1. Screening Period 115
6.2. Treatment Period 116
6.3. End of Treatment 116
6.4. Follow-Up Period 116
6.4.1. Safety Follow-Up 116
6.5. Unscheduled Visits 116
6.6. Early Termination 116
7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES 117
7.1. Study Procedures 117
7.2. Administration of Informed Consent Form 117
7.3. Demography and History 117
7.3.1. Demographics and Medical History 117
7.3.2. Prior Medications 117
7.3.3. Concomitant Medications 118
7.3.4. Post-Treatment Anticancer Therapy Status 118
7.4. Safety Assessments 118
7.4.1. Adverse Events 118
7.4.2. Comprehensive Physical Examination 118
7.4.3. Targeted Physical Examination 118
7.4.4. Vital Signs 119
7.4.5. Twelve-Lead Electrocardiograms 119
7.4.6. Laboratory Assessments 119

Printed on: , ; Printed by: .

7.4.6.1. Chemistry, Hematology, Coagulation Panel, Serology, and Endocrine Function Testing 119
7.4.6.2. Urinalysis 119
7.4.6.3. Liver Chemistry Tests 120
7.4.6.4. Pregnancy Testing 120
7.5. Efficacy Assessments 120
7.5.1. Initial Tumor Imaging 120
7.5.2. Tumor Imaging During the Study 121
7.5.3. Assessment of Disease by Cheson Criteria for Lymphomas 121
7.5.3.1. CT Scan or MRI for Lymphoma Evaluation 122
7.5.3.2. FDG-PET or Combined PET-CT 122
7.5.4. Assessment of Disease by RANO Criteria for Glioblastoma 122
[redacted] 125
[redacted] 125
[redacted] 127
[redacted] .127
7.7. Other Study Procedures 127
7.7.1. Study Compliance 127
7.7.2. Administration of Nivolumab and Compliance 127
7.7.3. Administration of Epacadostat and Compliance 128
7.7.4. Dispensing of Epacadostat 128
7.7.5. Dispensing of Nivolumab 128
7.7.6. Distribution of Subject Reminder Cards 128
7.7.7. Withdrawal or Discontinuation 128
8. SAFETY MONITORING AND REPORTING 129
8.1. Adverse Events 129
8.1.1. Definitions 129
8.1.2. Reporting 129
8.2. Laboratory Test Abnormalities 131
8.2.1. Definitions and Reporting 131
8.2.2. Potential Drug-Induced Liver Injury 131
8.3. Serious Adverse Events 132
8.3.1. Definitions 132

Printed on: , ; Printed by: .

8.3.2. Reporting 132
8.4. Emergency Unblinding of Treatment Assignment 133
8.5. Pregnancy 133
8.6. Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor 134
8.7. Warnings and Precautions 134
8.8. Safety Monitoring Committee 135
8.9. Adverse Events of Special Interest 135
8.10. Product Complaints 136
9. STATISTICS 136
9.1. Study Populations 136
9.2. Selection of Sample Size 137
9.2.1. Cohort Size in Part 1 and Part 2 of Phase 1 Study 137
9.2.2. Sample Size for the Dose-Expansion Portion (Phase 2) of the Study 137
9.3. Level of Significance 138
9.4. Statistical Analyses 138
9.4.1. Primary Analyses 138
9.4.2. Secondary Analyses 139
[redacted] [redacted] 140
9.4.4. Safety Analyses 140
9.4.5. Clinical Laboratory Tests 140
9.5. Analyses for the Safety Monitoring Committee 140
9.6. Interim Analysis 141
10. STUDY DRUG MATERIALS AND MANAGEMENT 142
10.1. Investigational Products Description 142
10.1.1. Packaging, Labeling, and Preparation of Study Drug or Placebo 142
10.1.1.1. Epacadostat 142
10.1.1.2. Nivolumab 142
10.1.2. Storage and Stability of Study Drugs 142
10.1.2.1. Epacadostat 142
10.1.2.2. Nivolumab 142
10.2. Accountability, Handling, and Disposal of Epacadostat and Nivolumab 143
10.2.1. Disposal of Epacadostat and Nivolumab 143

Printed on: , ; Printed by: .

11. STUDY ADMINISTRATION 144
11.1. Data Management 144
11.1.1. Data Collection 144
11.1.2. Data Management 144
11.2. Study Monitoring 144
11.3. Protocol Adherence 145
11.4. Financial Disclosure 145
11.5. Compliance With Study Registration and Results Posting Requirements 146
12. QUALITY CONTROL AND QUALITY ASSURANCE 146
12.1. Sponsor Audits 146
12.2. Inspection by Regulatory Authorities 146
13. ETHICS 147
13.1. Ethical Conduct of the Study 147
13.2. Written Informed Consent 147
13.3. Ethics Review 147
13.4. Data Privacy 148
14. DATA HANDLING AND RECORDKEEPING 149
14.1. Inspection of Records 149
14.2. Retention of Records 149
14.3. Confidentiality 149
15. PUBLICATION POLICY 150
16. REFERENCES 151
APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS 161
[redacted] 162
APPENDIX C. MANAGEMENT ALGORITHMS 163
APPENDIX D. PROHIBITED MONOAMINE OXIDASE INHIBITORS AND DRUGS ASSOCIATED WITH SIGNIFICANT MONOAMINE OXIDASE INHIBITORY ACTIVITY 171
APPENDIX E. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1 172
APPENDIX F. RESPONSE CRITERIA FOR LYMPHOMA 173
APPENDIX G. RESPONSE ASSESSMENT FOR WALDENSTRÖM'S MACROGLOBULEMIA 176

Printed on: , ; Printed by: .

APPENDIX H. RESPONSE CRITERIA FOR GLIOBLASTOMA 177

APPENDIX I. DOSE MODIFICATIONS FOR PACLITAXEL/PLATINUM (CARBOPLATIN OR CISPLATIN).....180

APPENDIX J. DOSE MODIFICATIONS FOR PEMETREXED/PLATINUM (CARBOPLATIN OR CISPLATIN).....184

APPENDIX K. DOSE MODIFICATIONS FOR PLATINUM (CARBOPLATIN OR CISPLATIN)/5-FLUOROURACIL 187

APPENDIX L. PROTOCOL AMENDMENT SUMMARY OF CHANGES.....191

LIST OF TABLES

Table 1: Phase 1 Part 1 Dose-Escalation Schema for Epacadostat in Combination With Nivolumab Once Every 2 Weeks (Combination Immunotherapy Cohorts) 70

Table 2: Epacadostat Dose De-Escalation Scenarios for Combination Chemo-Immunotherapy Cohorts 72

Table 3: Summary of Treatment Regimens for Each Possible Epacadostat Dose-Finding Scenario for Combination Chemo-Immunotherapy Cohorts in Part 2 73

Table 4: Tumor Types Eligible for Combination Immunotherapy Cohort Expansion.....75

Table 5: Nivolumab Doses and Schedules in Phase 1 and Phase 2 79

Table 6: Criteria for Defining Dose-Limiting Toxicities.....84

Table 7: Dose Reductions of Epacadostat 85

Table 8: Dose Modification Guidelines for Drug-Related Adverse Events for Combination Immunotherapy.....87

Table 9: General Approach to Handling Immune-Related Adverse Events.....90

Table 10: Recommended Approach to Handling Noninfectious Pneumonitis.....91

Table 11: Recommended Approach for Handling Enterocolitis.....92

Table 12: Recommended Approach for Handling Hepatitis.....93

Table 13: Recommended Approach for Handling Dermatitis 94

Table 14: Recommended Approach for Handling Neuropathies.....95

Table 15: Recommended Approach for Handling Endocrinopathies 96

Table 16: Signs and Symptoms of Serotonin Syndrome 98

Table 17: Warfarin Dose Adjustment Recommendation When Initiating Concurrent Epacadostat Treatment.....103

Printed on: , ; Printed by: .

Table 18: Schedule of Assessments for Screening Through Treatment Period (Combination Immunotherapy Cohorts With Nivolumab Q2W Dosing Schedule) 105

Table 19: Schedule of Assessments for Screening Through Treatment Period (Combination Immunotherapy Cohorts With Nivolumab Q4W Dosing Schedule) 106

Table 20: Schedule of Assessments End of Treatment Through Safety Follow-Up (Combination Immunotherapy Cohorts With Both Q2W and Q4W Nivolumab Dosing Schedules) 107

Table 21: Laboratory Assessments for Screening Through Treatment Period (Combination Immunotherapy Cohorts With Nivolumab Q2W Dosing Schedule) 108

Table 22: Laboratory Assessments for Screening Through Treatment Period (Combination Immunotherapy Cohorts With Nivolumab Q4W Dosing Schedule) 109

Table 23: Laboratory Assessments for End of Treatment Through Safety Follow-Up (Combination Immunotherapy Cohorts With Both Nivolumab Q2W and Q4W Dosing Schedules)....110

Table 24: Schedule of Assessments for Phase 1 Part 2 Subjects Treated With Epacadostat + Nivolumab (Q3W) + Platinum/Paclitaxel or Epacadostat + Nivolumab + Platinum/Pemetrexed or Epacadostat + Nivolumab + Platinum/5-FU (Combination Chemo-Immunotherapy Cohorts)....111

Table 25: Laboratory Assessments for Phase 1 Part 2 Subjects Treated With Epacadostat + Nivolumab (Q3W) + Platinum/Paclitaxel, Epacadostat + Nivolumab + Platinum/Pemetrexed or Epacadostat + Nivolumab + Platinum/5-FU (Combination Chemo-Immunotherapy Cohorts)....113

Table 26: Laboratory Tests: Required Analytes 115

Table 27: RANO Criteria for Response Assessment Incorporating MRI and Clinical Factors....123

Table 28: Assessment of Best Overall Response....124

[redacted] 125

[redacted] 126

[redacted]

Printed on: , ; Printed by: .

[redacted] 126

Table 32: Probability of Observing a Toxicity for Various Safety Event Rates 137

Table 33: Sample Size Calculation for Each Cohort: Comparing With a Known Proportion 138

Table 34: Sample Size Calculation for Glioblastoma Cohort: Comparing With a Known Proportion 138

Table 35: Probability of Early Termination for Various Safety Event Rates 141

Table 36: Nivolumab Product Description 142

LIST OF FIGURES

Figure 1: Study Design for Combination Immunotherapy Cohorts (Phase 1 Part 1 and Phase 2).....68

Figure 2: Study Design for Combination Chemo-Immunotherapy Cohorts (Phase 1 Part 2 Only).....69

Printed on: , ; Printed by: .

LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Term	Explanation
5-FU	5-fluorouracil
ACTH	adrenocorticotropic hormone
[redacted]	[redacted]
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransferase
BCG	Bacillus Calmette–Guérin
BID	twice daily
BMS	Bristol-Myers Squibb
BOR	best overall response
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CA	cancer antigen
C_{ave}	time-averaged concentration
CD	cluster of differentiation
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
$C_{max,ss}$	steady-state peak concentration
$C_{min,ss}$	steady-state trough concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
CV%	coefficient of variation
DC	dendritic cell
DLBCL	diffuse large B-cell lymphoma
DLCO	diffusing capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
eCRF	electronic case report form
ECG	. lectrocardiogram

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Term	Explanation
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
eIB	epacadostat Investigator's Brochure
EOI	end of infusion
EOT	end-of-treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FEF	forced expiratory flow
FIGO	International Federation of Gynecology and Obstetrics
FL	follicular lymphoma
FLAIR	fluid-attenuated inversion recovery
FoxP3	forkhead box P3
FVC	forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HL	Hodgkin lymphoma
HPV	human papilloma virus
HR	hazard ratio
ICD	immunogenic cell death
ICF	informed consent form
ICH	International Conference on Harmonisation
IDO1	indoleamine 2,3-dioxygenase-1
IEC	independent ethics committee
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
IN	Investigator Notification
INR	international normalized ratio
I/O	immuno-oncology
irAE	immune-related adverse event
IRB	institutional review board
irRC	immune-related response criteria
ITT	intent to treat
IV	intravenously
LFT	liver function (chemistry) test
LH	luteinizing hormone

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Term	Explanation
MAOI	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MEL	. elanoma
MRI	magnetic resonance imaging
MSI	microsatellite instability testing
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
nIB	nivolumab Investigator's Brochure
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PEF	peak expiratory flow
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
PT-DC	platinum-based doublet chemotherapy
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
RANO	Response Assessment in Neuro-Oncology
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SNRI	serotonin/norepinephrine reuptake inhibitors
SS	serotonin syndrome
SSRI	serotonin reuptake inhibitors
TKI	tyrosine kinase inhibitor

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Term	Explanation
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USPI	United States Package Insert
VA	alveolar volume
VEGF	vascular endothelial growth factor
WHO	World Health Organization

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1. INTRODUCTION

The INCB 24360-204 study is a Phase 1/2 dose-escalation and cohort expansion study of the safety, tolerability, and efficacy of epacadostat administered in combination with nivolumab. Epacadostat (INCB024360) is a novel, potent, and selective inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1), and nivolumab is a fully human immunoglobulin (Ig) G4 antibody that blocks the programmed death receptor-1 (PD-1), that is, an anti–PD-1.

Targeting the immune system is a proven and effective approach for the treatment of cancer, and immunotherapy is now an accepted standard of care in several tumor types. The blocking of immune cell co-inhibitory receptors such as cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) by ipilimumab; PD-1 by pembrolizumab or nivolumab; and programmed cell death ligand-1 (PD-L1) by atezolizumab or avelumab provides a critical mechanism for redirecting the host immune response against the tumor (Chen and Mellman 2013). It is anticipated that the combination of the oral IDO1 inhibitor (epacadostat) with anti–PD-1 (nivolumab) or with nivolumab and cytotoxic agents (chemotherapy regimens) will demonstrate adequate safety and tolerability at pharmacologically-relevant doses so as to permit further clinical testing.

For a thorough discussion of the pharmacology of epacadostat and nivolumab, refer to the Investigator's Brochure (eIB) and the nivolumab Investigator's Brochure (nIB).

1.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Dimery and Hong 1993, Disis 2010). The inability of the immune system to control tumor growth does not appear to result from an inability to recognize the tumor as foreign. Tumor cells have been shown to evade immune destruction despite displaying recognizable antigens on their surface and despite the presence of high-avidity T cells that are specific for these antigens (Boon and van der Bruggen 1996, Ercolini et al 2005). Histologic evaluation of many human cancers show extensive infiltration by inflammatory and immune cells (Gadgeel et al 2016, Galon et al 2006), suggesting that the immune system responds less effectively to malignancy. These observations have led to the hypothesis that dominant mechanisms of immune tolerance or immune suppression are responsible for the immune system's inability to effectively respond in a way that consistently results in rejection.

There are a number of inhibitory mechanisms that have been identified to be involved in tumor-mediated immune suppression and include expression of the programmed death ligand-1 (PD-L1), which can engage the inhibitory receptor PD-1 on activated T cells; the presence of the tryptophan-catabolizing enzyme IDO1, which exploits the exquisite sensitivity of T cells to tryptophan depletion and tryptophan metabolites; and infiltration with $FoxP3^+$ regulatory T cells (Treg), which can mediate extrinsic suppression of effector T-cell function. Therefore, agents that target these negative regulatory pathways, and thereby allow the expansion of effector T cells present in the tumor, may be beneficial in the clinic.

1.1.1. Inhibition of PD-1 as a Target for Cancer

The PD-1 receptor-ligand interaction is a major pathway stimulated by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses,

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including autoimmune reactions. Programmed death receptor-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2; Talmadge et al 2007, Usubütün et al 1998). The mechanism by which PD-1 down-modulates T-cell responses is similar to but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins (Hiraoka 2010, Nobili et al 2008).

Programmed death receptor-1 has been shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, Tregs, and natural killer cells (Hodi and Dranoff 2010, Kloor 2009). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as on subsets of macrophages and dendritic cells (DCs; Hillen et al 2008). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumors (Lee et al 2008, Leffers et al 2009, Nishimura et al 2000, Hiraoka 2010). Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. Programmed death ligand-2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (Hiraoka 2010). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. Programmed death receptor-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL; Liotta et al 2010). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Nivolumab is a fully human Ig G4 antibody that blocks PD-1, blocks interaction with PD-L1 and PD-L2, and restores T-cell antitumor function (Brahmer et al 2010). Nivolumab has been approved as monotherapy in the United States for metastatic NSCLC that has progressed on or after platinum-based chemotherapy, for advanced RCC after previous antiangiogenic therapy, for classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin, for recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy, for locally advanced metastatic urothelial carcinoma with disease progression during or after platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, for microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer and for melanoma in both the adjuvant and advanced/metastatic setting (Opdivo 2018). Nivolumab is approved in the European Union as monotherapy or in combination with ipilimumab for advanced (unresectable or metastatic) melanoma, as monotherapy for locally advanced or metastatic NSCLC after prior chemotherapy, for advanced RCC after prior therapy, for recurrent or metastatic SCCHN, for metastatic urothelial carcinoma with disease progression during or after platinum-containing chemotherapy, and for Hodgkin lymphoma following autologous stem cell transplant and treatment with brentuximab vedotin (Opdivo SmPC 2018).

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1.1.2. Inhibition of Indoleamine 2,3-Dioxygenase as a Target for Cancer

Recent interest has focused on the role of IDO1 as a mechanism of induction of tolerance to malignancy (Godin-Ethier et al 2011). Indoleamine 2,3-dioxygenase is a heme-containing monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. Indoleamine 2,3-dioxygenase is the first rate-limiting enzyme in one of the breakdown pathways of tryptophan. In another pathway, tryptophan hydroxylase catalysis of tryptophan leads to the formation of serotonin and melatonin.

The expression and activity profiles of IDO1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in the liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in areas of contact with potential sources of immune challenge (eg, gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment (Mellor and Munn 2004). Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation (Munn and Mellor 2007).

IDO1-driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell–mediated responses by blocking T-cell activation and inducing T-cell apoptosis (Mellor et al 2003). Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects (Frumento et al 2002). IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg; Fallarino et al 2006). Since increased Treg activity has been shown to promote tumor growth, and Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur (Zou 2006), IDO1 expansion of Tregs may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

The biological relevance of IDO1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO1 pathway, 1-methyl-tryptophan, could break the tolerogenic state that protects allogeneic concepti from the maternal immune system (Munn et al 1998). A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer (Mellor and Munn 2004). While IDO1 inhibition can exacerbate disease in models of autoimmune disorders (Mellor and Munn 2004), IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development (Mellor et al 2003), suggesting that IDO1 inhibition in a therapeutic setting may produce minimal side effects in subjects without pre-existing autoimmune conditions.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors (Uyttenhove et al 2003, Muller et al 2005). In addition, studies with 1-methyl-tryptophan demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum

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compounds, taxane derivatives, and cyclophosphamide) without increased toxicity (Muller et al 2005). Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell–deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in subjects with cancer, and IDO1 activation correlates with more extensive disease (Huang et al 2010, Weinlich et al 2007). IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types, as well as by the DCs that localize to the tumor-draining lymph nodes (Uyttenhove et al 2003, Munn et al 2004). Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced overall survival (OS) in subjects with MEL and ovarian, colorectal, and pancreatic cancer (Okamoto et al 2005, Brandacher et al 2006, Ino et al 2006, Nakamura et al 2007, Witkiewicz et al 2008, Hamid et al 2009).

Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat advanced malignancies, either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

1.1.3. Combined Immune Checkpoint Inhibition

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Ipilimumab, a fully human IgG1 monoclonal antibody blocking CTLA-4, improved OS in patients with advanced MEL (Hodi et al 2010, Robert et al 2011). Nivolumab, a fully human IgG4 antibody blocking PD-1, produced durable objective responses in patients with MEL, RCC, and NSCLC (Topalian et al 2012, Hamid et al 2013, Wolchok et al 2013). Although these single agents have antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect (Quezada and Peggs 2013).

For example, CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone (Curran et al 2010, Selby et al 2013).

On the basis of these observations, a Phase 1 study was conducted to investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively) in subjects with advanced MEL. The objective response rate (ORR; according to modified WHO criteria) for all subjects in the concurrent regimen group was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease [SD] for ≥ 24 weeks) was observed in 65% of subjects.

In 17 subjects treated at the maximum doses associated with an acceptable level of adverse events (AEs), 53% had an objective response compared with ipilimumab monotherapy (10.9%), all with a tumor reduction of ≥ 80%. Grade 3 or 4 AEs related to therapy occurred in 53% of

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subjects in the concurrent regimen group but were qualitatively similar to previous experience with monotherapy and were generally reversible. Among subjects in the sequenced-regimen group, 18% had Grade 3 or 4 AEs related to therapy, and the ORR was 20%. Grade 3 or 4 AEs, regardless of attribution, were observed in 72% of subjects, and Grade 3 or 4 treatment-related AEs were noted in 53% of subjects. Serious AEs (SAEs) related to the treatment were reported in 49% of subjects in the concurrent regimen group. Common Grade 3 or 4 selected AEs that were related to therapy included hepatic events (15%), gastrointestinal events (9%), and renal events (6%). Isolated cases of pneumonitis and uveitis were observed. In both regimen groups, treatment-related AEs were manageable and generally reversible with the use of immunosuppressants (or hormone-replacement therapy for endocrinopathies) according to previously-established algorithms (Yervoy 2012).

As described above, IDO1 is another negative regulatory mechanism that contributes to tumor-derived immune suppression. In preclinical models, IDO1 inhibition has been shown to synergize with blockade of either anti–CTLA-4 or anti–PD-1/PD-L1 in delaying tumor growth and increasing OS (Holmgaard et al 2013, Spranger et al 2013). This effect was shown to be T-cell dependent, leading to enhanced T-cell proliferation and interleukin-2 production within the tumor and to a marked increase in the effector-to-regulatory T-cell ratios in the tumor.

In 119 diffuse large B-cell lymphoma (DLBCL) patients treated with first-line (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy, IDO expression on lymphoma cells and DCs was associated with both a decrease in complete remission and a decrease in OS rate (Ninomiya et al 2011). In a survey of 57 newly diagnosed non-Hodgkin lymphoma (NHL) patients with diverse histologies including DLBCL, mantle cell lymphoma, and follicular lymphoma (FL), expression of IDO, mRNA, and protein were higher in the NHL tissues than in reactive lymph node tissues, and upregulation of IDO1 was correlated with advanced clinical stage, larger tumors, and poor prognosis (Liu et al 2014), suggesting a fundamental contribution of the local crosstalk between malignant lymphocytes and their microenvironment to lymphomagenesis. In a Phase 1 study of subjects with relapsed FL treated with the combination of the PD-1 inhibitor pidilizumab and rituximab, of 29 evaluable subjects, 19 achieved ORs for an ORR of 66%, 15 (52%) had CRs, and 4 (14%) had partial responses (PRs), and the median progression-free survival (PFS) was 21.1 months (Westin et al 2012). A recent study suggests that PD-1 blockade in high risk DLBCL subjects after autologous stem cell transplantation resulted in a longer than expected PFS as well as increases in circulating activated lymphocytes, suggesting an on-target effect (Armand et al 2013). These promising data suggest a strong foundation for immunomodulatory combinations.

In an ongoing, Phase 1, open-label, dose-escalation study of epacadostat with ipilimumab (3 mg/kg intravenously [IV]), daily doses of epacadostat have been evaluated in 21-day cycles in 3 cohorts thus far (300 mg, 100 mg, and 25 mg twice daily [BID]). Seven subjects were enrolled at 300 mg BID. When 5 subjects developed clinically significant alanine aminotransferase (ALT) elevations after 30 to 76 days on treatment, enrollment was stopped. The ALT elevations were reversible with corticosteroids and treatment discontinuation. Six of 7 subjects had evaluable scans either before discontinuation or within a few weeks of discontinuation of one or both agents, and all showed immune-related SD. Enrollment was restarted at 25 mg BID (n = 8), where 1 subject with progression of prior extensive liver metastases had a dose-limiting toxicity (DLT; Grade 3 aspartate aminotransferase [AST] elevation). Immune-related AEs (irAEs) were

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generally Grade 1/2 and manageable with continued administration or temporary dose interruption; 1 subject each discontinued for Grade 3 colitis and Grade 3 salivary amylase elevation. Six of 8 subjects had tumor reduction by the first evaluation. Confirmed disease control rate was 75% (6/8 subjects). Three subjects had confirmed immune-related PR (2 occurred by the first or second scan). A 50 mg BID cohort is enrolling and to date has 1 PR and 1 complete response (CR). Epacadostat 25 mg BID with ipilimumab was generally well-tolerated, and irAEs previously observed with ipilimumab were reversible with appropriate management. Tumor response and duration data suggest the potential for enhanced MEL patient outcomes compared with ipilimumab monotherapy.

Programmed death ligand-1 has been shown to be expressed in the tumor microenvironment of SCCHN. Programmed death ligand-1 staining by IHC is seen in both human papilloma virus (HPV)-positive tumors and HPV-negative tumors, although HPV positivity does appear to correlate with a higher probability of PD-L1 expression in the tumor microenvironment (Lyford-Pike et al 2013). In early clinical studies, a subject with metastatic SCCHN was treated with the anti–PD-L1 monoclonal antibody MDPL3280A and experienced a response by the second cycle of treatment (Herbst et al 2013). Additional studies of anti–PD-1 and anti–PD-L1 agents in the setting of metastatic SCCHN are ongoing.

In summary, both IDO1 and PD-1 have been shown to suppress T-cell–mediated antitumor immunity, and IDO1 and the PD-1 ligand PD-L1 have been shown to be co-expressed in multiple cancer types and to correlate with poor prognosis. Combined inhibition of both pathways may therefore lead to greater suppression of antitumor immunity and to increased efficacy. Preclinical and clinical data indicate that these pathways are important in MEL as well as in other cancers.

1.1.4. Rationale for Studying Immunotherapy in Advanced or Metastatic Cancers

Cancer immunotherapies have demonstrated promising data in the NSCLC patient population. In 38 subjects with previously treated advanced NSCLC administered 10 mg/kg nivolumab every 2 weeks, an ORR of 24% as measured by the immune response criteria (irRC; Wolchok et al 2009) was observed, with similar results using RECIST v1.1 criteria (21%). Most responses were observed by the first planned assessment at Week 9. Median duration of response (DOR) by irRC has not been reached with a median duration of follow-up of 9 months (minimum, 6 months). Pretreatment tumor PD-L1 expression was a statistically significant predictor of response. In subjects with evaluable tumor PD-L1 expression, the majority of confirmed responses by RECIST v1.1 criteria (and irRC) occurred in subjects with tumors strongly positive for PD-L1. The most common AEs were fatigue, rash, and pruritus (16% each). The incidence of diarrhea was 13% (only Grade 1 or 2 reported). Only 1 drug-related Grade 3 or 4 AE (Grade 3 pulmonary edema; 3%) was seen (Garon et al 2013).

In a Phase 1 study of nivolumab, 42% and 24% of heavily pretreated subjects with NSCLC were alive at 1 and 2 years, respectively, based on Kaplan-Meier estimates, and median survival was 9.9 months. In all treated subjects, the ORR was 17% as measured by RECIST v1.1 criteria. Drug-related select AEs with potential immunologic etiologies, defined as AEs that require more frequent monitoring and/or specific interventions, included rash, diarrhea, and pruritus (Brahmer et al 2013). In addition to PD-1 inhibition, drugs targeting PD-L1 have also shown promising data. Atezolizumab, a humanized monoclonal antibody that blocks PD-L1 from

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binding to its receptors, including PD-1 and B7.1, has shown similar efficacy. In a Phase 1 study that included subjects with both squamous and nonsquamous NSCLC, ORR was 24% (9/37 subjects), and at the time of the abstract, all responses were ongoing and improving. The 24-week PFS was 46%. Analysis of biomarker data from archival tumor samples demonstrated a correlation between PD-L1 status and efficacy. Subjects with PD-L1–positive tumors showed an ORR of 100% (4/4), while subjects who were PD-L1 tumor status–negative had an ORR of 15% (4/26). The response rate in former or current smokers was 25% of subjects (8/37) versus 16% of subjects (1/6) who were never smokers. The incidence of Grade 3/4 AEs, regardless of attribution, was 34%, including pericardial effusion (6%), dehydration (4%), dyspnea (4%), and fatigue (4%). No Grade 3 to Grade 5 pneumonitis or diarrhea was reported (Soria et al 2013). Targeting the IDO1 enzyme has been studied in subjects with metastatic NSCLC as well in the form of vaccination with an epitope derived from IDO1. In the Phase 1 study, no severe toxicities occurred. One of 15 HLA-A2–positive subjects treated developed a PR after 1 year of vaccine treatment, and SD of ≥ 8.5 months was reported in another 6 subjects. The median survival was 25.9 months, and long-lasting PR and SD were seen in 47% of the subjects. Expression of IDO1 was detected in 9 of 10 tumor biopsy specimens by immunohistochemistry (Iversen et al 2014).

Given the recent benefits in OS achieved with immunotherapeutics in MEL and prostate cancer, researchers have posited that immunotherapy approaches may offer promise in other difficult-to-treat cancers such as glioblastoma (Heimberger and Sampson 2011). Immunologic factors have clinically been associated with glioblastomas: a reduced risk of malignant gliomas and longer survival is observed in patients with elevated IgE levels compared with those with normal levels (Schwartzbaum et al 2012, Turner 2012, Lin et al 2011, Schlehofer et al 2011). In addition, immune checkpoint receptors such as PD-L1/B7-H1/CD274, a transmembrane receptor ligand and negative regulator of T-cell signaling, have been reported to be upregulated in glioblastoma (Parsa et al 2007, Jacobs et al 2009, Berghoff et al 2014). Studies have also suggested an association between malignancy grade of astrocytic tumors and tumor cell PD-L1 expression (Wilmotte et al 2005, Yao et al 2009).

Currently for glioblastoma, bevacizumab is approved as single agent for patients with progressive disease (PD) following prior therapy. This approval was based on demonstration of durable ORRs observed in 2 single-arm studies (AVF3708g and NCI 06-C-0064E; Avastin 2014). The ORR was 25.9% in Study AVF3708g, with a median DOR of 4.2 months, and was 19.6% in Study NIC 06-C-0064E, with a median DOR of 3.9 months. Another multicenter, randomized, noncomparative Phase 2 study evaluating bevacizumab alone or in combination with irinotecan in recurrent glioblastoma reported 6-month PFS rates of 42.6% and 50.3%, respectively and median OS rates of 9.2 months and 8.7 months, respectively (Friedman et al 2009).

Although the efficacy of checkpoint inhibitors such as nivolumab and ipilimumab have not previously been studied in glioblastoma, a multicenter Phase 2 study to evaluate the response of brain tumor metastases to ipilimumab was previously performed (CA184-042; Margolin et al 2012). Subjects (N = 71) with advanced Stage IV MEL and measurable active brain metastases were randomized to ipilimumab monotherapy. The study demonstrated that ipilimumab had clinical activity in subjects with MEL brain metastases, with some subjects showing prolonged clinical responses, disease control, and prolonged survival. Ipilimumab did

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not cause unexpected neurological toxicity in subjects with brain metastases. The DOR observed in the corticosteroid-free arm (Arm A; median of 10.4 months both by mWHO and irRC) was consistent with that observed in other ipilimumab studies and longer than that observed for other therapies commonly used to treat brain metastases in patients with MEL metastatic to the brain: temozolomide (median DOR = 2 months). The OS rates observed in Arm A of this study (26% at Year 2) are consistent with survival data observed in other ipilimumab monotherapy (10 mg/kg) studies and appear favorable to the survival recorded in historical studies, where 2-year survival is approximately 10% (Parsa et al 2007).

1.1.5. Overview of 5-Fluorouracil and Cisplatin in Squamous Cell Carcinoma of Head and Neck

Cisplatin-based combination therapy has become one of the major cornerstones for treatment of subjects with recurrent/metastatic SCCHN with approximately 35% response rates (Jacobs et al 1992). Responses are often short lasting, and recurrent disease is often resistant to second-line chemotherapy (Dimery and Hong 1993). Further investigation led to combination therapies with other cytotoxic agents (Gibson et al 2005, Bourhis et al 2006, Vermorken et al 2008). 5-FU, cisplatin, and cetuximab have become the standard of care for treatment of recurrent and/or metastatic head and neck cancer due to higher response rate being achieved in chemotherapy combination regimen compared to single agents (Sacco and Cohen 2015).

Despite the recent advances in treatment of SCCHN patients, OS in advanced and recurrent SCCHN requires further investigations with new combination therapies for an improved outcome. In 2016, the approval of nivolumab by the FDA for the treatment of subjects with recurrent or metastatic SCCHN has changed the therapeutic landscape in the investigation of treatment options for SCCHN subjects by introducing new alternatives with the addition of immune checkpoint inhibitors. Chemotherapy and checkpoint inhibitor combinations may be crucial for the broadest applications to achieve improved patient outcomes.

1.1.6. Overview of Platinum-Based Doublet Chemotherapy Compared With Immunotherapy in Squamous and Nonsquamous Non–Small Cell Lung Cancer

Platinum-based doublet chemotherapy (PT-DC), such as paclitaxel and pemetrexed, has become the standard of care first-line therapy for NSCLC patients (without sensitizing epidermal growth factor receptor [EGFR] mutations or anaplastic lymphoma kinase [ALK] translocation) with squamous and nonsquamous histologies, respectively (NCCN 2016, Novello et al 2016). However, most patients survive less than a year, and there are limited treatment options for squamous NSCLC (NCCN 2016).

Randomized studies comparing various PT-DC regimens in NSCLC have shown similar efficacy results, with ORRs ranging from 15% to 32%, median PFS ranging from 4.0 to 5.1 months, and median OS ranging from 8.1 to 10.3 months. One- and 2-year OS rates ranged from 30% to 44% and 10% to 19%, respectively (Kelly et al 2001, Sandler et al 2006, Scagliotti et al 2002, Scagliotti et al 2008, Schiller et al 2002). Bevacizumab and maintenance therapy with pemetrexed have improved clinical outcomes (Barlesi et al 2014, Scagliotti et al 2014, Patel et al 2013), but most subjects will eventually progress (Chang 2011).

A recent multicenter Phase 1 study has been conducted to explore the safety and efficacy of nivolumab as monotherapy or combined with current standard-of-care treatment PT-DC in

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first-line advanced NSCLC. Preliminary data from this study show that confirmed ORRs with nivolumab plus PT-DC ranged from 33% to 47% across arms, which compare favorably with previously reported rates of 15% to 32% for PT-DC alone (Rizvi et al 2016). Median OS was longer than expected in subjects on PT-DC alone (8.1-10.3 months). OS for nivolumab 5 mg/kg administered in combination with paclitaxel and carboplatin was particularly notable; median OS was not reached at the time of the reporting period (8.8-30.1 months), and 57% of subjects were still alive after a median follow-up time of more than 2 years. Although sample sizes were small, 1-year OS rates (50% to 87%) seemed similar to those seen with nivolumab monotherapy (73%) in NCT01454102 (CHECKMATE-012; Gettinger et al 2016). Overall, the safety profile of the combination arm was similar to the PT-DC monotherapy arm. Most treatment-related AEs reported during combination cycles were those associated with PT-DC and managed by chemotherapy dose delays and reductions, rather than discontinuation.

Activity of PD-1 monotherapy over a platinum-based chemotherapy regimen in subjects with previously untreated advanced NSCLC with PD-L1+ (expression ≥ 50% on tumor cells) was demonstrated in an open-label Phase 3 study (Reck et al 2016). The pembrolizumab monotherapy group showed a significantly longer median PFS of 10.3 months compared with 6.0 months with chemotherapy group hazard ratio (HR = 0.50; 95% confidence interval [CI], 0.37 to 0.68; $p < 0.001$). OS at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (HR for death = 0.60; 95% CI, 0.41 to 0.89; $p = 0.005$). The ORR was greater in subjects treated with PD-1 inhibitor versus investigator-choice chemotherapy (45% vs 28%). Treatment-related AEs of any grade were less frequent (occurring in 73.4% vs 90.0% of subjects), as were ≤ Grade 3 treatment-related AEs (26.6% vs 53.3%). Collectively, these results may provide the basis for PD-1 monotherapy to become more effective than chemotherapy in the first-line setting for advanced NSCLC without any overlapping toxicity profile.

Another Phase 2 study investigated the efficacy of the combination of pembrolizumab and pemetrexed/carboplatin versus pemtrexed/carboplatin alone in subjects with advanced nonsquamous NSCLC in the first-line setting. With a median follow-up of 19 months, the chemo-immunotherapy combination showed a significant improvement in ORR of 57% versus 32% and median PFS of 19.0 months versus 8.9 months (Borghaei et al 2017). This combination received accelerated approval from the FDA in May 2017.

Collectively, all these data show that the immunogenic effects of conventional chemotherapy and rapid emergence of chemotherapy resistance may present as a good rationale to combine chemotherapy doublets with immunotherapy, particularly checkpoint inhibitors (Schvartsman et al 2016, Rizvi et al 2016). Combining immune checkpoint inhibitors with platinum-based doublets may also provide a rapid and large initial response through the action of the cytotoxic chemotherapy, thus releasing tumor antigens in the tumor microenvironment to be recognized by the immune system. This may later be durable and trigger a response with checkpoint inhibition.

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1.2. Study Rationale

1.2.1. Rationale for Combining PD-1 Inhibitor and IDO1 Inhibitor [redacted]

The goal of cancer immunotherapy is to initiate or reinitiate a self-sustaining cycle of cancer immunity, enabling it to amplify and propagate. Cancer immunotherapies must overcome the negative feedback mechanisms inherent in most cancers. The current approach will attempt to further amplify an immune response by targeting multiple nonredundant immune checkpoints. Expression of IDO1 represents an early checkpoint that results in a diminished immune response and tolerance to tumor antigen.

Another common rate-limiting step is the expression of PD-L1 as a distal immune modulator expressed in 20% to 50% of human cancers (Hiraoka 2010, Herbst et al 2013), including, but not limited to, the ones selected for investigation in this study: advanced or metastatic NSCLC, MEL, ovarian cancer, colorectal cancer (CRC), SCCHN, and DLBCL. Expression of IDO and PD-1/L1 have been found to be increased in NSCLC as the disease progresses, and expression of these markers in tumor cells has been associated with shorter subject survival (Iversen et al 2014). Anti–PD-1 monotherapy response rates of 17% to 24% have been reported in refractory NSCLC (Garon et al 2013, Brahmer et al 2013) with survival medians of 8 to 18 months.

There is an urgent need for novel treatment interventions to improve clinical response for patients suffering from glioblastoma. Use of an inhibitor of PD-L1 in mouse glioblastoma models suggests benefit when given in combination with radiation therapy (Zeng et al 2013). In similar studies using an orthotopic, immunocompetent murine glioblastoma model, Reardon et al (2014) recently demonstrated that anti–PD-1 therapy eradicated established tumors in approximately 50% of treated animals. Long-term survivors did not grow tumors upon intracranial rechallenge, suggesting the generation of tumor-specific immune memory responses (Reardon et al 2014). Furthermore, in recent studies combining an IDO1 inhibitor with anti–PD-1 therapy increased the long-term survival rate to approximately 75% of treated animals (Wainwright et al 2014, Reardon et al 2016).

Although many studies have evaluated the efficacy of anti–PD-1, anti–PD-L1, and anti–CTLA-4 as first-line treatments for metastatic MEL (Redman et al 2016), the available data are limited for the efficacy of a combination of checkpoint inhibitors as the second-line treatment following anti–PD-1 or anti–PD-L1 monotherapy. There is currently no effective therapy for metastatic MEL that is relapsed or refractory after anti–PD-1/PD-L1 treatment; thus it remains as a substantial unmet medical need for advanced or metastatic MEL. Early data from a Phase 2 study of nivolumab (anti–PD-1) versus chemotherapy (CHECKMATE-037) in subjects with advanced MEL who progressed after anti–CTLA-4 therapy showed activity with an improved ORR in subjects who were administered nivolumab compared with subjects who were administered chemotherapy (Weber et al 2015). Additionally, a Phase 1/2 study of pembrolizumab (anti–PD-1) versus investigator-choice chemotherapy for ipilimumab-refractory MEL (KEYNOTE-002) also demonstrated clinical activity with improved ORR, PFS, and OS in subjects who progressed after anti–CTLA-4 therapy and were administered pembrolizumab, compared with subjects who were administered chemotherapy (Ribas et al 2015) . Most

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recently, a Phase 1/2 study of pembrolizumab with epacadostat (KEYNOTE-037) also showed an improved ORR and disease control rate in advanced MEL (Gangadhar et al 2016). These data support promising activity of epacadostat in combination with an anti–PD-1 inhibitor in subjects with advanced MEL and likely activity of the combination immunotherapy in subjects who progressed after previous PD-1/PD-L1 therapy.

In APR 2018, an eDMC review of ECHO-301/KEYNOTE-252 study, a Phase 3 study evaluating the anti–PD-1 antibody pembrolizumab in combination with epacadostat versus pembrolizumab with placebo as first-line treatment in subjects with unresectable or metastatic melanoma, concluded that the coprimary endpoint of improvement in PFS was not met (HR = 1.00; 95% CI: 0.83, 1.21) and that the coprimary endpoint of improvement in OS was also not expected to reach statistical significance (HR = 1.13; 95% CI: 0.86, 1.49). Based on these results, and on the recommendation of the eDMC, the study was stopped. The safety profile observed in the ECHO-301/KEYNOTE-252 study was consistent with that observed in previously reported studies of epacadostat in combination with pembrolizumab. The purpose of this study is to test the combination of different mechanisms for overcoming tumor tolerance. Targeting PD-1 pathway assumes that the T cells are essentially exhausted (and thus tolerant of the tumor) and that this exhaustion may be reversed by blocking PD-1 signaling. Targeting IDO1 pathway will concurrently decrease infiltration of regulatory CD4+ cells and immune-suppressive cytokines. [redacted]

1.2.2. Rationale for Combining PD-1 Inhibitor and IDO1 Inhibitor With Chemotherapy [redacted]

While chemotherapy has largely been thought to be immunosuppressive and exert its effect via direct cytotoxicity, there is an emerging body of evidence to suggest that some chemotherapies may influence an immune response to tumors via induction of immunogenic cell death (ICD), elimination of immunosuppressive cells, or sensitization of tumor cells to immune effector cells (Apetoh et al 2015). Platinum agents have demonstrated immunogenic effects via ICD and enhancement of effector immune response through PD-L1 receptor expression (Hato et al 2014). Paclitaxel and 5-FU have been shown to restore antitumor activity of CD8+ T cells (Sevko et al 2013, Vincent et al 2010). Given these findings, the combination of chemotherapy with immunotherapy is a rational choice, especially in patients for whom these chemotherapies are the accepted standard of care. Initial treatment options for patients with recurrent or metastatic solid tumors include various chemotherapy agents (platinum agent [cisplatin or carboplatin], 5-FU, or taxanes), either alone or in combination, and the biologic agent cetuximab (NCCN 2016). In patients with non-nasopharyngeal SCCHN, the addition of cetuximab to a platinum agent [cisplatin or carboplatin] and 5-FU (EXTREME regimen) prolonged median OS from 7.4 to 10.1 months (hazard ratio [HR] = 0.80; $p = 0.04$) and median PFS from 3.3 to 5.6 months (HR = 0.54; $p < 0.001$) compared with a platinum agent−5-FU doublet. Additionally, ORR increased from 20% with platinum/5-FU to 36% with the EXTREME regimen ($p < 0.001$; Vermorken et al 2008). Based on these results, the EXTREME regimen has become the standard

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of care for subjects with non-nasopharyngeal SCCHN in the recurrent and metastatic setting (NCCN 2016).

While AEs of ≥ Grade 3 were comparable between the treatment groups (EXTREME: 82%; platinum/5-FU: 76%), the most common AEs observed with EXTREME (anemia, neutropenia, thrombocytopenia) and cetuximab-specific AEs (Grade 3 skin toxicities, Grade 3/4 infusion-related reactions) limit the use of this regimen to younger patients with good performance status. In those who are eligible to receive this regimen, many will stop therapy prematurely due to toxicity, as demonstrated by a 20% discontinuation rate due to AEs in the pivotal Phase 3 study (Vermorken et al 2008). Common comorbidities in patients with SCCHN such as diminished hepatic, cardiac, and pulmonary function from previous alcohol and tobacco use and poor nutritional status from the clinical manifestations of the cancer and/or previous radiation can further limit the use of EXTREME. Second-line treatment regimens are limited and primarily palliative, resulting in very poor long-term survival rates for this patient population. There remains a substantial unmet need for well-tolerated therapies that offer sustained responses and prolonged survival compared with EXTREME in the first-line setting for recurrent or metastatic SCCHN.

PD-1 and PD-L1 blocking agents have currently been investigated in several clinical trials in subjects with recurrent/metastatic SCCHN. A Phase 1b study with anti–PD-1 in recurrent and metastatic SCCHN (KEYNOTE-012) showed 18% (34 out of 192 subjects) best ORR regardless of HPV status (25% HPV[+] and 14% HPV[-]). Duration of response was approximately 12 months. In a recent Phase 2 study (KEYNOTE-055) evaluating anti–PD-1 antitumor activity after platinum and cetuximab failure in SCCHN showed 16% (95% CI, 11%-23%) ORR (Bauml et al 2017). The preliminary efficacy and safety results were consistent with KEYNOTE-012, and anti–PD-1 was well-tolerated among heavily pretreated recurrent or metastatic SCCHN subjects. A preliminary analysis from Phase 3 (CHECKMATE-141) study to evaluate anti–PD-1 activity against single-agent chemotherapy of the investigator's choice (docetaxel, methotrexate, or cetuximab) in recurrent or metastatic SCCHN subjects also demonstrated a significant OS benefit with anti–PD-1 treatment (with an increase from 16% to 36% in 1-year OS) (Ferris et al 2016).

PD-1/PD-L1 blockade is being investigated in combination with chemotherapeutic agents in various tumor types. In a Phase 1 study (n = 56), nivolumab in combination with PT-DC in chemotherapy-naive NSCLC showed ORR ranging from 33% to 50% and PFS ranging from 4.8 to 6.1 months, and ≥ Grade 3 treatment-related AEs were observed in 45% of subjects (Rizvi et al 2016). More promising efficacy signals have been observed in the KEYNOTE-021 study of pembrolizumab in combination with PT-DC from open-label cohorts (n = 74, ORR 48%-71%, PFS ~10 months, ≥ Grade 3 treatment-related AEs 56%-71%; Gadgeel et al 2016) and a randomized cohort of pembrolizumab/PT-DC versus PT-DC (n = 123, ORR 55% vs 29%, respectively, PFS 13 vs 8.9 months, respectively, ≥ Grade 3 treatment-related AEs 39% vs 26%, respectively; Langer et al 2016) as well as a Phase 1 study of atezolizumab (n = 58 safety evaluable, n = 41 efficacy evaluable, ORR 50%-77%, PFS immature at time of analysis; Giaccone et al 2015). Confirmatory Phase 3 clinical studies in advanced/metastatic NSCLC are ongoing for these 3 therapies.

The IDO pathway inhibitor indoximod has been evaluated in combination with chemotherapy in clinical studies. In a Phase 1 study (n = 27), indoximod in combination with docetaxel in

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pretreated subjects with metastatic solid tumors was well-tolerated with no unexpected toxicities and had a modest ORR of 18% (Soliman et al 2014). Based on encouraging activity observed in subjects with breast cancer from this study, a Phase 2 study of indoximod in combination with docetaxel or paclitaxel was initiated. Preliminary safety data showed AEs were similar to those typically seen with taxanes, and no unexpected AEs were observed (Tang et al 2015). Indoximod in combination with gemcitabine and nab-paclitaxel in subjects with metastatic pancreatic cancer was also well-tolerated in a Phase 1/2 study, and preliminary efficacy results showed durable responses in 42% of subjects (Bahary et al 2016).

Overall, the data suggest that combining the IDO1 inhibitor epacadostat, a PD-1 inhibitor, and chemotherapy may result in a further increase of immunomodulatory effects in the tumor microenvironment and ultimately improve the overall clinical benefit in patients with advanced or metastatic solid tumors without overlapping toxicity profiles.

1.2.3. Preclinical and Clinical Study Data for Epacadostat and Nivolumab

Refer to the eIB and the nIB.

1.3. Potential Risks and Benefits of the Treatment Regimen

[redacted]

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[redacted]

1.3.2. Risks From Nivolumab

Potential safety concerns and recommended management guidelines regarding pulmonary toxicities, GI toxicities, hepatotoxicity, endocrinopathies, dermatologic toxicities, and other toxicities of concern are summarized in the nIB, and details regarding immune-related toxicities can be found in Section 5.7.3, Table 9, and Appendix C.

1.3.3. Risks for the Combination of Epacadostat and Nivolumab

The combination of epacadostat and nivolumab has the potential to precipitate more frequent, more severe, and/or new immune-related toxicities as compared with each individually.

1.3.4. Risks From 5-Fluorouracil/Platinum (Cisplatin or Carboplatin)

The most common adverse reactions (occurring in greater than 30%) with 5-FU are diarrhea, nausea with occasional vomiting, mucositis, loss of appetite, photophobia, dysgeusia, phlebitis, and low blood cell counts. Nephrotoxicity is dose dependent and is the DLT of cisplatin. Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin. Myelosuppression occurs in 25% to 30% of patients treated with cisplatin, with leukopenia and thrombocytopenia more pronounced at higher doses (> 50mg/m^2). Elderly patients may be more susceptible to myelosuppression. When 5-FU is used in combination with cisplatin, hematological AEs were observed more often (> 40%) and mainly consisted of granulocytopenia, anemia, thrombocytopenia, and infection. Nausea and vomiting rates were similar in frequency (18% and 11%, respectively). Stomatitis was also common (> 25%) in the patients taking the combination regimen. Neurological toxicities were similar to single-agent regimens (< 5%; Gibson et al 2005).

In a retrospective clinical study conducted to determine and to compare the efficacy of palliative chemotherapy with carboplatin plus 5-FU versus cisplatin plus 5-FU for subjects with recurrent and metastatic SCCHN, no Grade 3/4 adverse reactions were reported in subjects who received cisplatin in combination with 5-FU. Grade 3/4 hematologic toxicities were more common with the carboplatin plus 5-FU group (granulocytopenia [41.6%], anemia [37.5%], and thrombocytopenia [16.6%]). Nausea, vomiting, and diarrhea were the most frequent events reported. Nonhematological toxicities were more pronounced in the cisplatin plus 5-FU group. The most common Grade 1/2 adverse reactions were nausea (94.1%) and vomiting (82.4%) in the cisplatin plus 5-FU group. Grade 1 peripheral neuropathy and ototoxicity were more likely to develop in subjects who used carboplatin plus 5-FU (16.7% and 12.5 %, respectively) compared with those who used cisplatin plus 5-FU (11.8% and 0%, respectively; Kua et al 2013).

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Renal toxicities are more likely to develop in subjects treated with cisplatin plus 5-FU and are least common in subjects treated with carboplatin plus 5-FU (Forastiere et al 1992). Also, in rare cases, fatal reactions may develop with either cisplatin or carboplatin and 5-FU combination regimens.

1.3.5. Risks From Paclitaxel/Carboplatin

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the DLT of carboplatin. Anaphylactic reactions to carboplatin may occur within minutes of administration. Carboplatin can induce emesis, which can be more severe in patients who have previously received emetogenic therapy. Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the DLT of paclitaxel. Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of subjects receiving paclitaxel in clinical trials. Fatal reactions have occurred in subjects despite premedication.

1.3.6. Risks From Paclitaxel/Cisplatin

In a randomized Phase 3 study conducted to determine the response rate, survival, and toxicity of cisplatin and fluorouracil (CF) versus cisplatin and paclitaxel (CP) in subjects with advanced SCCHN, the most common Grade 3/4 adverse reactions were hematologic events, which were more common in the CF group than in the CP group (leukopenia, 63% vs 35%; granulocytopenia, 67% vs 55%; thrombocytopenia, 23% vs 4%, respectively). Infection rate (≥ Grade 3) was 21% in the CF group versus 13% in the CP group. Grade 3/4 anemia and thrombocytopenia occurred in 33% and 23% of subjects in the CF group, respectively, versus in 13% and 4% of subjects in the CP group, respectively. Nausea and vomiting rates were similar in frequency (19% and 18%, respectively, in the CF group; 18% and 10%, respectively, in the CP group). Grade 3/4 stomatitis was more frequent in the group that received infusional fluorouracil (31% in the CF group; 0% in the CP group). Neurotoxicity and metabolic events were equivalent between groups. The Kruskal-Wallis test for comparing the distribution of worst degree (≤ Grade 3) toxicities between 2 treatment groups indicated no significant difference between the groups treated with CF and CP (Gibson et al 2005).

1.3.7. Risks From Pemetrexed/Carboplatin

The most common events (incidence ≥ 20% with single-agent use) with pemetrexed are fatigue, nausea, and anorexia. When pemetrexed is used in combination with a platinum agent, common AEs include the following: vomiting (40%), nausea (56%), neutropenia (29%), leukopenia (18%), anemia (33%), stomatitis/pharyngitis (14%), thrombocytopenia (10%), and constipation (21%). Refer to the US prescribing information (Alimta 2013) or the EU SmPC (Alimta 2016) for pemetrexed for full details.

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1.3.8. Risks From Pemetrexed/Cisplatin

Use of pemetrexed and cisplatin in combination has been approved by the FDA for patients with nonsquamous NSCLC as first-line therapy. The most common AEs (incidence ≥ 20%) during pemetrexed monotherapy were fatigue, nausea, and anorexia. The most common AEs (incidence ≥ 20%) when pemetrexed was administered in combination with cisplatin include vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation (Alimta 2013).

1.3.9. Risks From Combining an IDO Inhibitor With Chemotherapy

In a Phase I study of the IDO pathway inhibitor indoximod with docetaxel in advanced solid tumors, the most frequent AEs were fatigue (58.6%), anemia (51.7%), hyperglycemia, (48.3%), infection (44.8%), and nausea (41.4%; Soliman et al 2014). In a Phase 2 study of indoximod with docetaxel in subjects with metastatic breast cancer, the most common indoximod-related AEs of any grade occurring in ≥ 10% of subjects were fatigue (21%), nausea (20%), diarrhea (13%), and headache (12%). Twenty-eight percent of subjects treated with indoximod and docetaxel experienced at least 1 Grade 3 or 4 AE. The safety profile of indoximod with docetaxel was compatible with the safety profile of taxane monotherapy (Tang et al 2015).

Recently presented safety data from a Phase 1/2 study evaluating the combination of indoximod with gemcitabine/nab-paclitaxel in subjects with metastatic pancreatic cancer showed that the most frequently reported any grade AEs (regardless of attribution) occurring in ≥ 10% of subjects were fatigue (40%); weight loss, diarrhea, peripheral edema, and asthenia (20% each); and anemia, decreased appetite, nausea, myalgia, rash, decreased neutrophil count, and decreased platelet count (13.3% each; Bahary et al 2016).

1.3.10. Risks From Combining a PD-1 Inhibitor With Chemotherapy

In an investigator-initiated Phase 1 study of subjects with metastatic CRC, common AEs when pembrolizumab was combined with mFOLFOX6 were neutropenia (40%) and hyponatremia (30%; Stenehjem et al 2016). The most common AE in 11 subjects with metastatic pancreatic cancer treated with gemcitabine/nab-paclitaxel plus nivolumab was anemia (33%; George et al 2016).

Recently updated safety data from a randomized cohort of the KEYNOTE-021 study where subjects with nonsquamous NSCLC were treated with carboplatin/pemetrexed with pembrolizumab showed the most common ≥ Grade 3 treatment-related AEs were anemia (12%), decreased neutrophil count (7%), and fatigue (3%; Papadimitrakopoulou et al 2017). Overall, treatment-related AEs ≥ Grade 3 occurred in 39% subjects treated with the PD-1/chemotherapy combination versus 29% with chemotherapy alone.

1.4. Justification for Treatment Regimens

The goal of the present study is to explore doses of the IDO1 inhibitor epacadostat that may synergize or otherwise augment the efficacy observed with the PD-1 inhibitor nivolumab in subjects with advanced cancer. In Phase 1 of the study for combination immunotherapy (epacadostat + nivolumab), the established regimen of nivolumab (3 mg/kg every 2 weeks) will be combined with doses of epacadostat that provide partial and more complete IDO1 inhibition based on observations from the Phase 1 study INCB 24360-101. The starting dose selected for

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epacadostat in combination with nivolumab is 25 mg BID with escalation up to 300 mg BID. This is based on the preliminary observation that the average kynurenine inhibition for epacadostat 25 mg BID and 100 mg BID is 66% and 89%, respectively, and on the safety of these doses, as well as doses up to 700 mg BID in the Phase 1 study INCB 24360-201 as monotherapy and in combination with ipilimumab. Pharmacokinetic (PK) and pharmacodynamic (PD) observations from Studies INCB 24360-101 and INCB 24360-201 in cancer subjects support these doses, which provide a differential pharmacologic effect. Based on a 6-hour observation period at steady state on Day 15 after administration of epacadostat, kynurenine levels are incompletely inhibited (66%) compared with baseline levels in subjects treated with 25 mg BID but are nearly maximally inhibited (89%) in subjects treated with 100 mg BID.

Doses of epacadostat ≥ 300 mg BID are associated with > 94% average inhibition of kynurenine, and based on this small difference in the average kynurenine inhibition, a final escalation of epacadostat to 300 mg BID may be evaluated. Target coverage at 25 mg BID is consistent with the level needed to achieve maximal efficacy as well as to demonstrate synergy with an anti–PD-1 in preclinical models.

In general, as single agents, epacadostat and ipilimumab have been well-tolerated in the subjects who had significant comorbidities. Initial evaluation of epacadostat 300 mg BID in combination with ipilimumab (3 mg/kg IV every 3 weeks, up to 4 doses) in this study was terminated because of the occurrence of Grade 3 or 4 ALT/AST elevations in 5 of 7 subjects treated at this dose. These AEs were reversible in all subjects upon discontinuation of study therapy and institution of corticosteroids based on an established protocol for the management of immune toxicities related to ipilimumab therapy. However, subsequent cohorts with lower doses of epacadostat in combination with ipilimumab (25 mg BID, 50 mg BID, and 50 mg once every morning/25 mg once every evening) were well-tolerated (Gibney et al 2015). In addition, early safety analysis of epacadostat in combination with another PD-1 inhibitor (pembrolizumab) achieved dose combinations of 300 mg BID (Gangadhar et al 2015). It is expected that achieving similar dose combinations with nivolumab will result in a clinically active combination regimen. Complete inhibition of the IDO1 target is not required for maximally effective activity in preclinical models, and as monotherapy, maximally effective doses in preclinical models result in exposures that are comparable to doses of 50 to 300 mg BID in humans.

Population PK (PPK) analyses using data from various tumor types including NSCLC, MEL, RCC, classical HL, and UC have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no differences in PK across ethnicities and solid tumor types were observed. To provide additional flexibility and convenience when combining with other anticancer agents, such as chemotherapy, the PPK model was used to simulate dosing regimens with less frequent administration (Q3W and Q4W). These regimens were selected such that they would provide similar exposures to those following administration of the approved q2w dosing regimens.

Using the PPK model, the exposures following the administration of nivolumab 360 mg Q3W and 480 mg Q4W were simulated. Based on this analysis, it is predicted that steady state average concentrations (C_{ave}) of nivolumab 240 mg q2w or nivolumab 3 mg/kg q2w are similar following the administration in subjects who have an approximate median weight of 80 kg. The steady state peak concentrations ($C_{max,ss}$) following the administration of nivolumab 360 mg

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Q3W and 480 mg Q4W are predicted to be approximately 26% and 40% higher than following the administration of nivolumab 3 mg/kg, respectively. However, $C_{max,ss}$ of nivolumab 360 mg Q3W and 480 Q4W is predicted to be less than those following the administration of nivolumab 10 mg/kg q2w, and this provides sufficient safety margins for these dosing regimens (Zhao et al 2017).

Both nivolumab 360 mg Q3W and 480 mg Q4W dosing regimens are currently being investigated in multiple tumor types, such as NSCLC and MEL, as monotherapy and in combination with other agents, including the combination with platinum-doublet chemotherapy in Phase 2 and Phase 3 studies (ie, Studies NCT03041181 and NCT02713867).

In Part 2 of the Phase 1 study, the dosing regimen and schedule of nivolumab in combination chemo-immunotherapy cohorts will be a flat dose of 360 mg IV infusion administered Q3W. Since nivolumab 240 mg q2w and 480 mg Q4W dosing regimens and schedules have been supported by the safety, efficacy, and exposure-response analyses results (Zhao et al 2017), these dosing regimens and schedules of nivolumab will be used in Phase 2 for the dose expansion of combination immunotherapy cohorts.

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over a long treatment duration. In Study CA209010 (a Phase 2, randomized, double-blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All of the events were either Grade 1 or Grade 2 and were manageable. An infusion duration of 30 minutes for a 240 mg dose, 360 mg dose, and 480 mg dose (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience with 10 mg/kg nivolumab dose infused over a 60-minute duration. For Phase 2 of the study, nivolumab infusion time will be 30 minutes. For those experiencing an infusion reaction, infusion time may be increased to 60 minutes.

In the present study, epacadostat has been studied in subjects at both 100 mg BID and 300 mg BID with nivolumab 240 mg IV Q2W. In Part 1 of Phase 1, 13 subjects were treated at 300 mg BID, and no DLTs were observed during a 42-day observation period, and an MTD was not defined. As of 13 FEB 2017, 174 subjects were treated at 300 mg BID (13 subjects in Part 1 of Phase 1; 161 subjects in Phase 2). The most common treatment-related AEs (≥ 10%) were rash, fatigue, nausea, diarrhea, pruritus, AST increased, and decreased appetite. The pooled safety data from Part 1 of Phase 1 and Phase 2 demonstrated that there were fewer dose reductions (4% [n = 3] in 100 mg BID and 5% [n = 8] in 300 mg BID) and study treatment discontinuations (6% [n = 4] in 100 mg BID and 12% [n = 20] in 300 mg BID) in subjects treated with epacadostat 100 mg BID compared to 300 mg BID in combination with nivolumab (Perez et al 2017). There were no treatment-related deaths. The overall frequency of all-grade treatment-related AEs in subjects treated with epacadostat 100 mg BID or 300 mg BID in combination with nivolumab was 83% and 73%, respectively. Treatment-related Grade 3 or 4 AEs were 25% in 100 mg BID and 27% in 300 mg BID. The frequency of dose interruptions due to any grade treatment-related AEs were 26% (n = 18) in 100 mg BID and 30% (n = 48) in 300 mg BID.

Based on the published safety and PK profiles for both epacadostat and nivolumab, the starting dose of epacadostat will be 100 mg BID in combination with nivolumab 360 mg Q3W and chemotherapy regimen in Part 2 of Phase 1. For I/O-relapsed and I/O-refractory MEL cohorts in

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Phase 2, epacadostat dose will also be 100 mg BID in combination with nivolumab 480 mg Q4W. Alternative doses of epacadostat may be explored [redacted] and safety results at the sponsor discretion.

1.4.1. Rationale for 2-Year Duration of Treatment

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion study evaluating the safety and clinical activity of nivolumab in subjects with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive after > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years (Brahmer et al 2017). These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29%, and 3-year OS rates of 16%-18% for squamous and nonsquamous NSCLC, respectively; Felip et al 2017). Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized Phase 3 study of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in subjects with previously treated, PD-L1–positive, advanced NSCLC that specified a maximum treatment duration of 2 years for pembrolizumab. Overall survival was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, $p = 0.00017$) and pembrolizumab 10 mg/kg (HR 0.60, $p < 0.00001$) compared with docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years (Herbst et al 2016). Keynote-006 was a randomized Phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2-year duration of pembrolizumab treatment. One hundred four (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients (Robert et al 2017).

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

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2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objectives

2.1.1. Phase 1

- **Part 1 Safety:** To assess the safety and tolerability of epacadostat BID orally in combination with nivolumab and to identify DLTs and the recommended Phase 2 dose (RP2D) of the combination immunotherapy, in subjects with select advanced (metastatic and/or unresectable) cancers (solid tumors and B-cell NHL or HL).
- **Part 2 Safety:** To assess the safety and tolerability and to determine a maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD) of epacadostat in combination with nivolumab and chemotherapy in subjects with advanced or metastatic SCCHN and in subjects with advanced or metastatic NSCLC.

2.1.2. Phase 2

- **Efficacy:**
  - To assess ORR and PFS at 6 months in subjects with select solid tumors or subjects with DLBCL).
  - To assess OS at 9 months for subjects with glioblastoma.

2.2. Secondary Objectives

2.2.1. Phase 1

- **Part 1 Efficacy:** To assess the preliminary antitumor activity of the combination of epacadostat and nivolumab in subjects with select advanced solid tumors, B-cell NHL or HL, or glioblastoma by assessing ORR.
- **Part 2 Efficacy:** To explore the preliminary efficacy of epacadostat administered in combination with nivolumab and chemotherapy in subjects with advanced or metastatic SCCHN and advanced or metastatic NSCLC by assessing ORR, DOR, and PFS.

2.2.2. Phase 2

- **Efficacy:**
  - To assess the preliminary antitumor activity of the combination of epacadostat and nivolumab in subjects with select advanced solid tumors and DLBCL by assessing DOR and duration of disease control.
  - To evaluate OS in subjects with select solid tumors and DLBCL.
  - To evaluate ORR, PFS, DOR, and duration of disease control for subjects with glioblastoma.

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- **Safety:**
  - To assess the safety and tolerability of epacadostat BID orally when given in combination with nivolumab 240 mg every 2 weeks.
  - To assess the safety and tolerability of epacadostat BID orally when given in combination with nivolumab 480 mg every 4 weeks.

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3. SUBJECT ELIGIBILITY

3.1. Study Population

Subjects with Stage IIIB, Stage IV, or recurrent NSCLC; unresectable or Stage IV MEL; recurrent (unresectable) or metastatic CRC; recurrent (unresectable) or metastatic SCCHN; International Federation of Gynecology and Obstetrics (FIGO) Stage Ic, II, III, or IV recurrent ovarian cancer (unresectable); relapsed or refractory B-cell NHL or HL (including relapsed or refractory DLBCL); and relapsed or refractory glioblastoma after standard-of-care therapy may enroll. Subjects with these select tumors must have had disease progression on treatment or intolerance to treatment, or subjects who have refused currently approved treatment may enroll with medical monitor approval (except for subjects with MEL, who may be enrolled as described in the inclusion/exclusion criteria in Sections 3.2 and 3.3).

3.2. Subject Inclusion Criteria

The following criteria are required for inclusion in the study:

1. Male or female subjects, age 18 years or older.
2. Ability to comprehend and willingness to sign an informed consent form (ICF).
3. Subjects with histologically or cytologically confirmed NSCLC, MEL, CRC, SCCHN, ovarian cancer, recurrent B-cell NHL or HL, or glioblastoma.
4. Subjects with Stage IIIB, Stage IV, or recurrent NSCLC; unresectable or Stage IV MEL; recurrent (unresectable) or metastatic CRC; recurrent (unresectable) or metastatic SCCHN; FIGO Stage Ic, II, III, or IV recurrent ovarian cancer (unresectable); relapsed or refractory B-cell NHL or HL (including relapsed or refractory DLBCL); and relapsed or refractory glioblastoma and meet the following tumor-specific criteria:
   a. Subjects with Stage IIIB, Stage IV, or recurrent NSCLC:
      - **For all NSCLC subjects (Phase 1 and Phase 2):**
        - Subjects with nonsquamous NSCLC must be screened for EGFR and ALK fusion oncogene status.
        - Tumors with driver mutations (EGFR mutation–positive or ALK fusion oncogene–positive) previously treated with an approved tyrosine kinase inhibitor (TKI) must have progressed on or been intolerant to the TKI therapy. (Note: For subjects with driver mutations and treated with a prior TKI therapy, up to 2 additional lines of therapy that include a TKI therapy are permitted.)
        - Maintenance or switch maintenance therapy after first-line chemotherapy is acceptable.
        - Malignancy must be deemed unresectable.

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- **For combination immunotherapy cohorts (Part 1 of Phase 1 and Phase 2)**, subjects with nonsquamous, squamous, or adenosquamous NSCLC, or NSCLC NOS histology who have received up to 1 prior systemic regimen for Stage IIIB, Stage IV, or recurrent NSCLC. Prior systemic regimen must have contained a platinum-based therapy (at least 2 cycles with or without bevacizumab).
  - Subjects ineligible for platinum-based therapy who have received alternative chemotherapy regimens or are intolerant of platinum-based therapy may enroll with medical monitor approval.
  - Subjects who completed and progressed on a platinum-containing regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy within the 6 months before screening would be counted as having received 1 prior platinum-containing regimen and, therefore, would not require re-treatment with a platinum-containing regimen for advanced or metastatic disease.
- **For combination chemo-immunotherapy cohorts (Part 2 of Phase 1 only)**, subjects with nonsquamous or squamous NSCLC must have received no more than 1 prior line of therapy for Stage IIIB, Stage IV, or recurrent NSCLC.
  - Subjects must not have received previous PT-DC for Stage IIIB, Stage IV, or recurrent NSCLC.
  - Subjects who completed a platinum-based chemotherapy doublet regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible for combination chemo-immunotherapy only. If progression occurred < 6 months after completing therapy, the subject will not be eligible.
  - In the dose-finding cohorts, subjects may have received a prior TKI for tumors with any driver mutation (EGFR mutation–positive or ALK fusion oncogene–positive).
  - In the safety expansion cohorts, subjects must not have received any prior therapy for advanced or metastatic disease, except TKI for driver mutations.

b. Subjects with unresectable or Stage IV MEL. **Note:** There will be 3 MEL cohorts in Phase 2, which will include I/O-naive, I/O-relapsed, and I/O-refractory cohorts as defined below:
   - For all MEL subjects **(Phase 1 and Phase 2):**
     - Documentation of V600E-activating BRAF mutation status or consent to BRAF V600E mutation testing during the screening period. Testing should be performed in a Clinical Laboratory Improvement Amendments–certified laboratory. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criteria for BRAF mutation testing.
     - No nitrosoureas (eg, carmustine or lomustine) within the past 6 weeks and during study treatment.

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  - Must not have any prior ocular toxicity on any prior therapy, including immune checkpoint inhibitors.

    No more than 2 prior lines of therapy for advanced/metastatic disease, only 1 of which can be a prior anti–PD-1/PD-L1 therapy with or without anti–CTLA-4 therapy. Prior anti–CTLA-4 monotherapy is not permitted.

  - Must not have ocular melanoma.

- For subjects with advanced or metastatic **I/O-naive MEL (Part 1 of Phase 1 and Phase 2):**
  - Subjects must be treatment-naive or have received only 1 prior treatment for advanced or metastatic disease, including targeted therapy.
  - Subjects must not have received any prior anti–PD-1/PD-L1 therapy.

    Note: Anti–CTLA-4 given as in the adjuvant setting or as first-line treatment for advanced or metastatic disease will be permitted. These subjects must have discontinued anti–CTLA-4 therapy at least 12 weeks before first dose of epacadostat.

- For subjects with advanced or metastatic MEL who were relapsed on or after the previous anti–PD-1/PD-L1 therapy following an initial response to PD-1 pathway–targeted therapy **(I/O-relapsed MEL; Phase 2 only):**
  - **Relapsed** is defined as having a best response of CR, PR, or SD with a subsequent confirmed radiographic progression per RECIST v1.1 on or after anti–PD-1/PD-L1 therapy with or without anti–CTLA-4 therapy.

    Note: Disease progression may be confirmed based on study investigator's certification at screening assessment.

  - If with known BRAF mutations, subjects may have had prior BRAF/MEK inhibitors following the last anti–PD-1/PD-L1 therapy (with or without anti–CTLA-4 therapy).
  - No more than 2 prior lines of therapy for advanced/metastatic disease, only 1 of which can be a prior anti–PD-1/PD-L1 therapy, with or without anti–CTLA-4 therapy. Prior anti–CTLA-4 monotherapy is not permitted.

- For subjects with advanced or metastatic MEL who were refractory to previous anti–PD-1/PD-L1 therapy **(I/O-refractory MEL; Phase 2 only):**
  - **Refractory** is defined as having a best response of confirmed radiographic progression per RECIST v1.1 to a prior anti–PD-1/PD-L1 therapy with or without anti–CTLA-4 therapy.

    Note: Disease progression may be confirmed based on study investigator's certification at screening assessment.

  - If with known BRAF mutations, may have had prior BRAF/MEK inhibitors following the last anti–PD-1/PD-L1 therapy (with or without anti–CTLA-4 therapy).

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- No more than 2 prior lines of therapy for advanced/metastatic disease, only 1 of which can be a prior anti–PD-1/PD-L1 therapy, with or without anti–CTLA-4 therapy. Prior anti–CTLA-4 monotherapy is not permitted.

c. Subjects with recurrent (unresectable) or metastatic CRC:

- Histologically or cytologically confirmed metastatic or recurrent adenocarcinoma of the colon or rectum.
- Prior treatment: Previous treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti–vascular endothelial growth factor (VEGF) therapy (if no contraindication); and, if KRAS wild type and no contraindication, an anti-EGFR therapy and progressed following the last administration of approved therapy.
- Subjects who have discontinued treatment due to unacceptable toxicity may enroll.

d. Subjects with recurrent (unresectable) or metastatic SCCHN:

- Histologically confirmed squamous cell carcinoma not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy). Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and salivary gland or nonsquamous histologies will be excluded.
- For combination immunotherapy cohorts in Phase 1 Part 1 and Phase 2: No more than 2 prior systemic regimens for advanced disease. Prior systemic regimens must include a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Subjects who relapsed within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
- For combination chemo-immunotherapy cohorts in Phase 1 Part 2: Subjects must not have received a previous platinum-based chemotherapy for recurrent or metastatic SCCHN.

  Note: Subjects who completed a platinum based chemotherapy as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing the therapy, the subject will not be eligible.
- Documentation of HPV status (eg, p16-status) of tumor.

e. Subjects with FIGO Stage Ic, Stage II, Stage III, Stage IV, recurrent, or persistent (unresectable) histologically confirmed epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube carcinoma:

- Subjects must have received a platinum-taxane–based regimen as frontline therapy.
- Subjects who received maintenance paclitaxel, bevacizumab, or alternative maintenance therapy (eg, vaccines) are eligible for enrollment provided that they have discontinued therapy at least 4 weeks for prior taxane and at least 8 weeks for bevacizumab, or they have received medical monitor approval for time lapse

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from alternative maintenance therapy before enrollment and recovered from toxicities to ≤ Grade 2.

- Borderline, low malignant potential epithelial carcinoma per histopathology is excluded.

f. Subjects with relapsed or recurrent B-cell NHL or HL (including relapsed or refractory DLBCL, excluding Burkitt's lymphoma and precursor B-lymphoblastic leukemia/lymphoma):
   - Prior allogeneic stem cell transplantation is excluded.
   - Not a candidate for curative therapy or hematopoietic stem cell transplantation (due to disease burden, fitness, or preference).
   - Subjects must have relapsed or have had refractory DLBCL specifically for Phase 2 but may have any B-cell NHL or HL as noted above for Phase 1 dose escalation.
   - Subjects with HL must be brentuximab vedotin–refractory or intolerant.

g. Subjects with histologically confirmed diagnosis of relapsed or refractory glioblastoma:
   - Previous first-line treatment with at least radiotherapy and temozolomide.
   - Documented first recurrence of glioblastoma by diagnostic biopsy or contrast-enhanced magnetic resonance imaging (MRI) per Response Assessment in Neuro-Oncology (RANO) criteria.

     Note: Relapse is defined as progression following initial line of therapy (ie, radiation ± chemotherapy). If the participant had a surgical resection for relapsed disease and no antitumor therapy was instituted for up to 12 weeks, this is considered 1 relapse or recurrence.
   - MRI within 14 days before start of study drug. MRIs should include vascular imaging when possible. Corticosteroid dose must be stable or decreasing for at least 5 days before the scan. If steroids are added or the steroid dose is increased between the date of the screening MRI and the start of treatment, a new baseline MRI is required.
   - An interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either 1) histopathologic confirmation of recurrence of tumor or 2) new enhancement on MRI outside of the radiotherapy treatment field.
   - An interval of ≥ 21 days and full recovery (ie, no ongoing safety issues) from surgical resection before enrollment.

5. Presence of measurable disease per RECIST v1.1 (Appendix E) for solid tumors or Response criteria for Lymphoma (Cheson et al 2007; Appendix F) for B-cell NHL (including DLBCL) or HL. For subjects with glioblastoma, presence of measurable disease is not required.

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7. Fresh baseline tumor biopsies (defined as a biopsy specimen taken since completion of the most recent prior systemic regimen) are required for all cohorts except glioblastoma. For I/O-relapsed MEL and I/O-refractory MEL cohorts (Phase 2) as well as all combination chemo-immunotherapy cohorts (Part 2 of Phase 1), biopsies will be confirmed to contain adequate tumor tissue by a local pathology review. If a subject has inaccessible lesions, such as in ovarian cancer, the subject may be enrolled with medical monitor approval. In this case, submission of archived tumor tissue may be acceptable.

   For archived tumor tissue, a formalin fixed paraffin-embedded tumor tissue block is preferred. If a block is not available, a minimum of 20 unstained freshly cut slides may be submitted to the testing laboratory as specified in the Laboratory Manual.

   Note: Unstained slides must have been prepared from a formalin-fixed paraffin-embedded block obtained within 6 months before screening.

8. Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy and are not postmenopausal as defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test at screening. All female (and male as appropriate for Protocol) subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy (or fathering children), with at least 99% certainty, from screening through 150 days after the last dose of epacadostat. Permitted methods that are at least 99% effective in preventing pregnancy (Appendix A) should be communicated to the subject and their understanding confirmed.

3.3. Subject Exclusion Criteria

If met, any of the following criteria will lead to subject exclusion from the study:

1. Laboratory and medical history parameters not within Protocol-defined range unless directly resulting from the bone marrow infiltration of the underlying malignancy. All screening laboratory tests should be performed within 7 days of the first dose of epacadostat (C1D1) and must be independent of hematopoietic growth factor support:
   a. Absolute neutrophil count < 1.5×10^9/L (in no case < 1.0×10^9/L).
   b. Platelets < 100×10^9/L (in no case < 50×10^9/L).
   c. Hemoglobin < 9 g/dL or ≤ 5.6 mmol/L (transfusion is acceptable to meet this criterion).
   d. Serum creatinine ≥ 1.5 × institutional upper limit of normal (ULN), or measured or calculated creatinine clearance (CrCl) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.
   e. AST, ALT > 2.5 × ULN OR ≥ 5 × ULN for subjects with liver metastases.
   f. Total bilirubin ≥ 1.5 × ULN or conjugated (direct) bilirubin ≥ ULN (need only be tested if total bilirubin exceeds ULN). If an institutional ULN for conjugated bilirubin is not available, then conjugated bilirubin should be < 40% of total bilirubin to be considered eligible.

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g. International normalized ratio (INR) or prothrombin time (PT) > 1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants.
h. Activated partial thromboplastin time (aPTT) > 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.

2. Current pregnancy or breastfeeding.
3. Participation in any other study in which receipt of an investigational study drug occurred within 28 days or 5 half-lives (whichever is longer) before C1D1. For investigational agents with long half-lives (eg, 5 days), enrollment before the fifth half-life requires medical monitor approval.
4. Subjects who have received prior immune checkpoint inhibitors (eg, anti–CTLA-4, anti–PD-1, anti–PD-L1, and any other antibody or drug specifically targeting T-cell costimulation) or an IDO inhibitor (except as required for I/O-relapsed and I/O-refractory MEL cohorts [Phase 2], see inclusion criteria above). Subjects who have received experimental vaccines or other immune therapies should be discussed with the medical monitor to confirm eligibility.
5. Any prior irAEs must have resolved to ≤ Grade 1 before first dose of epacadostat and nivolumab (C1D1). Any ≥ Grade 3 irAEs (except lymphopenia or asymptomatic amylase/lipase elevations) from prior immunotherapies, including CTLA-4 treatment, are excluded.

   Note: Subjects with history of ≥ Grade 3 endocrinopathies must be discussed with the medical monitor to determine eligibility.
6. Subjects who are receiving an immunologically based treatment for any reason, including chronic use of systemic steroid or prednisone equivalent at doses ≥ 10 mg/day within 7 days before the first dose of epacadostat and nivolumab (C1D1). Use of inhaled or topical steroids or systemic corticosteroids < 10 mg is permitted. (Note: There are some exceptions in use of systemic corticosteroids or physiological replacement doses of steroids for subjects with glioblastoma; see Section 5.13).
7. Subjects who have received any anticancer medication in the 21 days before C1D1 or has any unresolved toxicity greater than Grade 1 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity, alopecia, and fatigue.
8. Prior monoclonal antibody within 4 weeks before starting C1D1 or not recovered (≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier. Exception to this rule would be use of denosumab.
9. If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention before starting therapy. For subjects with glioblastoma, it must be ≥ 21 days since prior surgery and full recovery (ie, no ongoing safety issues) from surgical resection before enrollment.

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10. Has a history of other malignancy within 2 years of study entry, with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma *in situ* of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for ≥ 1 year, following treatment with curative intent.
11. Untreated central nervous system (CNS) metastases or CNS metastases that have progressed (eg, evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases or cerebral edema). Subjects with previously treated and clinically stable CNS metastases (without evidence of radiographic progression shown by imaging at least 28 days before C1D1) and off all corticosteroids for at least 2 weeks before C1D1 are eligible.
12. Subjects with any active or inactive autoimmune process (eg, rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, inflammatory bowel disease) or who are receiving systemic therapy for an autoimmune or inflammatory disease.
    a. Exceptions include subjects with vitiligo, hypothyroidism stable on hormone replacement, controlled asthma, Type I diabetes, Graves' disease, Hashimoto's disease, or with medical monitor approval.
13. Evidence of interstitial lung disease or active, noninfectious pneumonitis including symptomatic and/or pneumonitis requiring treatment.
14. Subjects who have had prior radiotherapy within 2 weeks of C1D1. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week wash out is permitted for palliative radiation to non-CNS disease with medical monitor approval.
15. Presence of a gastrointestinal condition that may affect drug absorption.
16. Active infection requiring systemic therapy
17. Has a known history of or is positive for hepatitis B (HBsAg reactive) or has active hepatitis C (HCV RNA). Note: Testing must be performed to determine eligibility.
    a. HBV DNA must be undetectable and HBsAg negative at screening visit.
    b. Hepatitis C Ab testing is allowed for screening purposes in countries where HCV RNA is not part of SOC. In these cases, HCV antibody positive participants will be excluded.
    c. Participants who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening visit. (Includes serology testing shown in the laboratory analytes; see Table 26).
18. Known history of human immunodeficiency virus.
19. Subjects receiving MAOIs within the 21 days before screening.
20. Any history of SS after receiving 1 or more serotonergic drugs.

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21. Receipt of live attenuated vaccine within 30 days before C1D1. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
22. History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is > 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded (see Section 7.4.5 for details).
23. Use of any UGT1A9 inhibitor from screening through follow-up period, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid. See Section 5.13 for more details.
24. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy.
25. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
26. Known allergy or reaction to any component of epacadostat, nivolumab, 5-FU, cisplatin, carboplatin, paclitaxel, pemetrexed, or their formulation components or mannitol.
27. Exclusion criteria for subjects with glioblastoma:
    a. More than 1 recurrence of glioblastoma.
    b. Presence of extracranial metastatic or leptomeningeal disease.
    c. Diagnosis of secondary glioblastoma (ie, glioblastomas that progress from low-grade diffuse astrocytoma or anaplastic astrocytoma).
    d. Previous radiation therapy with anything other than standard therapy (ie, focally directed radiation).
    e. Subjects requiring escalating (within 7 days of C1D1) or chronic supra physiologic doses (to be more than 2 mg of Decadron® or biologic equivalent per day) of corticosteroids for control of their disease.
    f. Treatment with carmustine wafer except when administered as first-line treatment and at least 6 months before C1D1.
    g. Evidence of > Grade 1 CNS hemorrhage on the baseline MRI.
    h. History or evidence upon physical/neurological examination of CNS disease (eg, seizures) unrelated to cancer unless adequately controlled by medication or potentially interfering with Protocol treatment.

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i. Subjects unable (due to existent medical condition, eg, pacemaker or implantable cardioverter defibrillator device) or unwilling to have a head contrast-enhanced MRI.
j. History of intracranial abscess within 6 months before enrollment.
k. Prior VEGF or VEGF-receptor directed therapy (ie, bevacizumab).

28. Use of any prohibited medication listed in Section 5.13.

29. Subjects with bleeding associated with tumors that invade or are adjacent to major blood vessels, as shown unequivocally by imaging studies, or history of bleeding related to disease under study within 3 months of Cycle 1 Day1.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 1/2 open-label study that will be conducted in 2 phases. Phase 1 of the study will consist of 2 parts (Part 1 and Part 2). Part 1 of Phase 1 will consist of a standard dose-escalation design to determine the MTD or PAD of epacadostat when coadministered with nivolumab (defined as combination immunotherapy) in subjects with select advanced solid tumors and lymphomas, including MEL, NSCLC, CRC, SCCHN, ovarian cancer, glioblastoma, and B-cell NHL or HL. The study design for Part 1 of Phase 1 is shown in Figure 1.

Part 2 of Phase 1 will evaluate the preliminary safety of epacadostat in combination with nivolumab and several chemotherapy regimens (defined as combination chemo-immunotherapy) in subjects with SCCHN and NSCLC by using a dose de-escalation design. The starting dose of epacadostat in Part 2 will be the RP2D of epacadostat selected for the use of combination immunotherapy in Part 1. Initial dose-finding cohorts in Part 2 will be expanded to safety expansion cohorts and will further evaluate tolerated dose(s) of epacadostat when given in combination with nivolumab and chemotherapy regimens (see Figure 2 for study design of Phase 1 Part 2).

Phase 2 of the study will include 9 expansion cohorts in tumors types tested in Phase 1 Part 1 (except DLBCL will be the only lymphoma permitted) with a) historically high activity under nivolumab monotherapy and b) with historically low activity with nivolumab monotherapy. In Phase 2 of the study, nivolumab will be administered at 240 mg IV every 2 weeks or 480 mg IV every 4 weeks for specific tumor types as described in Figure 1. (Note: In Phase 2, subjects enrolled into I/O-relapsed and I/O-refractory MEL cohorts will be administered epacadostat 100 mg BID.)

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Figure 1: Study Design for Combination Immunotherapy Cohorts (Phase 1 Part 1 and Phase 2)

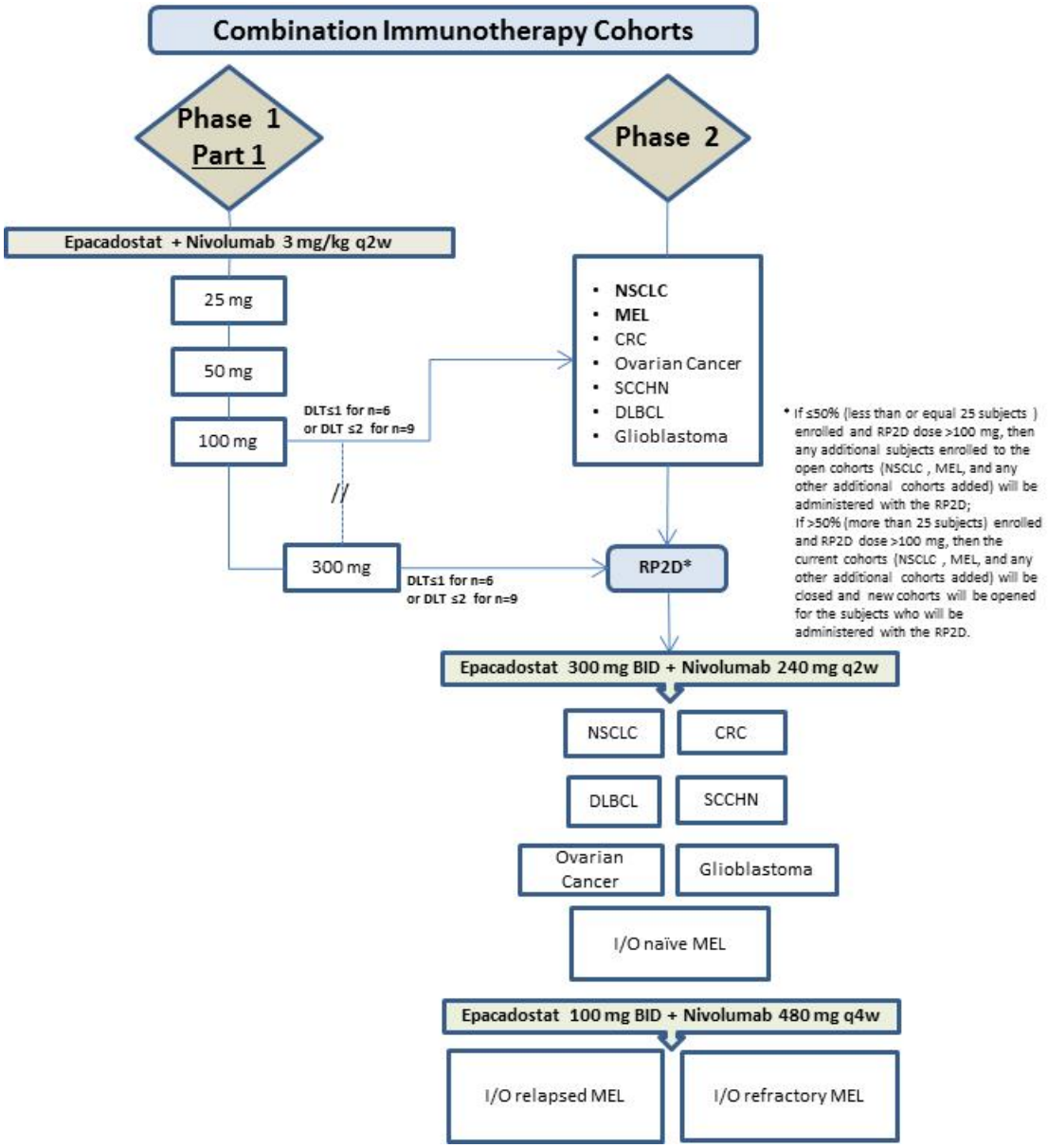

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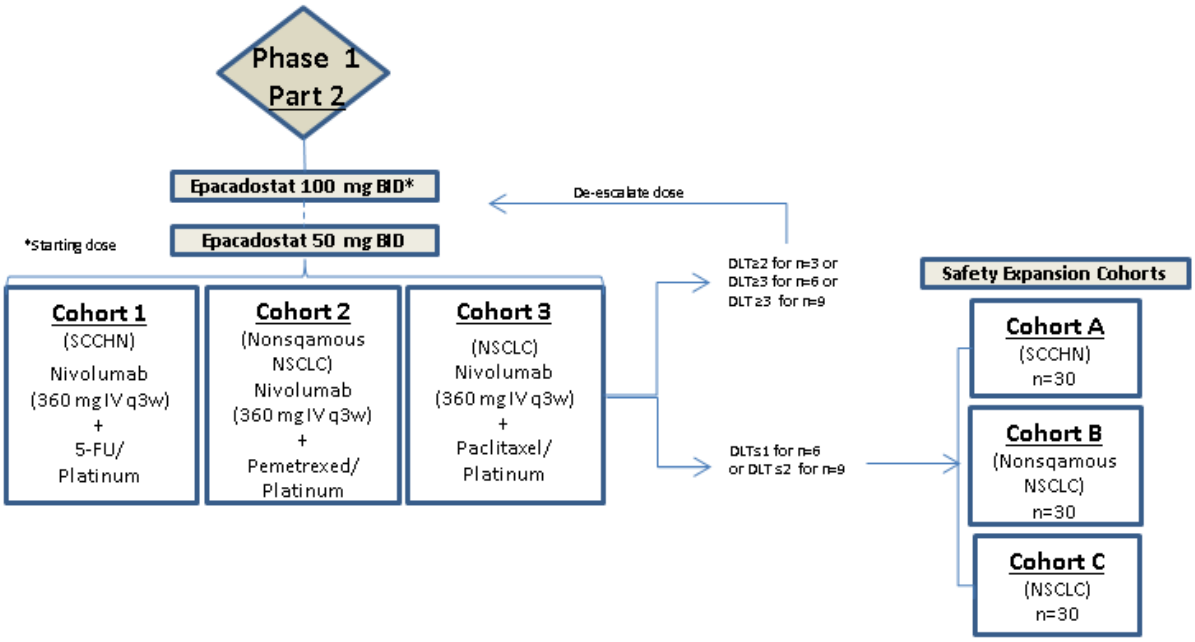
Figure 2: Study Design for Combination Chemo-Immunotherapy Cohorts (Phase 1 Part 2 Only)



4.1.1. Phase 1 Dose-Finding and Safety Expansion (Part 1 and Part 2)

In Part 1, for combination immunotherapy cohorts, a 3 + 3 + 3 standard dose-escalation design will be used to assess the safety of epacadostat when given in combination with nivolumab.

In Part 2, for combination chemo-immunotherapy cohorts, a (3 + 3) + 3 dose de-escalation study design will be used to evaluate the safety of epacadostat when administered in combination with nivolumab and chemotherapy regimen. Part 2 will be initiated after Phase 1 Part 1 of the study is completed and the Phase 2 dose of epacadostat for the combination immunotherapy is determined.

4.1.1.1. Combination Immunotherapy Cohorts (Part 1)

The starting dose of epacadostat when given in combination with nivolumab (3 mg/kg IV every 2 weeks, Q2W) is 25 mg BID continuous daily dose administration. The epacadostat dose regimens during dose escalation in combination immunotherapy cohorts are provided in Table 1.

The BID continuous administration cohorts will be tested first. If epacadostat 50 mg BID continuous daily administration is determined as tolerable, the investigators and sponsor may agree to only evaluate continuous daily administration. However, if epacadostat 50 mg BID exceeds the MTD, an every-other-week administration schedule of epacadostat administered BID may be tested. If a dose is determined safe for both schedules, a safety expansion cohort may be opened for each dose regimen to include approximately 9 subjects in each cohort before selecting the schedule to move to Phase 2. If at least 50 mg BID continuous or every other week cannot be combined safely with nivolumab 3 mg/kg, other alternative dose schedules (ie, other intermittent administration) of epacadostat may be tested, if needed, following the review of available safety data at the Dose Escalation/Cohort Review meetings. If an alternate schedule is

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tested and determined to be safe, re-escalation of epacadostat according to Table 1 will proceed with nivolumab 3 mg/kg every 2 weeks.

Table 1: Phase 1 Part 1 Dose-Escalation Schema for Epacadostat in Combination With Nivolumab Once Every 2 Weeks (Combination Immunotherapy Cohorts)

Dose Level Number	Total Subjects[a] (N)	Epacadostat (Oral)	Dose of Nivolumab (IV, Once Every 2 Weeks)
1	Approximately 3-9	25 mg BID	3 mg/kg
2a	Approximately 3-9	50 mg BID	3 mg/kg
2b	Approximately 3-9	50 mg BID every other week	3 mg/kg
3a	Approximately 3-9	100 mg BID	3 mg/kg
3b	Approximately 3-9	100 mg BID every other week	3 mg/kg
4a	Approximately 3-9	300 mg BID[b]	3 mg/kg
4b	Approximately 3-9	300 mg BID every other week[b]	3 mg/kg
Total	Approximately 21-63		

[a] Approximately 3 to 9 subjects will be enrolled during dose escalation. Additional subjects may be added to any dose level after determining the preliminary safety at that dose level for a minimum of 6 and maximum of 9 evaluable subjects per dose level. Dose level numbers marked "a" and "b" may occur in parallel. Oral administration of epacadostat BID will occur on a daily basis unless indicated by the weekly alternating schedule of BID each day for 1 week followed by no doses for the following week. Nivolumab administration will be 3 mg/kg IV every 2 weeks.

[b] If 300 mg BID is not tolerated, an intermediate dose of 200 mg BID may be tested on either a continuous schedule or every-other-week schedule.

The DLT observation period will last for 6 weeks (42 days). Three subjects will be treated initially at each dose level. If 0 DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects experience a DLT, that cohort will be expanded to 6 subjects. If 1 of 6 subjects experiences a DLT, a new cohort of 3 subjects will be treated at the next higher dose level. If 2 of 6 DLT subjects experience a DLT, that cohort will be expanded to 9 subjects. If ≥ 2/3, 3/6, or 3/9 subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD.

If epacadostat 100 mg BID is deemed tolerable, up to 6 additional subjects (for a minimum of 6 evaluable subjects) will be enrolled to confirm the safety of the dose in combination with nivolumab. If 1 of 6 or < 3 of 9 subjects experience DLTs, the Phase 2 MEL and NSCLC expansion cohorts will open epacadostat 100 mg BID in combination with nivolumab. The 300 mg BID dose in Phase 1 will be tested in parallel to the Phase 2 MEL and NSCLC cohorts opening. Additional Phase 2 cohorts in other tumor types may also be opened to test epacadostat 100 mg BID if it is deemed pharmacologically active and safe based on available data from Phase 1 cohorts.

Note: Up to 6 additional subjects may be enrolled into each cohort for a total of up to 9 evaluable subjects to further explore safety [redacted] objectives (original 3-9 subjects from dose escalation plus additional subjects required to have a total cohort size of 9).

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If epacadostat 300 mg BID is deemed tolerable, up to 6 additional subjects (for a minimum of 6 subjects) will be enrolled before opening Phase 2 to further confirm the safety of the dose in combination with nivolumab. If 1 of 6 or < 3 of 9 subjects experience DLTs, the remaining Phase 2 cohorts may be opened with 300 mg BID as the RP2D after reviewing the emerging data from Phase 2 cohorts testing 100 mg BID.

If 300 mg BID is tested and not tolerated, an intermediate dose of 200 mg BID may be tested on either a continuous schedule or every-other-week schedule or 100 mg BID may be selected as the RP2D. The RP2D decision for the remaining Phase 2 cohorts will be made based on the available data from ongoing Phase 2 cohorts administered 100 mg BID. If an MTD is not determined based on the data from Phase 1 and ongoing Phase 2 cohorts, then the remaining Phase 2 cohorts may be opened at a PAD of epacadostat (eg, 100 mg BID).

4.1.1.1.1. Phase 2 Dose Selection for Combination Immunotherapy (Phase 1 Part 1)

If 100 mg BID of epacadostat is determined as safe and tolerable in Phase 1 Part 1, Phase 2 of the study may begin to enroll in the I/O-naive MEL and NSCLC cohorts in parallel with the evaluation of epacadostat at 300 mg BID in Part 1. If 300 mg BID is then selected as the Phase 2 dose (RP2D), and if either I/O-naive MEL or NSCLC cohort enrolls < 50% of the total cohort (≤ 25 subjects) at 100 mg BID up to the RP2D decision, then any additional subjects in that specific cohort being enrolled will be treated with epacadostat 300 mg BID at the sponsor's discretion, in lieu of opening new cohorts of I/O-naive MEL and NSCLC with 300 mg BID. The same rule will apply to any additional Phase 2 tumor cohorts (ie, CRC, ovarian cancer, etc) that may be opened with epacadostat 100 mg BID before RP2D selection. (Note: Additional I/O-relapsed and I/O-refractory MEL cohorts will be opened at 100 mg BID.)

4.1.1.2. Combination Chemo-Immunotherapy Cohorts (Part 2 of Phase 1)

The starting dose of epacadostat when given in combination with nivolumab (360 mg IV every 3 weeks, Q3W) and chemotherapy will be 100 mg BID continuous daily dose administration, which is 1 dose level less than what was determined to be tolerable in Part 1 of Phase 1 and provides an adequate safety margin. Part 2 of Phase 1 will consist of 3 tumor cohorts (1 SCCHN cohort and 2 NSCLC cohorts) that will enroll in parallel. A minimum of 6 evaluable subjects will be enrolled in each tumor cohort epacadostat at 100 mg BID and each cohort will be observed for 42 days for DLTs.

In a tumor cohort the following rules will be applied to determine dose or dose de-escalation:

- If ≤ 1 of 6 evaluable subjects has a DLT, then 100 mg BID will be used in a safety expansion cohort (Cohort A, B, C) for that specific tumor type.
- If 2 of 6 evaluable subjects have a DLT, 3 additional subjects will be enrolled in the same cohort (Cohort 1, 2, 3). If there are no additional DLTs (≤ 2 DLTs occurred in a total of 9 evaluable subjects), then a safety expansion cohort (Cohort A or B or C) will start to enroll in that specific dose level.

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- If ≥ 2 of 3, 3 of 6, or ≥ 3 of 9 evaluable subjects have DLTs within a specific tumor cohort, epacadostat will be de-escalated to 1 lower dose level, 50 mg BID, and that tumor cohort will enroll 6 subjects to test this dose level as described above.
- **Note:** If different MTDs are determined for the 2 NSCLC cohorts (combination chemo-immunotherapy), 3 to 6 additional subjects may be enrolled in each NSCLC cohort to further evaluate the safety profile before dose selection for safety expansion.

The doses of epacadostat to be evaluated and scenarios for de-escalation are summarized in Table 2.

Table 2: Epacadostat Dose De-Escalation Scenarios for Combination Chemo-Immunotherapy Cohorts

Combination Chemo-Immunotherapy Cohort	Epacadostat Dose
Dose Level 1 (starting dose)	100 mg BID[a]
Dose Level -1	50 mg BID

[a] If epacadostat 100 mg BID is not tolerated within a specific cohort, the dose of epacadostat will be de-escalated to 50 mg BID for evaluation. Alternate doses may be evaluated at the sponsor discretion [redacted] and safety results.

Epacadostat dose regimens in combination chemo-immunotherapy cohorts by tumor types are provided in Table 3.

Once 100 mg BID or 50 mg BID of epacadostat in combination chemo-immunotherapy cohorts is determined as the MTD or PAD, each of the tumor cohorts will be expanded for safety evaluation at that dose level of epacadostat. Each of the safety expansion cohorts with combination chemo-immunotherapy will enroll approximately up to 30 evaluable subjects.

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Table 3: Summary of Treatment Regimens for Each Possible Epacadostat Dose-Finding Scenario for Combination Chemo-Immunotherapy Cohorts in Part 2

Tumor Types[a]	Cohort[b]	Total Subjects, N	Epacadostat (Oral)	Nivolumab (IV, Once Every 3 Weeks)	Chemotherapy Regimen
SCCHN	1	~6-9	100 mg BID	360 mg	Cisplatin (100 mg/m^2 IV Q3W for up to 6 cycles) or Carboplatin AUC 5 IV Q3W for up to 6 cycles 5-FU (1000 mg/m^2 continuous IV for 4 days Q3W for up to 6 cycles, on Day 1 of each cycle starting C1D1)
	1a	~6-9	50 mg BID	360 mg	Same as above
Nonsquamous NSCLC	2	~6-9	100 mg BID	360 mg	Pemetrexed (500 mg/m^2 IV Q3W for up to 6 cycles but no less than 4 cycles, on D1of each cycle starting C1D1) Carboplatin (AUC 5 IV Q3W up to 6 cycles but no less than 4 cycles, on Day 1 of each cycle starting C1D1) or Cisplatin (100 mg/m^2 IV Q3W up to 6 cycles but no less than 4 cycles)
	2a	~6-9	50 mg BID	360 mg	Same as above
NSCLC	3	~6-9	100 mg BID	360 mg	Paclitaxel (200 mg/m^2 IV Q3W for up to 6 cycles but no less than 4 cycles, on Day 1 of each cycle starting C1D1) Carboplatin (AUC 6 IV Q3W up to 6 cycles but no less than 4 cycles, on Day 1 of each cycle starting C1D1) or Cisplatin (100 mg/m^2 IV Q3W up to 6 cycles but no less than 4 cycles)
	3a	~6-9	50 mg BID	360 mg	Same as above
Total		~18-54			

[a] Cohort 1, Cohort 2, and Cohort 3 will enroll in parallel.
[b] If Cohort 1, Cohort 2, or Cohort 3 with epacadostat 100 mg BID proves intolerable, then Cohort 1a, Cohort 2a, or Cohort 3a may be evaluated with epacadostat 50 mg BID. If the epacadostat 100 mg BID is determined to be safe and tolerable at a specific tumor type, then the safety expansion cohort for that specific tumor type will enroll at 100 mg BID. Alternative doses of epacadostat may be investigated at the sponsor discretion.

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In Phase 1, no intrasubject dose escalation is allowed. In Phase 1 Part 1, additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects if discontinuations or dose interruptions or reductions occur that result in a subject being nonevaluable for DLTs. In Phase 1 Part 2, additional subjects will be enrolled in a cohort to achieve the minimum of 6 evaluable subjects. In both Part 1 and Part 2, subjects who withdraw from the study during the DLT period for reasons other than a DLT may be replaced within the same dose level.

For the purpose of making decisions on dose of epacadostat from a safety perspective, subjects will be considered evaluable if they meet 1 of the following criteria:

- In Part 1, in the combination immunotherapy cohorts, subjects must have received at least 2 out of the 3 scheduled nivolumab doses of 3 mg/kg through the 6-week (42-day) DLT observation period (only if the 1 missed dose was secondary to nonmedical reasons) and must have received at least 75% of the cohort-specified dose of epacadostat during the DLT observation period.
- In Part 2, in combination chemo-immunotherapy cohorts, subjects must have received 2 doses of nivolumab and chemotherapy regimen and must have received at least 75% of the cohort-specified dose of epacadostat during the 42-day DLT observation period.
- In addition, subjects with dose delays during the 42-day DLT observation period of > 1 week for non-DLT events will be considered not evaluable for making decisions on dose escalation or dose de-escalation and should be replaced.

Dose escalation in Part 1 or dose de-escalation in Part 2 of epacadostat will be based on the number of dose limiting toxicities (DLTs) experienced during the DLT observation period. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor.

4.1.2. Phase 2 Combination Immunotherapy Cohort Expansions

The purpose of the cohort expansions in Phase 2 is to gather additional safety, tolerability, preliminary efficacy, [redacted] information regarding the combination of epacadostat and nivolumab. Once the safety profile of active doses is characterized and the RP2D has been defined, the cohort expansions will be initiated at the RP2D. However, the I/O-naive MEL and NSCLC cohorts may be opened using epacadostat 100 mg BID in parallel to testing 300 mg BID if the 100 mg BID dose of epacadostat is deemed tolerable in Phase 1 Part 1. Treatment doses in the cohort expansion groups will not exceed the MTD. Nine expansion cohorts in Phase 2 will be restricted to the same tumor types tested in Phase 1 Part 1 (except DLBCL will be the only lymphoma permitted in Phase 2), and Phase 2 will also include a cohort for glioblastoma. The NSCLC and I/O-naive MEL cohorts, which have demonstrated activity with nivolumab monotherapy and are in Phase 3 evaluation in these indications, will be used to assess increased activity of the combination. In Phase 2, there will be 2 additional MEL cohorts to explore the activity of combination immunotherapy; one cohort will enroll subjects who relapsed on or after anti–PD-1/PD-L1 therapy (I/O relapsed) and the other cohort will enroll subjects who were refractory to prior anti–PD-1/PD-L1 therapy (I/O refractory) (for I/O relapsed MEL cohort and I/O refractory MEL cohort definitions, see Section 3.2). Subjects who are enrolled in these 2 new MEL cohorts will be administered nivolumab 480 mg IV every 4 weeks,

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whereas subjects who are enrolled in I/O-naive MEL, NSCLC, CRC, SCCHN, ovarian cancer, DLBCL and glioblastoma cohorts will be administered nivolumab 240 mg IV every 2 weeks. Subjects enrolled in I/O MEL cohorts will be administered epacadostat 100 mg BID; however, if there is no or minimal activity in tumor responses in these cohorts, alternative doses of epacadostat may be explored at the sponsor discretion. The CRC, SCCHN, ovarian cancer, DLBCL, and glioblastoma cohorts will explore activity of the combination in tumors with preliminary, unknown, or historically low responses to nivolumab monotherapy. Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If the cumulative incidence of Grade 3 or Grade 4 study treatment–related AEs exceeds 40% after enrolling the first 6 subjects in any of these cohorts, the findings will be reviewed and further enrollment will be interrupted until the sponsor(s), investigators, and regulatory authorities, if applicable, have determined the appropriate course of action. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level of epacadostat.

In each of the NSCLC and I/O-naive MEL cohorts, approximately 50 subjects will be enrolled to allow for a more precise estimate of the ORR in these tumors where activity for nivolumab as monotherapy has been established. The sample size for the I/O-relapsed MEL, I/O-refractory MEL, CRC, ovarian, SCCHN, and DLBCL cohorts will be approximately 25 subjects each. The sample size for the glioblastoma cohort will be approximately 28 (Table 4). The study schedules for Phase 2 are shown in Table 18, Table 19, and Table 20.

Table 4: Tumor Types Eligible for Combination Immunotherapy Cohort Expansion

Tumor Type	Approximate Number of Subjects to Be Enrolled (Phase 2 Only)
NSCLC	50
I/O-naive MEL	50
I/O-relapsed MEL	25
I/O-refractory MEL	25
CRC	25
Ovarian cancer	25
SCCHN	25
DLBCL	25
Glioblastoma	28
Totals	278

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4.2. Study Endpoints

4.2.1. Primary Endpoint

4.2.1.1. Phase 1

- **Safety:** In Part 1 and Part 2 of Phase 1 of the study, all subjects who receive at least 1 dose of epacadostat or nivolumab will be assessed for safety by monitoring the frequency and severity of AEs, SAEs, and deaths.

4.2.1.2. Phase 2

- **Efficacy:**
  - The ORR and PFS at 6 months will be assessed based on RECIST v1.1 criteria for subjects with select solid tumors or Cheson criteria for subjects with DLBCL.
  - OS will be assessed at 9 months for subjects with glioblastoma as determined by death due to any cause.

4.2.2. Secondary Endpoints

4.2.2.1. Phase 1

- **Part 1 Efficacy:** ORR will be assessed per RECIST v1.1 and modified RECIST for subjects with select advanced solid tumors, Cheson and modified Cheson criteria for B-cell NHL or HL, and RANO and modified RANO criteria for glioblastoma.
- **Part 2 Efficacy:** ORR, DOR, and PFS will be assessed per RECIST v1.1 and modified RECIST for subjects with advanced or metastatic SCCHN and advanced or metastatic NSCLC treated with epacadostat in combination with nivolumab and chemotherapy.

4.2.2.2. Phase 2

- **Efficacy:** The DOR and duration of disease control will be assessed based on RECIST v1.1 criteria and modified RECIST for select solid tumors, Cheson and modified Cheson criteria for DLBCL, or RANO and modified RANO criteria for subjects with glioblastoma. OS will be evaluated for solid tumors and DLBCL cohorts. ORR and PFS will be assessed for glioblastoma per modified RANO.
- **Safety:** All subjects who receive at least 1 dose of epacadostat or nivolumab will be assessed for safety by monitoring the frequency and severity of AEs, SAEs, and deaths.

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[redacted]

4.3. Measures Taken to Avoid Bias

The measurement of most toxicities using the CTCAE v4.0 and assessment of tumor size using the RECIST v1.1 and modified RECIST criteria, Cheson and modified Cheson criteria, or RANO and modified RANO criteria represent objective endpoints.

4.4. Number of Subjects

There will be approximately up to 207 subjects enrolled in Phase 1 of the study and up to approximately 278 subjects enrolled in Phase 2 for a total of approximately 485 subjects enrolled.

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4.5. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB or IEC in writing of the study's completion or early termination, and send a copy of the notification to the sponsor or sponsor's designee and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, or if required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT OF SUBJECTS

5.1. Administration of Study Drugs

5.1.1. Epacadostat

Subjects in Phase 1 Part 1 of the study will be administered epacadostat according to cohort enrollment (Table 1). The starting dose of epacadostat for combination immunotherapy cohorts is 25 mg BID daily.

Subjects enrolled in Phase 2 will receive the RP2D epacadostat determined in Phase 1 Part 1. (Note: Subjects enrolled into I/O-refractory and I/O-relapsed MEL cohorts in Phase 2 will be administered epacadostat 100 mg BID).

Subjects enrolled in Phase 1 Part 2 of the study will be administered the starting dose of epacadostat 100 mg BID continuously during 21-day cycles (every 3 weeks; Figure 2).

All BID doses of epacadostat will be taken orally morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual time. Doses of epacadostat will be self-administered except on the days scheduled to be given at the study clinic (see Section 7.6.1). Epacadostat will be given daily in combination with nivolumab as long as subjects are receiving benefit from treatment and have not met any criteria for study withdrawal. Intrasubject dose escalation of epacadostat is not permitted.

5.1.2. Nivolumab

All subjects enrolled in Phase 1 Part 1 will receive nivolumab 3 mg/kg via 60-minute IV infusion every 2 weeks on Days 1, 15, 29, and 43 of each 8-week cycle.

Subjects enrolled in Phase 1 Part 2 will receive nivolumab 360 mg via a 30-minute IV infusion on Day 1 of each 21-day cycle.

Subjects enrolled in Phase 2 will receive nivolumab 240 mg via 30-minute IV infusion every 2 weeks on Days 1, 15, 29, and 43 of each 8-week cycle.

Subject enrolled in the I/O-relapsed and I/O-refractory MEL cohorts of Phase 2 will receive nivolumab 480 mg via a 30-minute IV infusion every 4 weeks on Days 1 and Day 29 of each 8-week cycle. Nivolumab doses and schedules are summarized in Table 5.

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Subjects will continue to receive nivolumab as long as the subject is deriving benefit and has not met any Protocol-defined criteria for study treatment withdrawal. Intrasubject dose escalation of nivolumab is not permitted.

Table 5: Nivolumab Doses and Schedules in Phase 1 and Phase 2

Study Phases and Cohorts	Phase 1		Phase 2	
	Part 1 – dose-finding for combination immunotherapy cohorts	Part 2 – dose-finding for combination chemo-immunotherapy cohorts and safety expansion cohorts	Select tumor cohorts for combination immunotherapy	I/O-relapsed and I/O-refractory MEL cohorts
Nivolumab (Dose, schedule, infusion duration, cycle length)	3 mg/kg, Q2W 60 min IV 8-week cycle	360 mg, Q3W 30 min IV 21-day cycle	240 mg, Q2W 30 min IV 8-week cycle	480 mg Q4W 30 min IV 8-week cycle

In Phase 1 Part 1, the dose amount required to prepare the nivolumab infusion solution will be based on the subject's weight in kilograms. If the subject's weight on the day of administration differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

Details on the dose calculation, preparation, and administration are provided in the Pharmacy Manual.

5.1.2.1. Timing of Dose Administration of Nivolumab

Nivolumab should be administered after all procedures/assessments have been completed as detailed in the schedule of assessments (Section 6). All study treatments will be administered on an outpatient basis.

Nivolumab will be administered as a 30- or 60-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 or 60 minutes as possible. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline. On days when epacadostat is administered in the clinic, epacadostat should be taken just before beginning the infusion of nivolumab. Subjects who are enrolled in the combination chemo-immunotherapy cohorts must take chemotherapy IV after nivolumab infusion is completed. There should be approximately 30 minutes between the completion of nivolumab infusion and start of applicable chemotherapy infusion. Subjects may be administered nivolumab with no less than 11 days between doses and no more than 3 days after the scheduled administration date. Dose given after the 3-day window is considered a dose delay. A maximum delay of 42 days between doses is allowed. If the delay is greater than 42 days, this must be discussed with medical monitor.

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5.2. Background Therapies

5.2.1. Paclitaxel/Platinum (Carboplatin or Cisplatin)

5.2.1.1. Description and Administration

Subjects will receive paclitaxel 200 mg/m^2 IV over 3 hours (± 15 min) and either carboplatin AUC 6 IV over 30 minutes (± 5 min) or cisplatin 100 mg/m^2 IV on Day 1 of each 21-day cycle for a minimum of 4 cycles and up to 6 cycles.

Subjects must receive the following premedications: 1) dexamethasone 20 mg PO 12 hours and 6 hours before or dexamethasone 16 mg to 20 mg IV 30 minutes before, 2) chlorphenamine 10 mg IV 30 minutes before, and 3) ranitidine 50 mg IV 30 minutes before paclitaxel administration.

Epacadostat and nivolumab will be administered before premedications and IV chemotherapy. Premedications should be administered approximately 30 minutes (as applicable) following completion of the nivolumab infusion. The infusion of paclitaxel should be completed before beginning the infusion of cisplatin or carboplatin. Premedications may be adjusted based on institutional guidelines, investigator practice, or availability of similar medications on the investigative site's formulary.

Subjects must meet minimum criteria for the initiation of each chemotherapy cycle as outlined in Appendix I, Section I.1.

Sites will be instructed to consult local prescribing information for additional information and instructions for preparation and infusion of paclitaxel and cisplatin or carboplatin.

Subjects may receive prophylactic G-CSF support with filgrastim according to investigators discretion or per institutional guidelines, or when chemotherapy is held due to neutropenia. Granulocyte-colony stimulating factor should not be given in Cycle 1.

5.2.1.2. Supply, Packaging, and Labeling

In countries where paclitaxel, carboplatin, cisplatin, or their generic equivalents are commercially available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Study sponsor may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to any study-required therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.2.2. Pemetrexed/Platinum (Carboplatin or Cisplatin)

5.2.2.1. Description and Administration

Subjects will receive pemetrexed 500 mg/m^2 IV over 10 minutes (± 5 min) and either carboplatin AUC 5 IV over 30 minutes (± 5 min) or cisplatin 100 mg/m^2 IV on Day 1 of each 21-day cycle for a minimum 4 cycles and up to 6 cycles. Pemetrexed may continue as maintenance therapy after the 6 cycles.

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Subjects must also receive 1) dexamethasone 4 mg PO BID (or equivalent) taken the day before, the day of, and the day after pemetrexed administration; 2) folic acid 400 µg to 1000 µg PO once daily beginning 7 days before the first dose of pemetrexed and continued through the full course of therapy and for 21 days after the last dose of pemetrexed; and 3) vitamin B_{12} 1 mg intramuscularly 1 week before the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with pemetrexed.

Epacadostat and nivolumab will be administered before premedications and IV chemotherapy regimen. Premedications should be administered approximately 30 minutes (as applicable) after completion of the nivolumab infusion.

Premedications may be adjusted based on institutional guidelines, investigator practice, or availability of similar medications on the investigative site's formulary.

Subjects must meet minimum criteria for the initiation of each chemotherapy cycle as outlined in Appendix J, Section J.1.

Sites are instructed to consult local prescribing information for additional information and instructions for preparation and infusion of pemetrexed with cisplatin or carboplatin.

Subjects may receive prophylactic G-CSF support with filgrastim according to investigators discretion or per institutional guidelines, or when chemotherapy is held due to neutropenia. Granulocyte-colony stimulating factor should not be given in Cycle 1.

5.2.2.2. Supply, Packaging, and Labeling

In countries where pemetrexed, carboplatin, cisplatin, or their generic equivalents are commercially available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Study sponsor may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to any study-required therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.2.3. Platinum (Carboplatin or Cisplatin)/5-Fluorouracil

5.2.3.1. Description and Administration

Subjects will receive carboplatin AUC 5 IV over 30 minutes (± 5 min) or cisplatin 100 mg/m^2 IV on Day 1 of each cycle, followed by 5-FU 1000 mg/m^2 IV continuous infusion over 4 days for a total dose of 4000 mg/m^2. Subjects will be administered with this chemotherapy regimen for up to 6 cycles.

Epacadostat and nivolumab will be administered before IV chemotherapy regimen. Chemotherapy infusion will be initiated approximately 30 minutes following the completion of the nivolumab infusion. Subjects must meet minimum criteria for the initiation of each chemotherapy cycle as outlined in Appendix K, Section K.1.

Premedications, including corticosteroids, may be given based on institutional guidelines, study investigator practice, or availability of similar medications on the investigative site's formulary.

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Sites will be instructed to consult local prescribing information for additional information and instructions for preparation and infusion of carboplatin, cisplatin, and 5-FU.

Subjects may receive prophylactic G-CSF support with filgrastim according to investigators discretion or per institutional guidelines, or when chemotherapy is held due to neutropenia. Granulocyte-colony stimulating factor should not be given in Cycle 1.

5.2.3.2. Supply, Packaging, and Labeling

In countries where carboplatin, cisplatin, 5-FU, or their generic equivalents are commercially available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Study sponsor may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to any study-required therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.3. Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Subjects will bring all bottles of unopened, empty, and unused study drug with them to each study visit. Investigative site staff will perform a count of returned tablets to assess compliance, and this information will be entered into the electronic case report form (eCRF). Bottles of study drug, including all bottles of unopened, partially opened, or empty bottles cannot be destroyed or returned to the depot until a monitor reviews and verifies all tablet counts for compliance. Compliance with nivolumab will also be documented in the medical record and monitored by the sponsor or its designee.

5-Fluorouracil, carboplatin, cisplatin, paclitaxel, and pemetrexed are administered as an IV infusion by site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor/designee.

5.4. Randomization and Blinding

Not applicable.

5.5. Duration of Treatment and Subject Participation

Each subject enrolled in the study will continue receiving study treatment for up to 2 years in continuous 8-week cycles for combination immunotherapy or 21-day cycles for combination chemo-immunotherapy and may continue as long as the subject is receiving benefit from treatment and has not met any criteria for study withdrawal. If the subject discontinues all study treatment, the treatment period will end, and the subject will enter the safety follow-up period (see Section 6.4).

Individual subject participation will be approximately 12 to 18 months for Phase 1 and approximately 42 months for Phase 2 for a total of 60 months.

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5.6. Rationale for Dose Modifications

The purpose of the dose-escalation in Phase 1 Part 1 is to establish a suitable dose of epacadostat in combination with nivolumab. Thus, toxicities during the first 42 days of treatment will be used to define tolerability.

Modifications to epacadostat dose regimens are planned for Phase 1 Part 2 combination chemo-immunotherapy cohorts. Independent of the determination of tolerability during Phase 1 Part 1 or Part 2, subjects may require individual modification of epacadostat or nivolumab in Part 1 or modifications of epacadostat, nivolumab, or chemotherapy regimen if necessitated by drug-related or unrelated AEs, including irAEs or DLTs. Dose modifications are summarized in Section 5.7.1.

5.6.1. Definition of Dose-Limiting Toxicities

A DLT will be defined as the occurrence of any treatment-emergent AE in Table 6 occurring up to and including study Day 42 (6-week observation period) in Phase 1 Parts 1 and 2. Dose-limiting toxicities include all treatment-emergent AEs of the specified grades, regardless of investigator attribution or relatedness.

Only toxicities with a clear alternative explanation (eg, due to disease progression); transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination; or irAEs of Grade 3 or higher that improve to Grade 1 or lower by appropriate care or corticosteroid therapy within 14 days after the initiation of supportive care can be deemed a non-DLT.

For the purpose of making decisions on dose escalation from a safety perspective during the DLT observation period, subjects will be considered evaluable for dose tolerability if they meet 1 of the following criteria:

- In Phase 1 Part 1, subjects must have received at least 2 out of the 3 scheduled nivolumab doses (only if the 1 missed dose was secondary to nonmedical reasons) and must have received at least 75% of the cohort-specified dose of epacadostat through the 6-week (42-day) DLT observation period.
- In Phase 1 Part 2, subjects must have received at least 2 doses of the scheduled nivolumab doses, 75% of planned doses of chemotherapy regimen (only if the 1 missed dose was secondary to nonmedical reasons), and at least 75% of the cohort-specified dose of epacadostat in C1D1 during the DLT observation period.

In addition, subjects with dose delays of > 1 week for non-DLT events during the DLT observation period will be considered not evaluable for making decisions on dose-escalation cohorts or dose de-escalation cohorts and should be replaced.

Dose escalation (combination immunotherapy) or de-escalation (combination chemo-immunotherapy) of epacadostat will be based on the number of DLTs experienced during the DLT observation period. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor.

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Table 6: Criteria for Defining Dose-Limiting Toxicities

Toxicity
Hematologic Toxicities: • Any Grade 4 (life-threatening) thrombocytopenia or neutropenia lasting > 7 days. • Febrile neutropenia ≥ Grade 3 for 72 hours. • ≥ Grade 3 hemolysis. • Grade 4 (life-threatening) anemia not explained by underlying disease. • ≥ Grade 3 thrombocytopenia with clinically significant bleeding or requirement for a transfusion.
Nonhematologic Toxicities: • Any Grade 4 (life-threatening) irAE. • Grade 4 (life-threatening) nausea, vomiting, or diarrhea. • Grade 4 (life-threatening) electrolyte abnormality, regardless of duration or response to management. • Any ≥ Grade 3 AST, ALT, or total bilirubin elevation. • Grade 2 AST or ALT with symptomatic liver inflammation. • AST or ALT > 3 × ULN and concurrent total bilirubin > 2 × ULN without initial findings of cholestasis. • Any other ≥ Grade 3 toxicity EXCLUDING the following: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Grade 3 nausea/vomiting controlled by medical intervention within 48 hours. – Episcleritis, uveitis, or iritis of Grade 2 or higher. – Grade 3 rash in the absence of desquamation, without mucosal involvement, and not requiring systemic steroids and that resolves to Grade 1 by the next scheduled dose of nivolumab or ≤ 14 days, whichever is longer. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptomatic changes in lipid profiles. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions). – irAEs of Grade 3 or higher that improve to ≤ Grade 1 in ≤ 14 days by appropriate care or with corticosteroid therapy.

5.6.1.1. Procedures for Cohort Review and Dose Escalation

Telephone conferences will be scheduled by the sponsor with Phase 1 investigators in order to review cohort-specific data, overall safety data from prior cohorts (if applicable), and to agree on dose escalation. For additional safety oversight, this group will review and adjudicate individual high-grade AEs as potentially dose limiting and for guiding the study team on decisions regarding dose escalation and cohort expansion. The same method will be used for reviewing data at the end of the dose-escalation portion of the study to determine the recommended dose for the dose-expansion portion of the study.

5.6.1.2. Follow-Up for Dose-Limiting Toxicities

Subjects whose treatment is discontinued because of a DLT must be followed until resolution or stabilization of the DLT event, whichever comes first.

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5.7. Dose Modification of Study Drugs

5.7.1. Planned Dose Modifications

Intrasubject dose escalations are not permitted. Subjects will remain on their cohort-assigned dose, or a lower dose of epacadostat if required because of AEs, throughout the treatment and extension phases. Table 7 describes epacadostat dose reductions that may occur due to any related AEs.

There will be no dose reductions of nivolumab allowed for the management of toxicities of individual subjects. Doses of nivolumab may be delayed for toxicity management.

In combination chemo-immunotherapy cohorts, if cisplatin is selected as a part of a specific chemotherapy regimen, then the cisplatin starting dose will be 100 mg/m^2 at C1D1. However, if a subject develops ≥ Grade 3 nausea and/or vomiting that prevents administration of the daily epacadostat doses for more than 3 days within that cycle, then the cisplatin dose may be de-escalated to 75 mg/mg^2 starting on C2D1, with the medical monitor's approval. Once the cisplatin dose is reduced to 75 mg/m^2, it should remain reduced at subsequent doses and cycles. No dose escalation of cisplatin and/or any other chemotherapy drugs is permitted.

Table 7: Dose Reductions of Epacadostat

Current Dose	Dose Reduction
300 mg BID	100 mg BID
100 mg BID	50 mg BID
50 mg BID	25 mg BID

5.7.2. Criteria and Procedures for Interruption

In some circumstances, it may be necessary to temporarily interrupt study treatments as a result of AEs that may have an unclear relationship to the study drug(s). If an interruption is necessary, both study treatments should be interrupted.

Any dose interruptions of > 2 weeks for LFT abnormalities must be discussed with the medical monitor before resuming treatment. Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, nonhematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs.

Table 8 summarizes the dose administration guidance for nivolumab and epacadostat that should be implemented with the indicated drug-related AEs. Additional information related to dose changes for epacadostat and nivolumab for specific AEs can be found in Section 5.7.3 for irAEs and Section 5.7.4 for an AE of SS. Additional guidance for the management and follow-up for specific irAE can be found in Appendix C. For all dose decisions for nivolumab, Appendix C should be followed for those specific events of clinical interest. In the event guidance in Appendix C differs from Section 5.7.3, then Appendix C should be followed for any decision on dose administration for nivolumab and Section 5.7.3 should be followed for decisions on dose administration for epacadostat.

Except in cases of emergency, it is recommended that the investigator consult with the sponsor's medical monitor (or other representative of the sponsor) before temporarily interrupting therapy

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for reasons other than Protocol-mandated medication hold. Additionally, the investigator must notify the sponsor's medical monitor and study project manager via email or during safety teleconferences before restarting study drug that was temporarily interrupted because of an AE.

Dose modifications for hematologic and nonhematologic AEs related to chemotherapy may be managed per institutional guidelines. In the absence of these guidelines, recommendations for dose modifications for epacadostat, nivolumab, and applicable chemotherapy doublet regimen in the event of hematologic and nonhematologic AEs are provided in the Protocol appendices:

- Appendix I for subjects who receive paclitaxel/platinum
- Appendix J for subjects who receive pemetrexed/platinum
- Appendix K for subjects who receive platinum/5-FU

It is important to note that some AEs will overlap with potential irAEs. In these cases, both the AE and irAE guidance within the applicable appendix should be reviewed to determine the most appropriate management of study medications.

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Table 8: Dose Modification Guidelines for Drug-Related Adverse Events for Combination Immunotherapy

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Treatment Restart	Dose/Schedule for Treatment Restart		Discontinue Subject (After Medical Monitor Consultation)
				Epacadostat	Nivolumab	
Hematologic toxicity	1, 2, 3	No	N/A	N/A	N/A	N/A
	4	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Reduce dose by 1 dose level.	Restart at same dose for the following events: Grade 4 neutropenia lasting ≤ 7 days, Grade 4 lymphopenia or leukopenia. For all other Grade 4 Hematologic toxicities, treatment with nivolumab may not be restarted. (Note: In case nivolumab is discontinued permanently, epacadostat should be discontinued as well.)	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation should be considered for any severe or life-threatening event.

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Table 8: Dose Modification Guidelines for Drug-Related Adverse Events for Combination Immunotherapy (Continued)

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Treatment Restart	Dose/Schedule for Treatment Restart		Discontinue Subject (After Medical Monitor Consultation)
				Epacadostat	Nivolumab	
Nonhematologic toxicity Note: Exception to be treated to similar Grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue • Grade 3 rash in the absence of desquamation, without mucosal involvement, and not requiring systemic steroids and that resolves to Grade 1 within 14 days For additional information regarding AE with potential immune etiology, see Section 5.7.3.	1	No	N/A	N/A	N/A	N/A
	2	Consider holding for persistent symptoms	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose.	Restart at same dose.	Toxicity does not resolve within 6 weeks of last infusion.
	3[a]	Yes[a]	Toxicity resolves to ≤ Grade 1 or baseline	Restart at 1 dose level lower.	Restart at same dose.[a]	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation should be considered for any severe or life-threatening event.
	4	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Restart at 1 dose level lower.	Restart only as noted.[b] For all other Grade 4 nonhematologic toxicities, treatment with nivolumab may not be restarted. (Note: In case nivolumab is discontinued permanently, epacadostat should be discontinued as well.)	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation should be considered for any severe or life-threatening event.

Note: Subjects who experience a recurrence of the same severe or life-threatening AE at the same grade or greater treatment should be discontinued from study treatment.

[a] The following exceptions for asymptomatic amylase or lipase do not require a dose delay: Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the medical monitor for Grade 3 amylase or lipase abnormalities.

[b] Isolated Grade 4 lipase or amylase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. Medical monitor should be consulted for any G4 amylase or lipase abnormality.

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5.7.3. Procedures for Subjects Exhibiting Immune-Related Adverse Events

This section is meant to apply to suspected irAEs from epacadostat, nivolumab or the combination.

Immune-related AEs may be defined as an AE of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the nivolumab or epacadostat compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE. Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the sponsor.

General recommendations to managing irAEs not detailed elsewhere in the Protocol are detailed in Table 9. Recommendations for management of specific immune-mediated AEs such as pneumonitis (Section 5.7.3.1), enterocolitis (Section 5.7.3.2), hepatitis (Section 5.7.3.3), dermatitis (Section 5.7.3.4), neuropathies (Section 5.7.3.5), endocrinopathies (Section 5.7.3.6), and other immune-mediated AEs (Section 5.7.3.7) are detailed in the sections below and specific guidance related to immune toxicity management and follow-up related to nivolumab can be found in Appendix C.

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Table 9: General Approach to Handling Immune-Related Adverse Events

irAE	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold nivolumab and epacadostat per investigator's discretion.	May return to treatment if improves to Grade 1 or resolves within 6 weeks. If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3	Withhold or discontinue nivolumab and epacadostat. Discontinue if unable to reduce corticosteroid dose to < 10 mg/day of prednisone or equivalent within 6 weeks of toxicity.	Any restart of study treatment must be discussed with medical monitor before restarting treatment.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to prednisone 2 mg/kg or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.
Grade 4	Discontinue nivolumab and/or epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to prednisone 2 mg/kg or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.

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5.7.3.1. Procedures and Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving nivolumab and epacadostat and have an evaluation. The evaluation may include bronchoscopy to rule out other causes such as infection. If the subject is determined to have study drug–associated pneumonitis, the suggested treatment plan is detailed in Table 10.

Table 10: Recommended Approach to Handling Noninfectious Pneumonitis

Study Drug(s) Associated Pneumonitis	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1 (asymptomatic)	No action.	Not applicable.	Intervention not indicated.[a]
Grade 2	Withhold nivolumab and epacadostat.	**First episode of pneumonitis:** • If improves to near baseline: – Decrease the dose of epacadostat by 1 dose level, and for nivolumab, restart at same dose and schedule for subsequent cycles. • If not improved after 2 weeks or worsening permanently, discontinue nivolumab. Discuss with medical monitor if restart with epacadostat is permitted. (Note: In case nivolumab is discontinued permanently, epacadostat should be discontinued as well.) **Second episode of pneumonitis:** • Permanently discontinue nivolumab and epacadostat if upon rechallenge subject develops pneumonitis ≥ Grade 2.	Systemic corticosteroids are indicated. Taper if necessary.[a]
Grades 3 and 4	Discontinue nivolumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. See Appendix C for additional recommendations.

[a] See Appendix C for additional guidance.

5.7.3.2. Procedures and Guidance for Enterocolitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out and endoscopic evaluation should be considered for persistent or severe symptoms. Recommendations for management of enterocolitis are shown in Table 11 as well as additional information in Appendix C.

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Table 11: Recommended Approach for Handling Enterocolitis

Study Drug(s) Associated Enterocolitis	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. An antidiarrheal can be started.
Grade 2	Withhold nivolumab and epacadostat.	May return to treatment if improves to Grade 1. If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	An antidiarrheal should be started. If symptoms are persistent for > 1 week, systemic corticosteroids should be initiated (eg, 0.5-1 mg/kg per day of prednisone or equivalent). When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.
Grades 3 and 4	Discontinue nivolumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.

5.7.3.3. Procedures and Guidance for Hepatitis

Liver chemistry tests (hepatic transaminase and bilirubin levels) should be monitored and signs and symptoms of hepatotoxicity should be assessed before each dose of nivolumab and epacadostat. In subjects with hepatotoxicity, infectious or malignant causes should be ruled out and frequency of LFT monitoring should be increased until resolution. Recommendations for management of hepatitis are shown in Table 12 as well as additional information for management and follow-up in Appendix C. See Section 8.2.2 for reporting requirements for certain cases that may be considered SAEs.

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Table 12: Recommended Approach for Handling Hepatitis

Study Drug(s) Associated Hepatitis	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline.
Grade 2	Withhold nivolumab and epacadostat.	If AE resolves to ≤ Grade 1 or baseline within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued.	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline. If elevation persists for > 1 week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg per day of prednisone or equivalent). When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.
Grades 3 and 4	Discontinue nivolumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Increase frequency of LFT monitoring to every 1-2 days. Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.

5.7.3.4. Procedures for Immune-Mediated Dermatitis

Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune mediated. Recommendations for management of dermatitis are shown in Table 13 as well as additional information for management and follow-up in Appendix C.

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Table 13: Recommended Approach for Handling Dermatitis

irAE	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grade 2	No action.	Not applicable.	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grades 3 and 4	Withhold epacadostat and /or nivolumab in subjects with moderate to severe signs and symptoms of rash. Permanently discontinue epacadostat and nivolumab in subjects with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or by necrotic, bullous, or hemorrhagic manifestations.	If AE resolves to baseline within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Administer systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.

5.7.3.5. Procedures for Immune-Mediated Neuropathies

Subjects should be monitored for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Recommendations for management of neuropathies are shown in Table 14 as well as additional information for management and follow-up in Appendix C.

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Table 14: Recommended Approach for Handling Neuropathies

irAE	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold nivolumab and epacadostat.	If AE resolves to ≤ Grade 1 or baseline within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grades 3 and 4	Discontinue nivolumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day prednisone or equivalent for severe neuropathies. Institute medical intervention as appropriate for management of severe neuropathy.

5.7.3.6. Procedures for Immune-Mediated Endocrinopathies

Subjects should be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension or with nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Thyroid function tests and clinical chemistries should be monitored at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of subjects, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Recommendations for management of endocrinopathies are shown in Table 15. For additional information on detailed management of asymptomatic thyroid-stimulating hormone (TSH) elevation versus symptomatic endocrinopathy, see Appendix C.

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Table 15: Recommended Approach for Handling Endocrinopathies

irAE	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold nivolumab and epacadostat.	If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued.	Initiate systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.
Grade 3	Withhold or discontinue both nivolumab and epacadostat.	If AE resolves or is controlled within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Consider initiating systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.
Grade 4	Discontinue both nivolumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.

5.7.3.7. Procedures for Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

Epacadostat and nivolumab should be permanently discontinued for severe immune-mediated adverse reactions. Systemic corticosteroids treatment should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent for severe immune-mediated adverse reactions.

Corticosteroid eye drops should be administered to subjects who develop uveitis, iritis, or episcleritis. Epacadostat and nivolumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

For additional management and follow-up guidance for renal immune events see Appendix C.

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5.7.4. Procedures for Subjects Exhibiting Serotonin Syndrome

As noted in Section 1.3, there is a chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS (Boyer and Shannon 2005) when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, meperidine/pethidine, linezolid, or methylene blue; all of these agents are prohibited during the study. Serotonin reuptake inhibitors and SNRIs are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in Table 16) should be evaluated in the context of possible comorbid conditions as well.

The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Table 16, including tremor, hyperreflexia, spontaneous, ocular, or inducible clonus, together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt study treatment administration.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If etiologies other than serotonin syndrome are excluded, nivolumab administration may be resumed unless other AE management guidelines apply for the specific event.
- If subject chooses to remain in the study, restart treatment with epacadostat after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question and after resolution of signs/symptoms of SS. The SSRI or SNRI treatment MAY NOT be restarted.
- If subject chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If a subject has experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI or SNRI usage, or serotonergic concomitant medications, only nivolumab administration may be resumed; epacadostat treatment should be permanently discontinued.

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Table 16: Signs and Symptoms of Serotonin Syndrome

Seriousness	Autonomic Signs	Neurological Signs	Mental Status	Other
Mild	Afebrile or low-grade fever Tachycardia Mydriasis Diaphoresis or shivering	Intermittent tremor Akathisia Myoclonus Mild hyperreflexia	Restlessness Anxiety	
Moderate	Increased tachycardia Fever (up to 41 °C) Diarrhea with hyperactive bowel sounds Diaphoresis with normal skin color	Hyperreflexia Inducible clonus Ocular clonus (slow continuous lateral eye movements) Myoclonus	Easily startled Increased confusion Agitation and hypervigilance	Rhabdomyolysis Metabolic acidosis Renal failure Disseminated intravascular coagulopathy (secondary to hyperthermia)
Severe	Temperature often more than 41°C (Secondary to increased tone)	Increased muscle tone (lower limb > upper) Spontaneous clonus Substantial myoclonus or hyperreflexia	Delirium Coma	As above

Source: Boyer and Shannon 2005.

5.8. Criteria for Permanent Discontinuation of Study Drug(s)

Subjects may withdraw consent at any time for any reason or be withdrawn from the study at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.7.7, Withdrawal or Discontinuation.

Subjects must be withdrawn from the study treatment for the following reasons:

- In the investigator's medical judgment, further participation would be injurious to the subject's health or well-being.
- The subject becomes pregnant.
- Consent is withdrawn by the subject or legal representative (such as parent or legal guardian).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB/IEC.
- Radiographic progression of disease per RECIST (Appendix E), Cheson (Appendix F), or RANO (Appendix H). See Section 7.5.

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- The subject has experienced an unacceptable toxicity or a toxicity that does not recover in 6 weeks. Investigators who wish to continue treatment after a treatment delay of 4 weeks should consult with the sponsor's medical monitor for approval.
- Noncompliance with study treatment or procedure requirements.
- The subject is lost to follow-up.
- The subject has received study treatment for 2 years (ie, 2 years have elapsed since Cycle 1 Day 1).

A subject may be discontinued from study treatment as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, then the sponsor should be consulted for instruction on handling the subject.

The EOT and follow-up visit procedures are listed in Section 6 (Table 20 and Table 24). After the EOT, each subject will be followed for 2 safety follow-up visits at 30 and 100 days after the last dose of combination treatment for AE and SAE monitoring as described in Section 8.3.2.

5.9. Study Completion

5.9.1. Study Completion Criteria

Subjects will be considered completing the study if they met any of the following criteria:

- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained. (NOTE: every effort must be made to obtain the date of death.)
- Subject completes the 100-day safety follow-up period.
- Consent is withdrawn for any further contact related to this study.
  - Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.

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5.9.2. Withdrawal Procedures

In the event that any subject discontinues study drug and, subsequently, withdraws from the study before completion, regardless of reason, reasonable efforts should be made to have the subject return for the EOT procedures to be completed as described in Section 6.3. The date the subject was withdrawn from the study and the specific reason for withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT or early termination visit should be performed.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

5.10. Beginning and End of the Study

The study begins when the first subject signs the informed consent. The end of the study may be designated as the timepoint when all subjects have discontinued the study or are a minimum of 6 months after initial study medication administration. If by the end of the study there remains at least 1 subject still on study treatment for at least 6 months, the subject(s) may enter additional treatment cycles. At this point a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study medication per Protocol. The subject is considered on study until such time that he/she meets any of the study completion criteria and written notification is given to the sponsor.

5.11. Concomitant Medications and Measures

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for 1 of these or other medications or vaccinations specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study therapy or vaccination schedule requires the mutual agreement of the investigator, the sponsor, and the subject.

5.11.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug regimen, frequency, route, and date may also be included on the eCRF.

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All concomitant medications received within 28 days before C1D1 and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs and AEs as defined in Section 8.

5.11.2. Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator, including, but not limited to, the items outlined below:

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related AEs: See Section 5.7.3 regarding diagnosis and management of adverse experiences of a potential immunologic etiology.
- Management of infusion reactions from nivolumab (Section 5.11.3).

5.11.3. Management of Infusion Reactions From Nivolumab

Since nivolumab contains only human Ig protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions (current rate of reported infusion reactions for nivolumab 3 mg/kg is 6% [3/54] for any Grade, and 0 Grade 3 or 4 infusion reactions have been reported). However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) CTCAE (version 4.0) guidelines. In Phase 2, for those experiencing an infusion reaction, infusion time may be increased to 60 minutes.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (or acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≥ 24 hours)

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Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (or acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (or acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine, and H_2 antagonists (such as cimetidine or ranitidine) using applicable institutional guidelines. Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Subjects who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

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5.12. Restricted Medications and Measures

- Systemic steroids may be used at doses < 10 mg/day, and prednisone or equivalents with medical monitor approval.
- Use of coumarin-based anticoagulants (eg, warfarin) is discouraged. Low-dose warfarin (1 mg) is acceptable; however, doses that increase the INR are discouraged and will require dose modification. If an alternative to coumarin-based anticoagulants cannot be used, dose modifications of the warfarin may be needed. Based on the observed magnitude of epacadostat/warfarin PK interaction and PK/pharmacodynamic modeling results, for an epacadostat dose of 300 mg BID, the dose of warfarin should be reduced by approximately one-third after initiation of epacadostat administration based on approximately 30% to 40% reduction in S- and R-warfarin oral clearance values. Close INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat. Based on PK/pharmacodynamic modeling, recommendations for warfarin dose modifications for subjects receiving other epacadostat doses, are summarized in Table 17 based on the INR before starting epacadostat.

Table 17: Warfarin Dose Adjustment Recommendation When Initiating Concurrent Epacadostat Treatment

Stable Baseline INR	Epacadostat Dose		
	≤ 100 mg BID	200 mg BID	300 mg BID
INR ≤ 2.5	Close INR monitoring	Close INR monitoring	Reduce warfarin by ~33% and monitor INR
INR > 2.5	Close INR monitoring	Reduce warfarin by 20%-25% and monitor INR	Reduce warfarin by ~33% and monitor INR

- Use of the anticonvulsant carbamazepine (a UGT1A9 inducer) is discouraged. Because there is a potential interaction that could result in lower epacadostat exposures, an alternative to carbamazepine should be used, if possible.

5.13. Prohibited Medications and Measures

Subjects are prohibited from receiving the following therapies during the screening and treatment period of this study unless otherwise noted below:

- Any investigational medication other than the study drugs.
- Any anticancer medications, including chemotherapy or biologic therapy other than the study medications.
- Any immunological-based treatment for any reason.
  - Note: Inhaled or topical steroids are allowed, and systemic steroids at doses < 10 mg/day prednisone or equivalents are allowed with medical monitor approval, as described in Section 5.12, and immune suppressants are allowed for treatment for immune toxicities.

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  - For subjects with glioblastoma: Systemic corticosteroid use or physiologic replacement doses of steroids are permitted, even if > 10 mg/day prednisone equivalents, for: a) treatment-related AEs; b) sequelae of underlying glioblastoma treatment; or c) treatment of non-autoimmune conditions (such as prophylaxis for contrast dye allergy, delayed-type hypersensitivity reaction caused by contact allergen). Details regarding corticosteroid use before and during the study will be collected (name of medication, doses utilized, start and stop dates, frequency of use, route of administration). Information regarding concomitant corticosteroid use may be analyzed with regard to study outcome measures.

- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the sponsor's medical monitor.
- Administration of live attenuated vaccines within 30 days before C1D1 and while participating in the study is prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
- Administration of an injectable influenza vaccine is prohibited during the DLT observation period (ie, 42 days after C1D1).
- Any MAOI or drug associated with significant MAO inhibitory activity agents is prohibited from 21 days before Day 1 through 2 weeks after the final dose of epacadostat has been taken (see Appendix D).
- Any UGT1A9 inhibitor, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Subjects may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria (Section 3.3) describe other medications that are prohibited during this study. There are no prohibited therapies during the post-treatment follow-up period.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedules of assessments in Table 18 through Table 25. The order of assessments is suggested by the order of mention within the schedules. For instructions on each assessment, see Section 7. The required laboratory analytes are listed in Table 26.

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Table 18: Schedule of Assessments for Screening Through Treatment Period (Combination Immunotherapy Cohorts With Nivolumab Q2W Dosing Schedule)

		Treatment Period							
Visit Day (Range)	**Screening**	**C1D1**	**C1D8**	**Day 15, 29, and 43**	**C2D1**	**C2 Day 15, 29, 43**	**Day 1 All Subsequent Cycles**	**Day 15, 29, 43 All Subsequent Cycles**	**Every 12 Weeks**
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 7 Days**
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Prior medical and cancer history	X								
Concomitant medications review	X	X	X[a]	X	X	X	X	X	
Laboratory assessments	X	X		X	X	X	X	X	
Administer epacadostat at clinic		X		X[b]					
Administer nivolumab		X		X	X	X	X	X	
Comprehensive physical exam	X								
Targeted physical exam		X		X	X	X	X	X	
Vital signs and weight (height at screening only)	X	X		X	X	X	X	X	
12-lead ECG	X	X[c]		X[c]	X[d]		X[d]		
Reminder card		X		X	X	X	X	X	
AE assessment	X	X	X[a]	X	X	X	X	X	
Radiologic tumor assessments[e,f]	X								X[f]

[a] Concomitant medication and AE assessments for C1D8 will be collected by phone call.
[b] Epacadostat will need to be administered in the clinic on C1D1 and C1D15 only.
[c] The ECG should be performed within 60 to 90 minutes (unless emerging [redacted] data suggest alternate timing) after the first dose of epacadostat on C1D1 and C1D15 only. In addition, a predose ECG will be performed on C1D15.
[d] After C1D15, ECG need only be performed as clinically indicated.
[e] The same imaging technique should be used in a subject throughout the study. Local reading will be used to determine eligibility and for subject management.
[f] Imaging should be performed every 12 weeks (± 7 days) regardless of any treatment delays for up to 2 years after C1D1 and not be adjusted for delays in cycle starts or extension of combination treatment cycle frequencies.

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Table 19: Schedule of Assessments for Screening Through Treatment Period (Combination Immunotherapy Cohorts With Nivolumab Q4W Dosing Schedule)

		Treatment Period							
Visit Day (Range)	**Screening**	**C1D1**	**C1D15**	**C1D29**	**C2D1**	**C2D29**	**Day 1 All Subsequent Cycles**	**Day 29 All Subsequent Cycles**	**Every 12 Weeks**
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 7 Days**
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Prior medical and cancer history	X								
Concomitant medications review	X	X	X	X	X	X	X	X	
Laboratory assessments	X	X	X	X	X	X	X	X	
Administer epacadostat at clinic		X		X[a]					
Administer nivolumab		X		X	X	X	X	X	
Comprehensive physical exam	X								
Targeted physical exam		X		X	X	X	X	X	
Vital signs and weight (height at screening only)	X	X		X	X	X	X	X	
12-lead ECG	X	X[b]		X[b]	X[c]		X[c]		
Reminder card		X		X	X	X	X	X	
AE assessment	X	X	X	X	X	X	X	X	
Radiologic tumor assessments[d,e]	X								X[e]

[a] Epacadostat will need to be administered in the clinic on C1D1 and C1D29 only.
[b] The ECG should be performed within 60 to 90 minutes (unless emerging [redacted] data suggest alternate timing) after the first dose of epacadostat on C1D1 and C1D29 only. In addition, a predose ECG will be performed on C1D29.
[c] Starting from C2D1, ECG need only be performed as clinically indicated.
[d] The same imaging technique should be used in a subject throughout the study. Local reading will be used to determine eligibility and for subject management.
[e] Imaging should always be performed every 12 weeks (± 7 days) regardless of any treatment delays for up to 2 years after C1D1 and should not be adjusted for delays in cycle starts.

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Table 20: Schedule of Assessments End of Treatment Through Safety Follow-Up (Combination Immunotherapy Cohorts With Both Q2W and Q4W Nivolumab Dosing Schedules)

Visit Day (Range)	EOT	Safety Follow-Up Period[a]	
		30 Days After EOT or Last Dose of Nivolumab	100 Days After Last Dose of Nivolumab
Evaluation/Window	**+ 5 Days**	**± 7 Days**	**± 7 Days**
Concomitant medications review	X	X	X
Comprehensive physical exam			
Targeted physical exam	X	X	X
Vital signs and weight (height at screening only)	X		
AE assessment	X	X	X
Laboratory assessments[b]	X		

[a] Subjects must be followed for AEs and SAEs for 100 days after the last dose of study drug.
[b] Safety laboratory assessments will be collected at EOT.

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Table 21: Laboratory Assessments for Screening Through Treatment Period (Combination Immunotherapy Cohorts With Nivolumab Q2W Dosing Schedule)

		Treatment Period					
Visit Day (Range)	**Screening**	**C1D1**	**C1 Day 15, 29, and 43**	**C2D1**	**C2 Day 15, 29, 43**	**Day 1 All Subsequent Cycles**	**Day 15, 29, 43 All Subsequent Cycles**
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**
Chemistry	X	X[a]	X	X	X	X	X
Hematology	X	X[a]	X	X	X	X	X
Liver chemistry tests	X	X		X[b]		X	
Coagulation panel (PT, aPTT, INR)	X	X[a]					
Endocrine function testing	X	X[a]		X		X[c]	
Urinalysis	X						
Serum pregnancy	X[d]						
Urine pregnancy test[e]				X		X	
Serology for hepatitis B and hepatitis C testing[f]	X						

[redacted]

[a] C1D1 laboratory tests may be omitted if the screening laboratory tests were performed within 7 days before treatment initiation. If performed more than 7 days before study treatment initiation, screening laboratory tests must be repeated to confirm the subject's eligibility on C1D1.
[b] If LFTs are abnormal, twice weekly monitoring of LFTs are required until they return to baseline (LFTs include ALT, AST, and total bilirubin).
[c] To be repeated every other cycle.
[d] Serum pregnancy test required for women of child-bearing potential only and must be performed and confirmed negative within 72 hours before C1D1.
[e] Urine pregnancy should be repeated on Day 1 of each cycle or as required by local regulations.
[f] Hepatitis B and C serologies should be obtained for subjects without a known history of hepatitis B or C. Those with a known history are ineligible. See Table 26 for list of laboratory tests.

[redacted]

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Table 22: Laboratory Assessments for Screening Through Treatment Period (Combination Immunotherapy Cohorts With Nivolumab Q4W Dosing Schedule)

		Treatment Period						
Visit Day (Range)	**Screening**	**C1D1**	**C1D15**	**C1D29**	**C2D1**	**C2D29**	**Day 1 All Subsequent Cycles**	**Day 29 All Subsequent Cycles**
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**
Chemistry	X	X[a]	X	X	X	X	X	X
Hematology	X	X[a]	X	X	X	X	X	X
Liver chemistry tests	X	X	X		X[b]		X	
Coagulation panel (PT, aPTT, INR)	X	X[a]						
Endocrine function testing	X	X[a]			X		X[c]	
Urinalysis	X							
Serum pregnancy[d]	X							
Urine pregnancy test[e]					X		X	
Serology for hepatitis B and hepatitis C testing[f]	X							

[redacted]

[a] C1D1 laboratory tests may be omitted if the screening laboratory tests were performed within 7 days before treatment initiation. If performed more than 7 days before study treatment initiation, screening laboratory tests must be repeated to confirm the subject's eligibility on C1D1.
[b] If LFTs are abnormal, twice weekly monitoring of LFTs are required until they return to baseline (LFTs include ALT, AST, and total bilirubin).
[c] To be repeated every other cycle.
[d] Serum pregnancy test required for women of child-bearing potential only and must be performed and confirmed negative within 72 hours before C1D1.
[e] Urine pregnancy should be repeated on Day 1 of each cycle or as required by local regulations.
[f] Hepatitis B and C serologies should be obtained for subjects without a known history of hepatitis B or C. Those with a known history are ineligible. See Table 26 for list of laboratory tests.

[redacted]

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Table 23: Laboratory Assessments for End of Treatment Through Safety Follow-Up (Combination Immunotherapy Cohorts With Both Nivolumab Q2W and Q4W Dosing Schedules)

		Safety Follow-Up Period	
Visit Day (Range)	**EOT**	**30 Days After EOT or Last Dose of Nivolumab**	**100 Days After Last Dose of Nivolumab**
Evaluation/Window	**+ 5 Days**	**± 7 Days**	**± 7 Days**
Chemistry	X	X	
Liver chemistry testing	X	X	
Hematology	X	X	
Urine pregnancy test	X		
[redacted]			

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Table 24: Schedule of Assessments for Phase 1 Part 2 Subjects Treated With Epacadostat + Nivolumab (Q3W) + Platinum/Paclitaxel or Epacadostat + Nivolumab + Platinum/Pemetrexed or Epacadostat + Nivolumab + Platinum/5-FU (Combination Chemo-Immunotherapy Cohorts)

Visit	Screening	Treatment Period[a]							EOT	Follow-Up Period		Comments
		C1		C2		C3+		Q12W		Safety Follow-Up[b]		
		D1	D8	D1	D8	D1	D8					
Evaluation Window (Days)	**Day -28 to -1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**+5**	**30 Days After EOT ±7**	**100 Days After EOT ± 7**	
Administrative procedures												
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Prior medical and cancer history (tumor-specific)	X											
Concomitant medication review	X	X (continuous)								X	X	
Comprehensive physical exam	X											
Targeted physical exam		X		X		X			X	X	X	
12-lead ECG	X	X		X								ECG should be performed within 60 to 90 minutes after the first dose of epacadostat on C1D1 and C2D1 only. In addition, a predose ECG will be performed on C2D1. After C2D1, ECG need only be performed as clinically indicated.
Vital signs and weight (height at screening only)	X	X		X		X			X			
Reminder card		X	X	X	X	X	X		X	X	X	
AE assessment	X (continuous)									X	X	Subjects must be followed for AEs and SAEs throughout the study and for 100 days after the last dose of study drug.
Laboratory assessments	X	X	X	X	X	X	X		X	X		Laboratory assessments will be conducted on D1 of each cycle starting at Cycle 4 and will be performed before the administration of any study drug. Safety laboratory assessments will be collected at EOT and at the 30- and 100-day safety follow-up visits. [redacted]

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Table 24: Schedule of Assessments for Phase 1 Part 2 Subjects Treated With Epacadostat + Nivolumab (Q3W) + Platinum/Paclitaxel or Epacadostat + Nivolumab + Platinum/Pemetrexed or Epacadostat + Nivolumab + Platinum/5-FU (Combination Chemo-Immunotherapy Cohorts) (Continued)

Visit	Screening	Treatment Period[a]							EOT	Follow-Up Period		Comments
		C1		C2		C3+		Q12W		Safety Follow-Up[b]		
		D1	D8	D1	D8	D1	D8					
Evaluation Window (Days)	**Day -28 to -1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**+5**	**30 Days After EOT ±7**	**100 Days After EOT ± 7**	
Administer nivolumab		X		X		X						Nivolumab will be administered on D1 of every 3 week cycle (21 days).
Administer IV chemotherapy doublet		X		X		X						Epacadostat should be administered before the start of nivolumab infusion. Nivolumab should be administered before IV chemotherapy (5-FU/cisplatin, platinum/ paclitaxel or platinum/pemetrexed). Platinum/paclitaxel or platinum/pemetrexed should be administered for a minimum of 4 cycles and up to 6 cycles. Platinum/5-FU should be administered up to 6 cycles. 5-FU will be administered as continuous infusion over 4 days (starting on D1 and ending on D4) for up to 6 cycles.
Radiological tumor assessments	X							X				Imaging should be performed at 8 and 16 weeks after the start of treatment and every 12 weeks (± 7 days) thereafter for up to 2 years after C1D1 regardless of any treatment delays.

[a] Treatment cycles are every 21 days (± 3 days).
[b] The mandatory safety follow-up visits should be conducted approximately 30 days and 100 days after EOT or the last dose of nivolumab or before the initiation of a new anticancer treatment, whichever comes first.

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Table 25: Laboratory Assessments for Phase 1 Part 2 Subjects Treated With Epacadostat + Nivolumab (Q3W) + Platinum/Paclitaxel, Epacadostat + Nivolumab + Platinum/Pemetrexed or Epacadostat + Nivolumab + Platinum/5-FU (Combination Chemo-Immunotherapy Cohorts)

Visit	Screening[a]	Treatment Period[b]									EOT	Safety Follow-Up[c]		Comments
		Cycle 1			Cycle 2	Cycle 3+								
		D1	D8	D15	D1	D8	D15	D1	D8	D15		30 Days After EOT	100 Days After EOT	
Evaluation Window (Days)	**Day -28 to -1**	**±3**	**±3**		**±3**	**±3**		**±3**			**+7**	**±7**	**±7**	
Laboratory assessments[d]														
Comprehensive serum chemistry	X	X[e]	X		X	X		X	X		X	X		Beginning with Cycle 4, laboratory assessments may be performed on D1 of each subsequent cycle as clinically indicated (see Section 7.4.6)
Hematology with differential	X	X[e]	X		X	X		X	X		X	X		Beginning with Cycle 4, laboratory assessments may be performed on D1 of each subsequent cycle as clinically indicated (see Section 7.4.6).
Liver chemistry tests	X	X	X		X	X		X	X		X	X		Beginning with Cycle 4, LFTs will be performed on D1 of every cycle, at EOT, and at the 30-day safety follow-up visit. Additional assessment of LFTs with differential may be conducted as clinically indicated.
Coagulation panel	X	X[e]												
Endocrine function tests	X	X[e]			X			X			X			After C3D1 every third cycle (at C6, C9, etc), performed every 12 weeks.
Urinalysis	X													
Serum pregnancy test (childbearing females only)	X													A serum pregnancy test is required for all women of childbearing potential during screening and must be within 72 hours before the first dose of study treatment.
Urine pregnancy test (childbearing females only)					X			X			X			Urine pregnancy should be repeated on D1 of each cycle or as required by local regulations.
Serology for hepatitis B and C testing	X													Hepatitis B and C serologies should be obtained for subjects without a known history of hepatitis B or C. Those with a known history are ineligible. See Table 26 for list of laboratory tests.

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Table 25: Laboratory Assessments for Phase 1 Part 2 Subjects Treated With Epacadostat + Nivolumab (Q3W) + Platinum/Paclitaxel, Epacadostat + Nivolumab + Platinum/Pemetrexed or Epacadostat + Nivolumab + Platinum/5-FU (Combination Chemo-Immunotherapy Cohorts) (Continued)

Visit	Screening[a]	Treatment Period[b]									EOT	Safety Follow-Up[c]		Comments
		Cycle 1			Cycle 2	Cycle 3+								
		D1	D8	D15	D1	D8	D15	D1	D8	D15		30 Days After EOT	100 Days After EOT	
Evaluation Window (Days)	Day -28 to -1	±3	±3		±3	±3		±3			+7	±7	±7	
[redacted]														

[a] All safety laboratory assessments will be performed locally.
[b] Treatment cycles are every 21 days (± 3 days).
[c] The mandatory safety follow-up visits should be conducted approximately 30 days and 100 days after EOT, the last dose of nivolumab, or before the initiation of a new anticancer treatment, whichever comes first.
[d] Laboratory assessments on D1 of each cycle should be performed before the administration of any study drug.
[e] C1D1 laboratory tests may be omitted if the screening laboratory tests were performed within 7 days before study treatment initiation. If performed > 7 days before C1D1, the tests must be repeated to confirm the subject's eligibility on C1D1.

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Table 26: Laboratory Tests: Required Analytes

Serum Chemistry	Hematology	Other
Albumin Amylase Bicarbonate Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Iron Lactate dehydrogenase Phosphorus Potassium Serum or plasma lipase Sodium Total protein Uric acid IgG	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count[a], including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	**Serology:** Hepatitis B surface antigen[b] HCV-RNA or hepatitis C virus (HCV) antibody where HCV RNA is not SOC HBV DNA
		Pregnancy test: Female subjects of childbearing potential only require a serum test at screening. Pregnancy tests (serum or urine) should be repeated if required by local regulations and at EOT.
		Urinalysis with microscopic examination: Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen
Standard LFT Monitoring	**Endocrine Monitoring**	**Coagulation:** PT aPTT INR
Alkaline phosphatase ALT AST Total bilirubin Direct bilirubin (only if total bilirubin is elevated above ULN).	ACTH Serum cortisol (9 AM)[c] LH[d] Prolactin TSH Free thyroxine (T4) Total triiodothyronine (T3) Serum testosterone (9 AM)[c,e]	

ACTH = adrenocorticotropic hormone; IgG = immunoglobulin G; LH = luteinizing hormone.
[a] Differential is preferred to be reported in absolutes.
[b] Hepatititis B surface antigen testing will only include antigen testing.
[c] Serum cortisol and testosterone ideally should be drawn close to 9 AM but can be performed anytime before noon.
[d] Not needed in subjects taking thyroid hormone replacement therapy.
[e] Not needed in women, surgically castrated men, or men taking LH-releasing hormone agonist therapy.

6.1. Screening Period

The screening period will be up to 28 days. Screening is the interval between the signing of the ICF and the day the subject received the first dose of treatment in the study (C1D1). Informed consent must be obtained before performing any study-specific procedures not considered standard of care. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this period.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening period if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening

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process 1 time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection). Rescreened subjects must be assigned a new subject number.

6.2. Treatment Period

The treatment period with the combination immunotherapy therapy will continue every 56 days (Phase 1 Part 1 and Phase 2) and with the combination chemo-immunotherapy (Phase 1 Part 2) will continue every 21 days and may continue for up to 2 years as long as subjects are receiving benefit from treatment and have not met any criteria for study withdrawal.

6.3. End of Treatment

If a decision is made that the subject will permanently discontinue study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. The subject should be encouraged to return for the follow-up visit.

6.4. Follow-Up Period

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the last dose of study treatment and the 3 scheduled safety follow-up visits, which should occur 30 and 100 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 100 days after the last dose of study drug, the date of the follow-up visit, or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. If a subject initiates a new anticancer therapy within 100 days after the last dose of study treatment, reasonable efforts should be made to conduct the next scheduled safety follow-up visit before the first dose of the new therapy. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period. [redacted]

6.5. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

6.6. Early Termination

Not applicable.

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7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Study Procedures

Section 6 summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled timepoints if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the sponsor and/or BMS for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.2. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures. The granting of informed consent for study participation must be documented in writing, using an ICF that contains all the elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; a copy of the signed ICF must be provided to the study subject. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (Appendix A).

7.3. Demography and History

7.3.1. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity (where allowed by local regulations), medical and surgical history, and concurrent illnesses assessed using the NCI CTCAE v4.0 (NCI 2010). Medical history should include all active conditions and any condition considered to be clinically significant by the investigator. Details regarding the disease for which the subject has enrolled in this study (eg, date of diagnosis, primary tumor histology, prior systemic therapies, surgeries, radiation therapy, and stage of cancer) will be recorded separately and not listed in medical history.

7.3.2. Prior Medications

Prior and ongoing medications will be reviewed to determine study eligibility. The investigator or qualified designee will review prior medication use, including any Protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the study. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

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7.3.3. Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the study. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. All medications related to reportable SAEs should be recorded as defined in Section 8.1.

7.3.4. Post-Treatment Anticancer Therapy Status

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of study treatment. If a subject initiates a new anticancer therapy within 100 days after the last dose of study treatment, reasonable efforts must be made to conduct the next scheduled safety follow-up (30 or 100 day) visit before the first dose of the new therapy.

7.4. Safety Assessments

7.4.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

All AEs of unknown etiology associated with nivolumab and epacadostat exposure should be evaluated to determine if it is possibly an irAE. See Section 5.7.3 regarding the identification, evaluation, and management of AEs of potential immunological etiology.

7.4.2. Comprehensive Physical Examination

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurological examination. Before the first dose of study treatment, clinically significant abnormal findings should be recorded as medical history. After C1D1, new clinically significant abnormal findings should be recorded as AEs.

7.4.3. Targeted Physical Examination

For cycles that do not require a full physical examination per the schedules of assessments (Table 18, Table 19, and Table 24), the investigator or qualified designee will perform a directed physical examination as clinically indicated before study treatment administration. A targeted physical examination will be a symptom-directed evaluation conducted by the investigator or designee. The targeted physical examination will include assessment(s) of the body systems or

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organs, as indicated by subject symptoms, AEs, or other findings. New clinically significant abnormal findings should be recorded as AEs.

7.4.4. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and weight. Height will be measured at screening only.

7.4.5. Twelve-Lead Electrocardiograms

Baseline ECGs will be obtained at screening. Additional ECGs will be performed on study at C1D1 and C1D15 for Phase 1 Part 1 and at C1D1 and C2D1 for Phase 1 Part 2; within 60 to 90 minutes of first dose of epacadostat (unless emerging [redacted] data suggest alternate timing); predose on C1D15 for Phase 1 Part 1 and predose on C2D1 for Phase 1 Part 2. Clinically significant abnormal findings at screening will be recorded as medical history. Clinically significant abnormal findings after C1D1 should be recorded as an AE. Subsequently, ECGs will be conducted only as clinically indicated.

The 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Prolonged QTc intervals must be read by a cardiologist. The correction method (Fridericia or Bazett) used for calculating QTc will need to be provided in the eCRF.

7.4.6. Laboratory Assessments

Laboratory tests for screening period should be performed within 7 days before C1D1. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study drug administration. Results must be reviewed by the investigator or qualified designee and found to be acceptable before each dose of study treatment.

In Part 2 of Phase 1, for the combination chemo-immunotherapy cohorts, laboratory assessments will be conducted on C1D1, C1D8, C2D1, C2D8, C3D1, and C3D8 and as needed as part of standard practice to evaluate laboratory analytes during chemotherapy regimen. Subsequently, laboratory assessments will be performed on Day 1 of each cycle in the absence of clinically significant abnormalities, which should be monitored at a frequency sufficient to provide adequate surveillance.

All safety laboratory assessments will be performed locally.

7.4.6.1. Chemistry, Hematology, Coagulation Panel, Serology, and Endocrine Function Testing

Chemistry, hematology, coagulation panel, and endocrine function will all be analyzed by the site local laboratory. Differential counts for hematology should be provided in absolutes.

7.4.6.2. Urinalysis

Urinalysis will be analyzed by the site laboratory.

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7.4.6.3. Liver Chemistry Tests

Liver chemistry tests (ALT, AST, total bilirubin, and alkaline phosphatase) will be conducted at screening, on C1D1, on Day 1 of every subsequent cycle, at EOT, and at safety follow-up (30 days after EOT) for combination cohorts with Q2W nivolumab schedule. LFT monitoring will be conducted at screening, on C1D1, C1D15, on Day 1 of every subsequent cycle, at EOT, and at safety follow-up (30 days after EOT) for combination cohorts with Q4W nivolumab schedule. For combination chemo-immunotherapy cohorts, LFT monitoring will occur on C1D1, C1D8, C2D1, C2D8, C3D1, and C3D8; after Cycle 3, LFTs will be on Day 1 of each subsequent cycle, at EOT, at the 30-day safety follow-up visit, and as clinically indicated. Liver chemistry tests will be performed by the site's local laboratory, as well as any twice-per-week LFT monitoring if it is required. If LFT results (ALT, AST, or total bilirubin) are abnormal, twice weekly testing of these LFTs will be required until results return to baseline. Liver chemistry test monitoring for persistent low-grade abnormalities does not need to be monitored twice a week indefinitely. Appropriate LFT monitoring intervals should be discussed with the medical monitors for these circumstances. Throughout the Protocol, LFT refers specifically to liver chemistry testing, and required analytes for LFTs are listed in Table 26.

7.4.6.4. Pregnancy Testing

Serum pregnancy tests will be analyzed by the site laboratory at screening. Subsequently, urine pregnancy tests will be conducted on Day 1 of each cycle or as required by local regulations.

If a subject inadvertently becomes pregnant while on study treatment, the subject will immediately be withdrawn from the study. The site will contact the subject and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the sponsor and followed as described above and in Section 8.5.

7.5. Efficacy Assessments

Process for image collection and transmission to the central vendor can be found in the Site Imaging Manual.

7.5.1. Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days before C1D1. The site study team must confirm the subject has measurable disease per RECIST v1.1 for solid tumors, Cheson for lymphomas, or RANO for glioblastoma. The baseline imaging scan (or photographs if skin lesions present and assessed clinically) should also be submitted to the central imaging vendor. Subjects with all tumor types, except subjects with glioblastoma, are required to have a chest and abdominal CT scan for baseline. Brain MRI at baseline should also be considered when disease burden due to any targeted tumor types is extensive (ie, when ≥ 3 metastatic disease sites are involved). For subjects with MEL, baseline brain MRI is required. In addition, subjects with

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ovarian cancer must also have a pelvic CT scan performed. For subjects with SCCHN a neck CT scan is also required. For subjects with B-cell NHL or HL, baseline PET scans should be performed if standard of care. If performed as part of standard of care at baseline, imaging should continue at specified intervals during study treatment. Brain imaging for subjects whose primary disease is not glioblastoma should only be performed if there are signs or symptoms suggesting CNS disease. For subjects with glioblastoma, tumor measurements and volumetric MRI of the head is also required within 14 days before the start of study drug. Subjects with glioblastoma who are unable (due to existent medical condition, ie, pacemaker or implantable cardioverter defibrillator device) or unwilling to have a head MRI at baseline are excluded from the study.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before C1D1. The same imaging technique should be used in a subject throughout the study.

For selection of target lesions, RECIST v1.1 (Appendix E), Cheson (Appendix F), or RANO (Appendix H) criteria should be followed. For example, RECIST discourages selection of target lesions inside the field of prior irradiation. Lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless it is the solitary site of measurable disease AND there has been demonstrated progression in the lesion. Also, if a subject has only 1 measurable lesion, this lesion should not be biopsied.

7.5.2. Tumor Imaging During the Study

Tumor imaging should be continued on study treatment including photographs if skin lesion is present and assessed clinically, and the same imaging technique should be used in a subject throughout the study. Imaging should be performed 8 and 16 weeks (± 7 days) after the start of treatment for subjects in the combination chemo-immunotherapy cohorts (Phase 1 Part 2) and then every 12 weeks thereafter. All other subjects (Phase 1 Part 1 and Phase 2) will have efficacy assessments every 12 weeks. All subjects will continue to have efficacy assessments until the end of treatment; no efficacy assessments are required during the safety follow-up period. Imaging may be performed more frequently if clinically indicated. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Per RECIST v1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response or at the next scheduled scan, whichever is clinically indicated.

7.5.3. Assessment of Disease by Cheson Criteria for Lymphomas

An objective assessment of disease status is required at baseline (screening) using a method that is appropriate for disease subtype, per established and modified guidelines (Cheson et al 2007 or Owen et al 2013 for Waldenström's macroglobulinemia; Appendix G), to account for the unique tumor response seen in this class of therapeutics.

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7.5.3.1. CT Scan or MRI for Lymphoma Evaluation

Subjects with HL will undergo CT or MRI to evaluate measurable disease during the screening period. If CT/MRI assessment was performed, under standard of care, before signing of the ICF but within 28 days of C1D1, the result of that assessment may be recorded in the CRF in lieu of a study-specific assessment. On-treatment assessments (for subjects with disease measurable by CT or MRI) should be performed every 8 weeks following C1D1.

7.5.3.2. FDG-PET or Combined PET-CT

If positron emission tomography (PET) using [^{18}F] fluorodeoxyglucose (FDG) or combined PET-CT is used as a functional imaging tool for staging or response assessment of lymphoma as a part of the standard of care, the results obtained during any study phase will be captured in the CRF.

7.5.4. Assessment of Disease by RANO Criteria for Glioblastoma

Investigator-assessed tumor response will be based on modified published RANO criteria (Appendix H) and will be adapted for defining PD to account for the unique tumor response seen in this class of therapeutics. Radiologic response will be assessed by comparing the pretreatment baseline and on-treatment MRI scans. Radiologic progression will be determined by using the smallest tumor measurement at either the pretreatment baseline or after initiation of study medication. Table 27 describes the radiologic and clinical criteria that will be used for determining tumor response.

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Table 27: RANO Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete response	Requires all of the following: • Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks. • No new lesions. • Stable or improved nonenhancing (T2/FLAIR) lesions. • Subjects must be off corticosteroids (or on physiologic replacement doses only). • Stable or improved clinically. Note: Subjects with nonmeasurable disease only cannot have a complete response; the best response possible is SD.
Partial response	Requires all of the following: • ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. • No progression of nonmeasurable disease. • No new lesions. • Stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. • The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan. • Stable or improved clinically. Note: Subjects with nonmeasurable disease only cannot have a PR; the best response possible is SD.
Stable disease	Requires all of the following: • Does not qualify for complete response, PR, or progression. • Stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: • ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.[a] • Significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy[a] not cause by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). • Any new lesion. • Clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose. • Failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

FLAIR = fluid-attenuated inversion recovery.
Note: Radiologic interpretation guidelines, definitions, and tumor measurement instructions will be provided separately. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
[a] Stable doses of corticosteroids include subjects not on corticosteroids.
Source: Wen et al 2010.

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For purposes of this study, the minimum time from baseline for determination of SD will be 6 weeks.

Best overall response should be determined based on response designations recorded per RANO-defined criteria. The subject's BOR assignment will depend on the findings of both target and nontarget disease, and will also take into consideration the appearance of new lesions.

The assessments that will contribute to the evaluation of BOR include the response assessment recorded between the date of randomization and the first to occur of the following:

1. The date of objectively documented progression per RANO criteria
   OR
2. The date of subsequent therapy
   OR
3. The date of pathology results from diagnostic surgical resection

Among the available response assessment, the criteria listed in Table 28 will be used to determine BOR.

Table 28: Assessment of Best Overall Response

Best Overall Response	Criteria
Complete response (CR)	CR observed in consecutive assessments ≥ 4 weeks apart per RANO.
Partial response (PR)	PR observed in consecutive assessments ≥ 4 weeks apart per RANO.
Stable disease (SD)[a]	SD observed and dose not quality for CR or PR. Or Suspected PD followed with histologic results not confirming PD, and no CR, PR, or SD observed.
Not evaluable (NE)	Insufficient data to determine disease progression or response.
Progressive disease (PD)	No CR, PR, or SD before PD.

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
[a] To qualify for SD there must be a minimum on-treatment period of 6 weeks.

In order to distinguish potential treatment-associated pseudoprogression from PD and minimize premature discontinuation of study medication, subjects who initially meet radiologic criteria for disease progression but are believed to derive clinical benefit and are tolerating study medication should continue receiving study medication until confirmation of progression with a follow-up MRI. Such patients may be allowed to continue on study therapy for up to 12 additional weeks as long as they are no developing significant new or worsened neurologic deficits related to underlying tumor.

If the follow-up imaging after 12 weeks from initial tumor progression confirms further progression, the date of progression will be the date at which progression was first determined. For purposes of this study, the minimum duration between baseline (start of treatment) and first on-study scan in order to determine BOR of SD is 6 weeks. If the minimum time is not met when SD is otherwise the best timepoint response, the subject's best response will depend on the subsequent assessments. For example, a subject who has SD at a timepoint < 6 weeks and PD at a second assessment will have a best response of PD.

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Subjects with a complete or PR must have that response sustained for 4 weeks. Subjects who do not qualify for complete response, PR, or confirmed progression will be considered as SD for the Protocol BOR analysis.

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7.7. Other Study Procedures

7.7.1. Study Compliance

Interruptions from the Protocol-specified treatment plan for > 6 weeks between nivolumab and epacadostat doses due to toxicity require consultation between the sponsor and investigator and written documentation of the collaborative decision on subject management.

7.7.2. Administration of Nivolumab and Compliance

Administration of nivolumab will be witnessed by the investigator and/or study staff. The total volume of study treatment infused will be compared with the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering nivolumab will be provided in the Procedures Manual.

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7.7.3. Administration of Epacadostat and Compliance

Subjects will self-administer their dose of epacadostat in the morning and evening, approximately 12 hours apart.

Epacadostat compliance will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). The objective is 100% compliance, and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

7.7.4. Dispensing of Epacadostat

An initial bulk supply of epacadostat will be provided to investigative sites before enrollment of the first subject. Thereafter, the site staff will contact the sponsor for re-supply of epacadostat. When dispensing to subjects, the investigator or designee will remove the appropriate quantity of epacadostat from their stock, dispense the medication, and enter the amount dispensed into the eCRF and drug accountability log. Full details will be provided in the Study Manual.

7.7.5. Dispensing of Nivolumab

An initial bulk supply of nivolumab will be provided to investigative sites before enrollment of the first subject. Thereafter, the site will contact the sponsor for re-supply of nivolumab. The investigator or designee will calculate the number of nivolumab vials needed, pull the appropriate number of vials to prepare the infusion solution, and enter the vials used into the eCRF and drug accountability log. Full details will be provided in the Study Manual.

7.7.6. Distribution of Subject Reminder Cards

Subjects will be provided with reminder cards at each visit. The subject reminder cards will indicate the date/time of the next visit and will also remind the subject when they should not take their morning dose of study drug and when they should arrive for the visit. On Day 1 only subjects will also be given an SS information sheet for signs and symptoms of SS. This information sheet also instructs subjects to seek immediate medical care if any of these symptoms are observed.

7.7.7. Withdrawal or Discontinuation

When a subject discontinues or withdraws before study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any AEs that are present at the time of discontinuation or withdrawal should be followed in accordance with the safety requirements outlined in Section 8.1.1. These subjects should return to the site for the safety follow-up visits (described in Section 6.4.1) during the 100-day safety follow-up period.

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8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events page of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History page of the eCRF. Adverse event monitoring should be continued for at least 100 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The severity of AEs will be assessed according to the CTCAE v4.0 Grades 1 through Grade 4. The CTCAE v4.0 severity Grade 5 (death) will not be used in this study; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.

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The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Reasonable possibility that the AE is related to the study treatment: unrelated (no) or related (yes).

  NOTE: Since this is a study of epacadostat combined with other study therapies, the relationship to study drug can be assessed for epacadostat alone, nivolumab alone, epacadostat combined with each study therapy administered, or not related to either epacadostat or other study therapies.
- Start and end dates, unless unresolved at final examination.
- Action taken with respect to study drug (eg, none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
- Outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- Whether it is serious, as per SAE definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 8.3.2.

All AEs should be treated appropriately. If a concomitant medication or nondrug therapy is given, this action should be recorded on the AE and Prior/Concomitant medications pages of the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

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8.2. Laboratory Test Abnormalities

8.2.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug), should be recorded on the AE page of the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE, as per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose interruption or adjustment for the laboratory abnormality may be required (see Section 5.7.2) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.2.2. Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur before the reporting of a potential drug-induced liver injury event. All occurrences of potential drug-induced liver injuries, meeting the defined criteria, must be reported as SAEs (see Section 8.3.2 for reporting details).

Potential drug-induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times ULN

   AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

   AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

In addition, Potential Hy's Law cases must also be reported as SAEs (Section 8.3.2). A Potential Hy's Law case is defined as any situation where a study subject has an increase in AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN, irrespective of alkaline phosphatase, at any point during the study following the start of study medication.

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8.3. Serious Adverse Events

8.3.1. Definitions

A SAE is defined as an event that meets 1 of the following criteria:

- Is fatal or life-threatening (ie, immediate risk of dying).
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.
- Is clinically meaningful (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above). Considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care, in the absence of any deterioration in the subject's general condition.
  - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the EOT visit, or up to 100 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence. Any SAEs experienced after this period should be reported to the sponsor (or designee) only if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

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Previously planned (before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than 1), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the sponsor or its designee. The investigator must assess if there is a reasonable possibility that the SAE is related to the study treatment: unrelated (no) or related (yes).

Serious AEs related to unblinded comparator drugs or concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The telephone and facsimile number of the sponsor's contact persons, specific to the study, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the eCRF documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each recurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation, or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, a sponsor's associate may urgently require further information from the investigator for reporting to health authorities.

The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed, including the pregnancy of a male subject's female partner that occurs during the study or within 150 days of completing the study, the following procedures should occur:

- The investigator must notify the sponsor or its designee immediately.
- The study drug must be discontinued immediately.

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- The subject must be withdrawn from the study.
- The EOT visit evaluations must be performed.
- The investigator must complete and submit the Pregnancy Initial and Follow-Up Report forms to the sponsor or its designee.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)

If a negative serum test does not confirm the urine pregnancy test result, then:

- The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the subject's best interest to resume study drug and continue participation in the study.

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study drug must be reported within 24 hours of learning of its occurrence. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up to each pregnancy should be conducted to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the sponsor's study drug of any pregnancy outcome and follow-up to the first well-baby visit. **Any SAE experienced during pregnancy must be reported on the SAE Report Form and to the sponsor or its designee.**

8.6. Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this study, an overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 8.3.2 for reporting details).

8.7. Warnings and Precautions

No evidence available at the time of the approval of this study Protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study as needed. If new, significant risks are identified, they will be added to the ICF.

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8.8. Safety Monitoring Committee

There will be no formal external Safety Monitoring Committee (SMC) for the combination immunotherapy Phase 1 and Phase 2 cohorts. For Phase 1, approximately weekly the sponsor will conduct telephone conferences with investigators in order to review cohort-specific data, overall safety data from prior cohorts (if applicable), and to agree on dose escalation, de-escalation, and cohort expansion decisions. For Phase 2, safety and tolerability will be carefully monitored throughout the study by the sponsor in accordance with interim safety analyses planned procedures as described in Section 9.6.

Due to the complexity of the study, for the combination chemo-immunotherapy cohorts in the Part 2 of Phase 1, an SMC will review safety data at regular intervals throughout the study. The frequency of meetings will be contingent upon enrollment and availability of safety data for analysis and review. Details regarding membership, roles, and responsibilities of the committee are specified in the SMC charter.

8.9. Adverse Events of Special Interest

Adverse events of special interest must be recorded as such in the eCRF and should be reported to the sponsor within 72 hours. These events include irAEs that are seen with nivolumab and epacadostat therapy and any other observed autoimmune phenomenon.

For this study they include:

1. An elevated AST or ALT laboratory value that is ≥ 3 × ULN and an elevated total bilirubin laboratory value that is ≥ 2 × ULN as determined by way of Protocol-specified laboratory testing or unscheduled laboratory testing.

   Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in Section 8.2.2.

2. Any of the following AEs:
   a. ≥ Grade 3 diarrhea
   b. ≥ Grade 3 colitis
   c. ≥ Grade 2 pneumonitis
   d. ≥ Grade 3 hypo- or hyperthyroidism
   e. ≥ Grade 3 rash or dermatitis
   f. Grade 4 laboratory abnormality

Adverse events of special interest include irAEs that are seen with immunotherapy and any other observed autoimmune phenomenon. Guidance regarding identification, evaluation, and management of irAEs are provided in Section 5.7.3.

The irAEs will be monitored carefully before each cycle and through post-treatment follow-up. Laboratory results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an AE thought to be immune-related should have additional testing to rule out other causes. If no other cause is found, then the event should be considered to be immune-related.

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Also, as noted in Section 1.3.1, there is a possibility that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS when administered in combination with other serotonergic agents (Boyer and Shannon 2005). This syndrome has been most closely associated with use of MAOIs, Demerol®, linezolid, or methylene blue; all of these agents are prohibited during the study. Selective serotonin reuptake inhibitors and SNRIs are permitted in the study. Procedures listed in Section 5.7.4 will be implemented if subjects exhibit the signs and symptoms of SS described in Table 16 , including tremor, hyperreflexia, and spontaneous, ocular, or inducible clonus together with agitation, fever, diaphoresis, or muscle rigidity.

Adverse events of special interest that occur to any subject from the date of C1D1 through 100 days after cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the sponsor's product, should be reported within 72 hours to the sponsor. A detailed narrative of the event should be reported to the sponsor within 24 hours of the event.

8.10. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint and any associated AEs via email or other written communication to the Incyte contact.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

- **Full analysis set (FAS):** All subjects enrolled in the study who received at least 1 dose of study drug.
- **Per protocol:** All subjects in the FAS population who are considered to be sufficiently compliant with the Protocol. The per protocol population will be defined in the Statistical Analysis Plan for the study.
- **Safety evaluable:** All subjects enrolled in the study who received at least 1 dose of study drug.

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9.2. Selection of Sample Size

9.2.1. Cohort Size in Part 1 and Part 2 of Phase 1 Study

The primary objective of the open-label Part 1 of Phase 1 study is to determine the RP2D of epacadostat in combination with nivolumab, and the primary objective of Part 2 of Phase 1 is to determine the safe dose of epacadostat in combination with nivolumab and chemotherapy. The total number of subjects will depend on the number of dose levels tested before the MTD or PAD is established. Up to approximately 63 subjects (9 subjects per dose level for 7 dose levels) will be enrolled in Part 1 of Phase 1 for the dose escalation of epacadostat when administered with nivolumab (the combination immunotherapy cohorts). Up to 81 subjects (9 subjects per dose level for up to 3 dose levels in 3 combination chemo-immunotherapy cohorts) will be enrolled in Part 2 of Phase 1 for the dose finding of epacadostat in combination with nivolumab and chemotherapy (the combination chemo-immunotherapy cohorts). Additionally, 30 subjects will be enrolled into each of the safety expansion of combination chemo-immunotherapy cohorts (epacadostat + nivolumab + chemotherapy): Cohort A, Cohort B, and Cohort C. Table 32 below tabulates the probability of observing a toxicity in a cohort of 30 subjects for various event rates. Overall sample size in Phase 1 (Part 1 and Part 2) will be up to approximately 234 subjects.

Table 32: Probability of Observing a Toxicity for Various Safety Event Rates

True Probability of Subjects Having an AE	Probability of Observing an AE
5%	78.5%
10%	95.8%
15%	99.2%
20%	99.9%

9.2.2. Sample Size for the Dose-Expansion Portion (Phase 2) of the Study

The sample size of 25 subjects are expected to be enrolled in each of the 4 low historic response expansion cohorts (CRC, SCCHN, ovarian cancer, and DLBCL) as well as in each of I/O-relapsed MEL and I/O-refractory MEL cohorts and 50 subjects in each of the 2 higher historic ORR cohorts (NSCLC and I/O-naive MEL). The sample size for each independent cohort yields a power of 80% to detect the following: 1) a target ORR of 17% to 26% increase (Ha) from historical response rate (H0) or 2) a PFS rate at 6 months of 14% to 22% increase (Ha) from historical survival probability (H0). This assumes a 1-sided alpha of 2.5% for each of the endpoint within a cohort (based on Bonferroni adjustment due to dual primary endpoints), 10% lost to follow-up, enrollment period of 6 to 10 months (depends on cohort), and 6 to 10 months of follow-up (depends on cohort) after last subject enrolled. See details in Table 33.
Twenty-eight subjects are expected to be enrolled in the glioblastoma cohort. This sample size for the glioblastoma cohort yields a power of 80% to detect an OS rate at 9 months of 25% increase (Ha) from historical survival probability (H0). This assumes a 1-sided alpha of 5%, 10% lost to follow-up, enrollment period of 4 months, and 9 months of follow-up after last subject enrolled. Details are shown in Table 34.

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Table 33: Sample Size Calculation for Each Cohort: Comparing With a Known Proportion

Tumor Type (Cohort)	ORR		PFS at 6 Months		Accrual Time	Minimum Follow-Up Time	Sample Size
	H0	Ha	H0	Ha			
NSCLC	24%	43%	45%	65%	6 months	6 months	50
I/O-naive MEL	32%	52%	50%	67%	6 months	10 months	50
I/O-relapsed MEL	5%	22%	5%	19%	10 months	6 months	25
I/O-refractory MEL	5%	22%	5%	19%	10 months	6 months	25
SCCHN	19%	44%	15%	37%	10 months	6 months	25
DLBCL	5%	22%	15%	37%	10 months	6 months	25
Ovarian cancer	20%	46%	15%	37%	10 months	6 months	25
CRC	5%	22%	15%	37%	10 months	6 months	25

Table 34: Sample Size Calculation for Glioblastoma Cohort: Comparing With a Known Proportion

Tumor Type (Cohort)	OS at 9 Months		Accrual Time	Minimum Follow-Up Time	Sample Size
	H0	Ha			
Glioblastoma	50%	75%	4 months	9 months	28

9.3. Level of Significance

The level of significance for the each of the 2 primary endpoints in Phase 2 is 1-sided 2.5% for the NSCLC, MEL (including I/O-naive, I/O-relapsed, and I/O-refractory cohorts), SCCHN, DLBCL, OC, and CRC cohorts, which is based on Bonferroni correction for Type I error 5% due to dual primary endpoints. The level of significance is 1-sided 5% for the glioblastoma cohort.

9.4. Statistical Analyses

9.4.1. Primary Analyses

Objective response rate and PFS are the dual primary endpoints for the solid tumor and DLBCL cohorts in Phase 2. Overall survival at 9 months is the only primary endpoint in the glioblastoma cohort. The Type I error will be controlled using Bonferroni method for each cohort with dual primary endpoints. As a result, the overall familywise Type I error of the study (across all tumor types studied) is not controlled, but within each Phase 2 cohorts, the Type I error is controlled at 1-sided 0.05. Treatment effect will be claimed in a given tumor type if any 1 of the 2 primary endpoints is significant in the cohorts with dual primary endpoints. Objective response rate is defined as the proportion of subjects with best response (CR or PR) by RECIST v1.1 and Cheson criteria for DLBCL. The 95% exact CI for the ORR will be estimated using the Clopper-Pearson method for all Phase 2 cohorts except glioblastoma. One-sample binomial test will be used to

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test the null hypotheses. Progression-free survival is defined as number of days from the first day of taking the study drug to the earlier of death or disease progression by RECIST v1.1 for select solid tumors and Cheson criteria for DLBCL. Overall survival is defined as number of days from the first day of taking study dose to the death. Time-to-event data will be analyzed by the Kaplan-Meier method, treating subjects with no observed death or progression as censored at their date of last valid response assessment (PFS) or last date known to be alive (OS). The PFS/OS rate and the corresponding 95% CI using log-log transformation will be estimated using the Kaplan-Meier method and will be provided by cohort at 6 months for PFS for the respective cohorts and 9 months for OS for the glioblastoma cohort. The back transformed CI for survival function will be used to determine whether the PFS and OS rate under the null hypothesis is covered.

9.4.2. Secondary Analyses

There is no hypothesis testing for secondary analyses. For objective responders, the DOR is the time from the first overall response contributing to an objective response (CR or PR) to the earlier of the subject's death and first overall response of PD (as determined per RECIST v1.1 and modified RECIST, Cheson and modified Cheson, or RANO and modified RANO) occurring after the first overall response contributing to the objective response. Median DOR will be estimated using the Kaplan-Meier method for all Phase 2 cohorts. Confidence intervals for median survival time will be calculated using the method of log-log transformation, which is the default method within SAS v9.1. Subjects who are still responding at the time of database freeze or discontinuation will be right-censored at the time of last valid response assessment.

Duration of disease control is the time from the first dose to the first objective response of PD, or death, whichever occurs first, for subjects who reported a BOR of SD or better. In case of SD, measurements must meet the SD criteria at least once after study entry at a minimum interval of 49 days. For subjects who have not subsequently progressed and who remain alive, duration of disease control will be censored on the date of last valid tumor response assessment. Median duration of disease control and CI will be estimated using Kaplan-Meier method for all Phase 2 cohorts.

Median OS and CIs will be estimated using the Kaplan-Meier method for all Phase 2 cohorts as secondary analysis except glioblastoma.

For the Phase 2 glioblastoma cohort, ORR and 95% exact CIs will be estimated; median PFS and CIs will be estimated using the Kaplan Meier method.

For subjects in Part 2 of Phase 1 treated with epacadostat in combination with nivolumab and chemotherapy (combination chemo-immunotherapy), ORR will be estimated with 95% exact binomial CI; median DOR, PFS, and CIs will be estimated using the Kaplan-Meier method.

Overall response rate and 95% exact binomial CI will be estimated for subjects in Part 1 of Phase 1 treated with epacadostat in combination with nivolumab.

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9.4.4. Safety Analyses

The principal analysis will be based on the safety evaluable population, according to treatment assignment.

Adverse events will be coded by the MedDRA, and incidences will be tabulated by preferred term and system organ class for all events, related events, and events from Grade 1 through Grade 4. Severity of AEs will be based on the CTCAE scale as indicated in Section 8.1.1. Quantitative safety variables and their changes from baseline (laboratory, vital signs) will be summarized with descriptive statistics. Clinically significant abnormal values will be flagged and tabulated based on predefined criteria.

Exposure will be analyzed by describing dose intensity, which is defined as the dose received divided by the dose planned over a given time interval. This will be done by cycle as well as overall cycles received. For each cycle, incidences of dose reductions and cycle delays will also be tabulated, by reason for the reduction or delay. The percentage of subjects with any delay and/or reduction will also be calculated.

9.4.5. Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics (eg, means and frequencies), and no formal statistical comparisons among the treatments are planned. In addition, distributions of key laboratory parameters (including hemoglobin, neutrophils, and platelets) will be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

9.5. Analyses for the Safety Monitoring Committee

There will be no formal SMC for the combination immunotherapy cohorts in Phase 1 Part 1 and Phase 2; however, ongoing safety reviews will be performed as described in Section 9.6.

Details regarding safety data to be evaluated by the SMC in Phase 1 Part 2 will be specified in the SMC charter.

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9.6. Interim Analysis

No formal interim analysis for futility or efficacy is planned for this study. An interim safety analysis is planned for Phase 2 after 20 subjects have been enrolled and treated for 8 weeks and then every 3 months thereafter. If the following is reported during these reviews, enrollment of subjects will be suspended until the sponsor(s), investigators, and regulatory authorities, if applicable, have determined the appropriate course of action:

- > 40% of subjects have had DLT defined AEs that were attributable to the investigational agents.

Based on these rules, the probabilities of stopping a treatment group for safety is provided in Table 35.

Table 35: Probability of Early Termination for Various Safety Event Rates

Proportion of Subjects Having an AE ≥ Grade 3 That Was Attributable to the Investigational Agent	Probability of Early Termination Based on an AE ≥ Grade 3 That Was Attributable to the Investigational Agent[a,b]
5%	0.0%
10%	0.1%
15%	0.6%
20%	3.3%
25%	10.2%
30%	23.3%
40%	80.7%

[a] Assumes the interim safety analyses occur when enrollment is 20, 80, 160, 240, and 276, etc, subjects. Probability estimated via simulation with 100,000 replications.

[b] The probability of early termination = Prob (≥ 40% of subjects in the active treatment group have had an AE ≥ Grade 3 at the first interim safety analysis OR at the second interim OR at the third interim OR at the fourth interim).

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10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Investigational Products Description

10.1.1. Packaging, Labeling, and Preparation of Study Drug or Placebo

10.1.1.1. Epacadostat

The study drug will be available as 25 mg and 100 mg tablets packaged in high-density polyethylene bottles. All bottles of Incyte investigational product will be labeled to comply with regulatory requirements of each country.

10.1.1.2. Nivolumab

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the Protocol and any applicable laws and regulations. Clinical supplies will be provided by BMS.

Clinical supplies will be labeled in accordance with local regulatory requirements.

The nivolumab product description is provided in Table 36.

Table 36: Nivolumab Product Description

Product Description and Regimen Form	Potency	Primary Packaging (Volume)/Label Type	Secondary Packaging (Qty)/Label Type	Appearance	Storage Conditions
Nivolumab (BMS-936558-01) solution for injection	100 mg (10 mg/mL)	10 mg/mL vial/open-label	10 vials per carton/open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles.	2°C to 8°C. Protect from light and freezing.

10.1.2. Storage and Stability of Study Drugs

10.1.2.1. Epacadostat

Clinical supplies must be stored as described in the eIB.

10.1.2.2. Nivolumab

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label and as described in the nIB. Receipt and dispensing of study drug must be recorded by an authorized person at the study site. Clinical supplies may not be used for any purpose other than that stated in the Protocol.

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10.2. Accountability, Handling, and Disposal of Epacadostat and Nivolumab

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until the end of the study. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

These records should include dates, quantities, batch or serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the correct study drug specified.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the completion of the study, the investigator or designee will oversee shipment of any remaining epacadostat back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Infusion related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) for nivolumab will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

10.2.1. Disposal of Epacadostat and Nivolumab

Upon completion or termination of the study, all unused and/or partially used nivolumab will be destroyed at the site per institutional policy. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

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11. STUDY ADMINISTRATION

11.1. Data Management

11.1.1. Data Collection

The investigator will be provided with a eCRF for each subject. Entries made in the eCRF must be verifiable against source documents; any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all responses.

11.1.2. Data Management

Data management will be performed from eCRFs. All eCRF data will be entered into a validated database. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

11.2. Study Monitoring

Qualified representatives of the sponsor or its designee, "study monitors," will monitor the study according to a predetermined monitoring plan. Monitoring visits provide the sponsor with the opportunity to:

- Evaluate the progress of the study.
- Verify the accuracy and completeness of eCRFs.
- Assure that all Protocol requirements, applicable laws and/or regulations, and investigator's obligations are being fulfilled.
- Resolve any inconsistencies in the study records.

The investigator must allow the study monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The eCRFs and other documentation supporting the study must be kept up-to-date by the investigator and the research staff at the investigative site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the sponsor or its designee, at each monitoring visit.

The study monitor will review the various records of the study (eCRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the eCRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

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11.3. Protocol Adherence

The principal investigator must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study including the subject ICF and recruitment materials must be maintained by the investigator and made available for inspection.

Each investigator must adhere to the Protocol as described in this document and agree that changes to the Protocol, with the exception of medical emergencies, must be discussed and approved, firstly, by the sponsor or its designee and, secondly, by the IRB or IEC. Each investigator is responsible for enrolling subjects who have met the Protocol inclusion and exclusion criteria. The IRB or IEC that granted original approval, or the IRB or IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the Protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB or IEC to the sponsor or its designee and retain the original in the site study regulatory file.

Major eligibility deviations must be reported to the IRB or IEC in accordance with the IRB or IEC requirements. During the course of the study, the monitor must notify the sponsor or its designee of subjects found not to have met eligibility criteria. The medical monitor, in collaboration with the investigator, will determine if the subject should be withdrawn from the study.

11.4. Financial Disclosure

All clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators, are required before study initiation to submit a completed Clinical Investigator Financial Disclosure Request Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, clinical investigator is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new investigators or subinvestigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Request Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligation to report to the sponsor or its designee any changes to the financial information previously reported. The clinical investigators will also be reminded that they must report any changes in their financial information for a period of 1 year after completion of the covered clinical study.

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11.5. Compliance With Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act and the Food and Drug Administration Amendments Act, the sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, www.clinicaltrials.gov. Information posted will allow individuals to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Sponsor Audits

At some point during the study, individuals from the sponsor's Quality Assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the investigator's adherence to the Protocol, applicable regulations, and the sponsor's procedures, in addition to assessing the accuracy of the study data. Before initiating this audit, the investigator will be contacted by the sponsor to arrange a convenient time for this visit. The investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the eCRFs and other study-related documents.

12.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

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13. ETHICS

13.1. Ethical Conduct of the Study

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, GCPs as defined in Title 21 of the US CFR Parts 50, 54 56, 312, and Part 11, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

13.2. Written Informed Consent

Informed consent documentation that includes both information about the study and the ICF will be prepared and given to the subject. This document will contain all elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

The principal investigator at each center will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, and the possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue study drug and withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The principal investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject. The investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

Preparation of the ICF is the responsibility of the investigator and must include all elements required by the ICH GCP, and applicable regulatory requirements, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and approve all changes to site-specific ICFs. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records. Before the beginning of the study, the IRB or IEC must provide the investigator with written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

13.3. Ethics Review

It is the responsibility of the investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in the ICH E6: Guideline for GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The Protocol and any information supplied to the subject to obtain informed consent, including written ICFs, subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), must be reviewed and approved by a qualified IRB/IEC before enrollment of participants in the study. Before initiation of the study,

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the sponsor or its designee must receive documentation of the IRB or IEC approval, which specifically identifies the study/Protocol, and a list of the committee members.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the Protocol in accordance with local requirements. Protocol amendments and revisions to the ICF must be submitted to and approved by the IRB or IEC.

Investigators must submit progress reports to the IRB or IEC in accordance with the IRB or IEC requirements and local regulations. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the sponsor or its designee.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor or its designee will provide this information to the principal investigator.

When the sponsor or its designee provides the investigator with a safety report, the investigator is responsible for ensuring that the safety report is reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their respective IRBs or IECs.

After completion or termination of the study, the investigator must submit a final report to the IRB or IEC and to the sponsor or its designee.

The investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB or IEC.

Each clinical investigator is responsible to conduct the study in accordance with the Protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

13.4. Data Privacy

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor (or its designee) are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

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14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

The sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The investigator must ensure that all records pertaining to the conduct of the clinical study (as listed above) are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal termination of clinical development of the investigational product.

14.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the termination of the test article for investigation. If it becomes necessary for the sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

The investigator must not destroy any records associated with the study without receiving approval from Incyte. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable, provided it is legible and is a verified copy of the original document.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

14.3. Confidentiality

Subject names will not be supplied to the sponsor or its designee if applicable. Only the subject number and subject's initials will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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15. PUBLICATION POLICY

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. The signed agreement is retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal ligation or occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
Source: CTFG 2014.

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APPENDIX C. MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the investigator and may be supplemented by discussions with the medical monitor representing the sponsor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Noninflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for I-O drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the I-O agent or regimen being used.

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GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u>: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and Infectious Disease (ID) consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: •Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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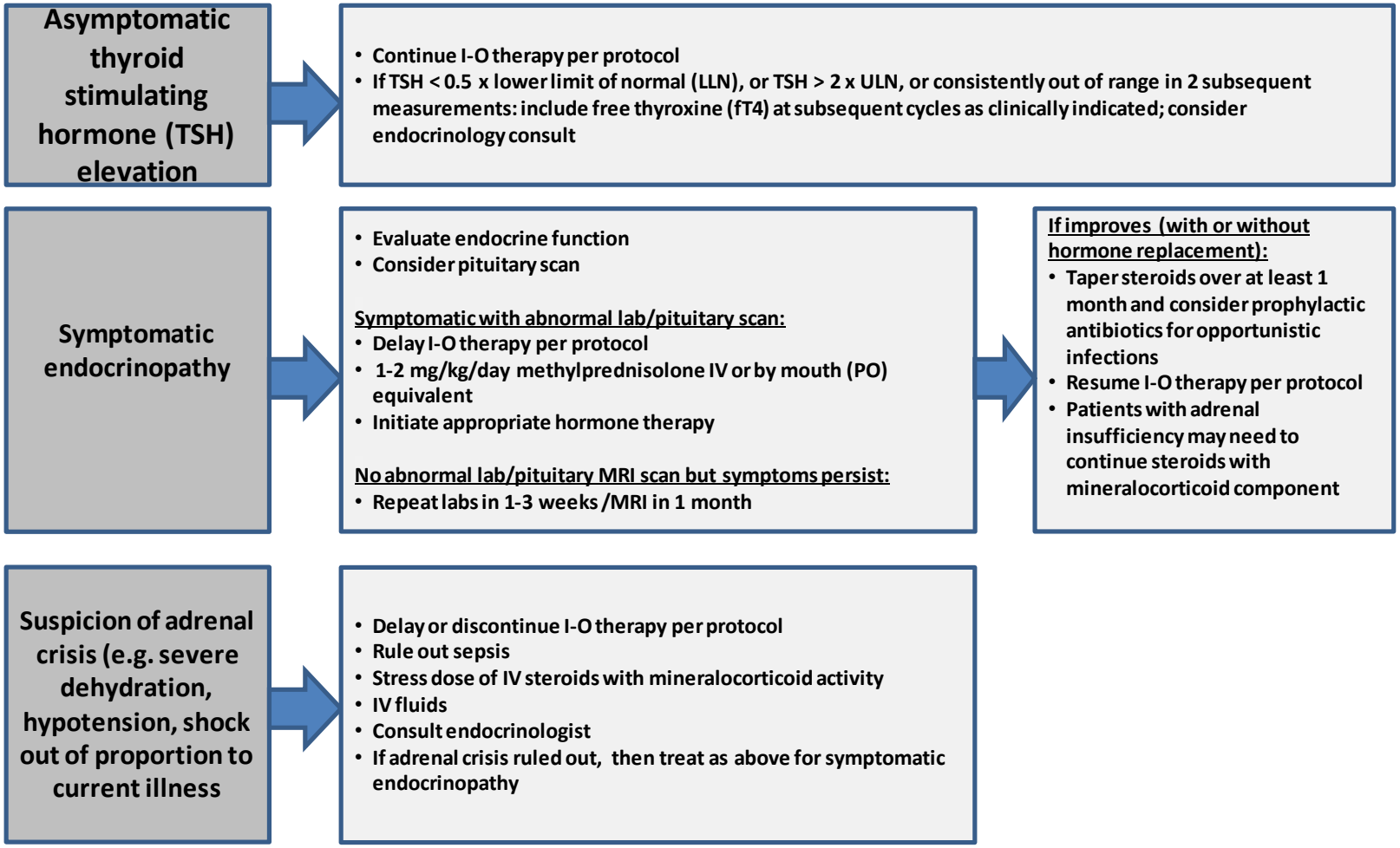
Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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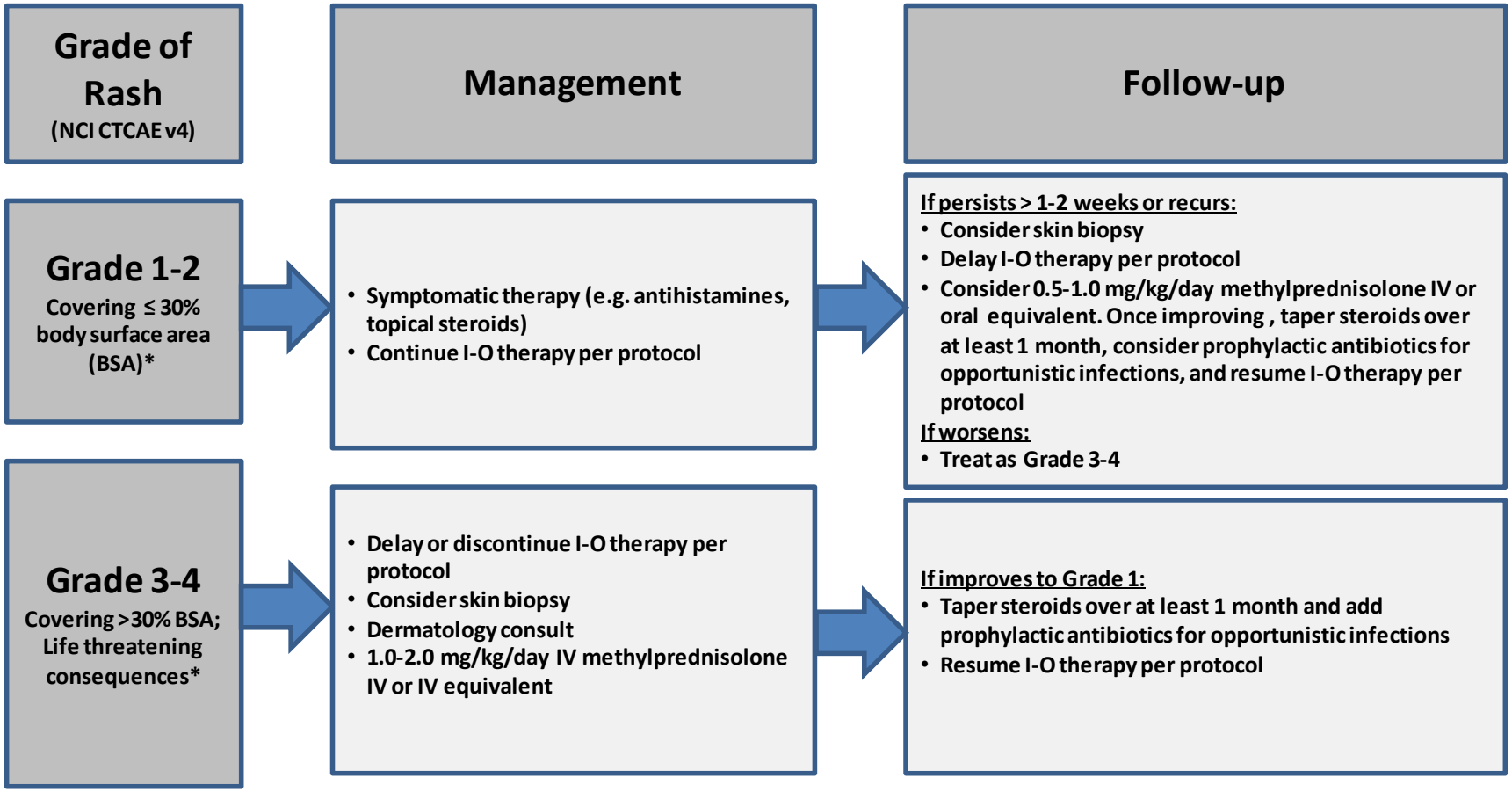
Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: •Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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APPENDIX D. PROHIBITED MONOAMINE OXIDASE INHIBITORS AND DRUGS ASSOCIATED WITH SIGNIFICANT MONOAMINE OXIDASE INHIBITORY ACTIVITY

Monoamine Oxidase Inhibitors	**Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity**
Hydrazines (example phenelzine)	Meperidine
Isocarboxazid	Linezolid
Tranylcypromine	Methylene blue
Brofaromine	
Rasagiline	
Selegiline	

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APPENDIX E. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1

RECIST v1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be used, as per RECIST v1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

Source: Eisenhauer et al 2009.

In addition, volumetric analysis will be explored by central review for response assessment.

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APPENDIX F. RESPONSE CRITERIA FOR LYMPHOMA

LYMPHOMA COMPLETE RESPONSE, PARTIAL RESPONSE, STABLE DISEASE, RELAPSED/PROGRESSIVE DISEASE RESPONSE CRITERIA (Cheson et al 2007)

Complete Response (CR)

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms such as 'B symptom' if present before therapy.
2. a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

   b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Response (PR)

The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

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4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B-cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least 1 previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pr-treatment PET scan was negative, CT criteria should be used.

Stable Disease (SD)

Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (After CR)/Progressive Disease (After PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes $\leq 1.0 \times \leq 1.0$ cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

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2. At least a 50% increase from nadir in the sum of the product diameters of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

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APPENDIX G. RESPONSE ASSESSMENT FOR WALDENSTRÖM'S MACROGLOBULEMIA

Categorical Response Definitions in Waldenström's Macroglobulinemia

Response Category	Response Definition
Complete Response	• Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level • Complete resolution of extramedullary disease, ie, lymphadenopathy and splenomegaly if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy
Very Good Partial Response	• Monoclonal IgM protein is detectable ≥ 90% reduction in serum IgM level from baseline* • Complete resolution of extramedullary disease, ie, lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Partial Response	• Monoclonal IgM protein is detectable ≥ 50% but < 90% reduction in serum IgM level from baseline* • Reduction in extramedullary disease, ie, lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Minor Response	• Monoclonal IgM protein is detectable ≥ 25% but < 50% reduction in serum IgM level from baseline* • No new signs or symptoms of active disease
Stable Disease	• Monoclonal IgM protein is detectable < 25% reduction and < 25% increase in serum IgM level from baseline* • No progression in extramedullary disease, ie, lymphadenopathy/splenomegaly • No new signs or symptoms of active disease
Progressive Disease	• ≥ 25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or • progression in clinical features attributable the disease

NOTE: Very good partial response will still be categorized as partial response (PR) and minor response should still be categorized as stable disease (SD) in the CRF.
*Sequential changes in IgM levels may be determined either by M protein quantification by densitometry or total serum IgM quantitation by nephelometry.
Source: Owen et al 2013.

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APPENDIX H. RESPONSE CRITERIA FOR GLIOBLASTOMA

RANO Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; subjects must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Subjects with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Subjects with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids[a]; significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy[a] not cause by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of non-measurable disease.

FLAIR = fluid-attenuated inversion recovery.
Note: Radiologic interpretation guidelines, definitions and tumor measurement instructions will be provided separately. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
[a] Stable doses of corticosteroids include subjects not on corticosteroids.
Source: Wen et al 2010.

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Summary of the RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium disease	None	≥ 50% decrease	< 50% decrease but , 25% increase	≥ 25% increase[a]
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase[a]
New lesion	None	None	None	Present[a]
Corticosteroids	None	Stable or decrease	Stable or decrease	NA[b]
Clinical status	Stable or increase	Stable or increase	Stable or increase	Decrease[a]
Requirement for response	All	All	All	Any[a]

RANO = Response Assessment in Neuro-Oncology; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; FLAIR = fluid-attenuated inversion recovery; NA = not applicable.

[a] Progression occurs when this criterion is present.

[b] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

For purposes of this study, the minimum time from baseline for determination of SD will be 6 weeks.

Best overall response should be determined based on response designations recorded per RANO defined criteria. The subject's BOR assignment will depend on the findings of both target and non-target disease, and will also take into consideration the appearance of new lesions.

The assessments that will contribute to the evaluation of BOR include the response assessment recorded between the date of randomization and the first to occur of the following:

1. The date of objectively documented progression per RANO criteria

   OR

2. The date of subsequent therapy

   OR

3. The date of pathology results from diagnostic surgical resection

Among the available response assessment, the criteria listed in the table below will be used to determine BOR.

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Assessment of Best Overall Response

Best Overall Response	Criteria
Complete Response (CR)	CR observed in consecutive assessments≥ 4 weeks apart per RANO
Partial Response (PR)	PR observed in consecutive assessments≥ 4 weeks apart per RANO
Stable Disease (SD)[a]	SD observed and dose not quality for CR or PR Or Suspected PD followed with histologic results not confirming PD, and no CR, PR or SD observed
Not Evaluable (NE)	Insufficient data to determine disease progression or response
Progressive Disease (PD)	No CR, PR, or SD prior to PD

[a] To qualify for SD there must be a minimum on-treatment period of 6 weeks.

In order to distinguish potential treatment-associated pseudoprogression from progressive disease and minimize premature discontinuation of study medication, subjects who initially meet radiologic criteria for disease progression but are believed to derive clinical benefit and are tolerating study medication should continue receiving study medication until confirmation of progression with a follow up MRI. Such subjects may be allowed to continue on study therapy for up to 12 additional weeks as long as they are no developing significant new or worsened neurologic deficits related to underlying tumor.

If the follow-up imaging after 12 weeks from initial tumor progression confirms further progression, the date of progression will be the date at which progression was first determined. For purposes of this study, the minimum duration between baseline (start of treatment) and first on-study scan in order to determine BOR of SD is 6 weeks. If the minimum time is not met when SD is otherwise the best timepoint response, the subject's best response will depend on the subsequent assessments. For example, a subject who has SD at a timepoint < 6 weeks and PD at a second assessment will have a best response of PD.

Subjects with a complete or partial response must have that response sustained for 4 weeks. Subjects who do not qualify for complete response, partial response, or confirmed progression will be considered as stable disease for the protocol BOR analysis.

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APPENDIX I. DOSE MODIFICATIONS FOR PACLITAXEL/PLATINUM (CARBOPLATIN OR CISPLATIN)

I.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table I-1, paclitaxel will be administered first, followed by platinum (carboplatin or cisplatin). If any criteria are not met, administration of therapy will be postponed. From the second cycle onwards, study treatment will be discontinued if administration of therapy has not been initiated by 14 days after the estimated Day 1.

Table I-1: Criteria for Administration of Carboplatin and Paclitaxel on Day 1 of Each Cycle

Parameter		Criterion for Start
WBC		$\geq 2.5 \times 10^9$/L
Neutrophil count		$\geq 1.0 \times 10^9$/L
Platelet count		$\geq 100 \times 10^9$/L
Renal function		≥ 50 ml/min for cisplatin or ≥ 20 mL/min for carboplatin AND < 10% change in GFR from previous cycle
Nonhematologic toxicities	Bilirubin	≤ ULN
	AST/ALT	< 2.5 × ULN

If platinum (carboplatin or cisplatin) and/or paclitaxel are held for any of the reasons noted in Table I-1 above, both epacadostat and nivolumab should be held as well, and the subject will be evaluated at least weekly until the toxicity has resolved. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table I-2, Table I-3, and Table I-4, taking tolerability of the most recent dose into account.

I.2. Platinum (Carboplatin or Cisplatin) and Paclitaxel Dose Modifications

Table I-2 and Table I-3 provide guidance for dose reductions for the first appearance of the specified toxicities for cisplatin/paclitaxel or carboplatin/paclitaxel, respectively.

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Table I-2: Criteria for Carboplatin and Paclitaxel Dose Reductions for Specified Toxicities

	ANC		Platelet Count	Action	Dose Modification Following Recovery	
					Paclitaxel	Cisplatin
Hematologic toxicity	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75%-100% dose	75% dose
	$< 1.0 \times 10^9$/L	AND	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75% dose reduction	75% dose
Renal impairment	If the calculated GFR falls by more than 10% from the previous cycle, then consider a dose modification.					
	GFR	**Cisplatin Dose**				
	$\geq$ 50 mL/min	Full dose per Protocol.				
	$\geq$ 30 to < 50 mL/min	Reduce cisplatin dose 50% or switch to carboplatin AUC 6.				
	< 30 mL/min	Discontinue cisplatin, continue paclitaxel.				
Additional toxicities	**Toxicity**	**Definition**			**Dose Modification**	
	Febrile neutropenia	ANC $< 0.5 \times 10^9$/L plus fever requiring IV antibiotics ± hospitalization			Dose cisplatin at 75% and dose paclitaxel at 135 mg/m^2.	
	Fatigue	Grade 3			At first occurrence, 25% dose reduction for paclitaxel; if persistent, 50% reduction or omit paclitaxel only.	
	Neuropathy	Grade 2			Reduce paclitaxel to 135 mg/m^2 in all subsequent cycles. If persistent, 90 mg/m^2 or omit.	
		Grade 3			Withhold paclitaxel until < Grade 1; restart at 90 mg/m^2. Discontinue if no recovery.	
	Arthralgia and/or myalgia	Grade $\geq$ 2 toxicity			Dose cisplatin at 75% and dose paclitaxel at 135 mg/m^2.	
	Other toxicities	Grade 3 toxicity (except alopecia, nausea, and vomiting)			Continue with 75% dose of cisplatin and/or paclitaxel at 135 mg/m^2 provided toxicity has resolved to Grade 1 or less. If further toxicity occurs, an additional reduction may be made after discussion with medical monitor.	
		Grade 4 toxicity (except alopecia, nausea, and vomiting)			Withhold treatment and discuss with medical monitor.	

Note: Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. All dose modifications should be made based on the worst grade toxicity per CTCAE v4.0.

Note: If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

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Table I-3: Criteria for Carboplatin and Paclitaxel Dose Reductions for Specified Toxicities

	ANC		Platelet Count	Action	Dose Modification Following Recovery	
					Paclitaxel	Carboplatin
Hematologic toxicity	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75%-100% dose	Reduce by 1 AUC
	$< 1.0 \times 10^9$/L	AND	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75% dose	Reduce by 1 AUC
Renal impairment	If the calculated GFR falls by more than10% from the previous cycle, then consider a dose modification.					
	GFR	**Carboplatin Dose**				
	≥ 30 mL/min	Use AUC as per Protocol.				
	20-30 mL/min	EDTA then use AUC as per protocol, or consider discontinuing carboplatin.				
	< 20 mL/min	Discontinue carboplatin, continue paclitaxel.				
Additional toxicities	**Toxicity**	**Definition**			**Dose Modification**	
	Febrile neutropenia	ANC $< 0.5 \times 10^9$/L plus fever requiring IV antibiotics ± hospitalization			Dose reduction of carboplatin 20% and dose paclitaxel at 135 mg/m^2.	
	Fatigue	Grade 3			At first occurrence, 25% dose reduction for paclitaxel; if persistent, 50% reduction or omit paclitaxel only.	
	Neuropathy	Grade 2			Reduce paclitaxel to 135 mg/m^2 in all subsequent cycles. If persistent, 90 mg/m^2 or omit.	
		Grade 3			Withhold paclitaxel until < Grade 1; restart at 90 mg/m^2. Discontinue if no recovery.	
	Arthralgia and/or myalgia	Grade ≥ 2 toxicity			Consider prednisolone 10 mg BID for 5 days starting 24 hours after paclitaxel. If arthralgia and/or myalgia persists, reduce subsequent paclitaxel dose to 135 mg/m^2.	
	Other toxicities	Grade 3 toxicity (except alopecia, nausea, and vomiting)			Continue with 20% dose reduction of carboplatin and/or paclitaxel at 135 mg/m^2 provided toxicity has resolved to Grade 1 or less. If further toxicity occurs, an additional reduction may be made after discussion with medical monitor.	
		Grade 4 toxicity (except alopecia, nausea, and vomiting)			Withhold treatment and discuss with medical monitor.	

Note: Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. All dose modifications should be made based on the worst grade toxicity per CTCAE v4.0.

Note: If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

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Table I-4 provides guidance for dose reductions for elevations of AST, ALT, and/or bilirubin.

Table I-4: Management Guidelines for Hepatic Toxicity

AST/ALT	Bilirubin	Epacadostat and Nivolumab	Platinum	Paclitaxel
Grade 1 (< 3 × ULN)	≤ 1.5 × ULN	Continue epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline.	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	≤ 1.5 × ULN	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 1 (ULN to 1.5 × ULN)	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Reduce dose to 135 mg/m^2
Grade 2 (3 × to < 5 × ULN)	Grade 2 (1.5 × to 3 × ULN) *Note: If > 2 × ULN, meets Hy's Law[a]	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT and/or bilirubin do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Reduce dose to 75 mg/m^2
ANY Grade 3 or Grade 4		Permanently discontinue study treatment.		
Hy's Law[a]		Permanently discontinue study treatment.		

LFT = liver chemistry test.

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) > 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

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APPENDIX J. DOSE MODIFICATIONS FOR PEMETREXED/PLATINUM (CARBOPLATIN OR CISPLATIN)

J.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table J-1, pemetrexed and carboplatin or pemetrexed and cisplatin may be administered. If any criteria are not met, administration of therapy will be postponed. From the second cycle onwards, the study treatment will be discontinued if administration of therapy has not been initiated by 14 days after the estimated Day 1.

Table J-1: Criteria for Administration of Platinum (Carboplatin or Cisplatin) and Pemetrexed on Day 1 of Each Cycle

Parameter		Criteria for Start
WBC		$\geq 2.5 \times 10^9$/L
Neutrophil count		$\geq 1.0 \times 10^9$/L
Platelet count		$\geq 100 \times 10^9$/L
Renal function		> 50 ml/min for cisplatin or > 20 mL/min for carboplatin AND < 10% change in GFR from previous cycle
Nonhematologic toxicities	Bilirubin	≤ ULN
	AST/ALT	< 2.5 × ULN

If pemetrexed and/or platinum (carboplatin or cisplatin) are held for any of the reasons noted in Table J-1 above, both epacadostat and nivolumab should be held as well, and the subject will be evaluated at least weekly until the toxicity has resolved. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table J-2, taking tolerability of the most recent dose into account.

J.2. Pemetrexed and Platinum (Carboplatin or Cisplatin) Dose Modifications

Table J-2 provides guidance for dose reductions for hematologic toxicities, and Table J-3 provides guidance for nonhematologic toxicities.

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Table J-2: Criteria for Dose Reductions for Hematologic Toxicities

	Nadir ANC		Nadir Platelet Count	Dose Modification Following Recovery	
				Pemetrexed	**Platinum**
Hematologic toxicity	≥ 0.5	AND	≥ 50	Full dose	Full dose
	Any	AND	≤ 50 without bleeding	75% of previous dose	75% of previous dose
	Any	AND	≤ 50 with bleeding	50% of previous dose	50% of previous dose
	Febrile neutropenia			75% of previous dose	75% of previous dose

Note: Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. All dose modifications should be made based on the worst grade toxicity per CTCAE v4.0.

Note: If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

Table J-3: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		Epacadostat and pembrolizumab	Pemetrexed	Platinum
Diarrhea **See also irAE of Colitis/enteritis* (See Section 5.7.3.2, Table 11)	Grade 1	Continue epacadostat and nivolumab, initiate supportive care.	No dose reduction	No dose reduction
	Grade 2	Hold epacadostat and nivolumab and initiate supportive care. Resume at previous dose if recovers to ≤ Grade 1 within 2 weeks. If diarrhea does not resolve within 2 weeks, consider steroids. When resolved to ≤ Grade 1 and steroids tapered, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	No dose reduction	No dose reduction
	Grade 3 or 4	Hold epacadostat and nivolumab, and initiate supportive care and steroids. When resolved to ≤ Grade 1 and steroids tapered, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	25% dose reduction	25% dose reduction
Mucositis	Grade 3	Reduce epacadostat 1 dose level and resume nivolumab at the same dose.	50% dose reduction	No dose reduction
Neurotoxicity	Grade 2	Resume epacadostat and nivolumab at the same dose.	25% dose reduction	25% dose reduction
	Grade 3 or 4	Reduce epacadostat 1 dose level and resume nivolumab at the same dose.	Discontinue study treatment	Discontinue study treatment
Other nonhematologic toxicity	Grade 3	Reduce epacadostat 1 dose level and resume nivolumab at the same dose.	25% dose reduction	25% dose reduction
	Grade 4	Permanently discontinue epacadostat and nivolumab unless discussed with medical monitor.	25% dose reduction	25% dose reduction

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Table J-3: Criteria for Dose Reductions for Nonhematologic Toxicities (Continued)

	If the calculated GFR falls by more than10% from the previous cycle, consider dose reduction.			
	GFR	**Cisplatin dose**	**GFR**	**Carboplatin dose**
Renal impairment	≥ 50 mL/min	Full dose per Protocol.	≥ 30 mL/min	Use AUC as per Protocol.
	≥ 30 to < 50 mL/min	Reduce cisplatin dose 50% or switch to carboplatin AUC 6.	20-30 mL/min	EDTA then use AUC as per Protocol, or consider to discontinue carboplatin.
	< 30 mL/min	Discontinue cisplatin, continue paclitaxel.	< 20 mL/min	Discontinue carboplatin, continue paclitaxel.

Note: If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

Table J-4 provides guidance for dose reductions for elevations of AST, ALT, and/or bilirubin.

Table J-4: Criteria for Dose Reductions for Hepatic Toxicity

AST/ALT	Bilirubin	Epacadostat and Nivolumab	Platinum	Pemetrexed
Grade 1 (< 3 × ULN)	≤ 1.5 × ULN	Continue epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline.	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	≤ 1.5 × ULN	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 1 (ULN to 1.5 × ULN)	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 2 (1.5 × to 3 × ULN) *Note: If > 2 × ULN, meets Hy's Law [a]	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT and/or bilirubin do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Continue same dose
ANY Grade 3 or Grade 4		Permanently discontinue study treatment.		
Hy's Law[a]		Permanently discontinue study treatment.		

LFT = liver chemistry test.

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) > 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

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APPENDIX K. DOSE MODIFICATIONS FOR PLATINUM (CARBOPLATIN OR CISPLATIN)/5-FLUOROURACIL

K.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table K-1, 5-FU and platinum may be administered. If any criteria are not met, administration of therapy will be postponed. From the second cycle onwards, the study treatment will be discontinued if administration of therapy has not been initiated by 14 days after the estimated Day 1.

Table K-1: Criteria for Administration of 5-FU/Platinum on Day 1 of Each Cycle

Parameter		Criterion for Start
WBC		$\geq 3.0 \times 10^9$/L
Neutrophil count		$\geq 1.5 \times 10^9$/L
Platelet count		$\geq 100 \times 10^9$/L
Infection		No fever (> 38.0°C or 100.4°F) suspect for infection
Nonhematologic toxicities	Diarrhea	No watery diarrhea
	Renal function	> 50 ml/min for cisplatin or > 20 mL/min for carboplatin AND < 10% change in GFR from previous cycle
	Others	< Grade 2 (except for nausea, vomiting, anorexia, and fatigue)

If 5-FU/platinum is held for any of the reasons noted in Table K-1 above, both epacadostat and nivolumab should be held as well, and the subject will be evaluated at least weekly until the toxicity has resolved. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table K-2 and Table K-3 for hematologic toxicities, taking tolerability of the most recent dose into account.

K.2. Dose Modifications for Hematologic Toxicities

Table K-2 provides guidance for dose reductions for hematologic toxicities.

Table K-2: Dose Reductions Criteria for Hematologic Toxicities

	Dose modifications based on neutrophil and/or platelet count on day of treatment (Day 1)					
	ANC		**Platelet Count**	**Action**	**Dose Modification Following Recovery**	
					5-FU	**Platinum**
Hematologic toxicity	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75%-100% dose	75% dose
	$< 1.0 \times 10^9$/L	AND	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75% dose	75% dose

Table K-3 provides guidance for dose reductions for the second appearance of the specified hematologic toxicities. Based on the most severe toxicity experienced since the last treatment,

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the dose modifications included in Table K-4 below will also be used for nonhematologic toxicities. When the dose of 5-FU is reduced, the dose of leucovorin will remain the same. If oxaliplatin is discontinued for peripheral neuropathy, 5-FU, leucovorin, nivolumab, and epacadostat may be continued until additional discontinuation criteria are met.

Table K-3: Dose Reductions Criteria for Recurrent Hematologic Toxicities

	ANC		Platelet Count	Action	Dose Modification Following Recovery	
					5-FU	Platinum
Hematologic toxicity	$\geq 1.0 \times 10^9$/L	AND	$\geq$ 100×10^9/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq$ 100×10^9/L	Delay 1 week until recovery	75%-100% dose	75% dose
	$< 1.0 \times 10^9$/L	AND	$\leq$ 100×10^9/L	Delay 1 week until recovery	75% dose	75% dose

After a second dose reduction, if any hematologic toxicities reoccur (third occurrence) and are clearly associated with chemotherapy regimen, chemotherapy regimen may be discontinued. However, epacadostat and nivolumab may be continued at the same dose at the discretion of the investigator and with the approval of the medical monitor.

K.3. Management Guidelines for Nonhematologic Toxicities

Table K-4 provides guidance for dose reductions for the appearance of nonhematologic toxicities. Toxicities must be resolved to ≤ Grade 1 before resuming study treatment. Some AEs may overlap with the occurrence of some potential irAEs (eg, diarrhea and colitis/enteritis). In these cases, both the AE and irAE guidances should be reviewed to determine the most appropriate management of dose interruptions and dose reductions for any study medications.

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Table K-4: Dose Reductions Criteria for Nonhematologic Toxicities

Criteria		Epacadostat and Nivolumab	5-FU	Platinum
Diarrhea *See also irAE of Colitis/enteritis (see Section 5.7.3.2, Table 11)	Grade 1	Continue epacadostat and nivolumab, initiate supportive care.	No dose reduction	No dose reduction
	Grade 2	Hold epacadostat and nivolumab, and initiate supportive care. Resume at previous dose if recovers to ≤ Grade 1 within 2 weeks. If diarrhea does not resolve within 2 weeks, consider steroids. When resolved to ≤ Grade 1 and steroids tapered, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, treatment with epacadostat and nivolumab should be discontinued or discussed with medical monitor.	No dose reduction	No dose reduction
	Grade 3 or 4	Hold epacadostat and nivolumab, and initiate supportive care and steroids. When resolved to ≤ Grade 1 and steroids tapered, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, treatment with epacadostat and nivolumab should be discontinued or discussed with medical monitor.	75% dose	75% dose
Mucositis	Grade 3	Hold epacadostat and nivolumab, and initiate supportive care. Resume at previous dose if recovers to ≤ Grade 1 within 2 weeks. If mucositis does not resolve within 2 weeks, epacadostat should be reduced 1 dose level, but nivolumab may be restarted at the same dose and schedule after resolution to ≤ Grade 1 and steroids tapered. If the mucositis is clearly attributed to 5-FU, epacadostat and nivolumab does not need to be held or dose reduced.	75% dose	No dose reduction
Mucositis	Grade 4	Permanently discontinue epacadostat and nivolumab unless discussed with medical monitor. If the mucositis is clearly attributed to 5-FU, no action is required with regard to nivolumab and epacadostat.	Discontinue	Discontinue
Neurologic toxicities	Grade 2	Resume epacadostat and nivolumab at same dose.	No dose reduction. Stop treatment for hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia or visual disturbances.	75% dose
	Grade 3	Reduce epacadostat 1 dose level and resume nivolumab at same dose.		Stop treatment

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Table K-3: Dose Reductions Criteria for Nonhematologic Toxicities (Continued)

Criteria		Epacadostat and Nivolumab	5-FU	Platinum
Other nonhematologic toxicity	Grade 3	Reduce epacadostat 1 dose level and resume nivolumab at same dose.	75% dose	75% dose
	Grade 4	Permanently discontinue epacadostat and nivolumab unless discussed with medical monitor.		Stop treatment

Note: If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

Table K-5 provides guidance for dose reductions for elevations of AST, ALT, and/or bilirubin.

Table K-5: Dose Reductions Criteria for Hepatic Toxicity

AST/ALT	Bilirubin	Epacadostat and Nivolumab	5-FU	Platinum
Grade 1 (< 3 × ULN)	≤ 1.5 × ULN	Continue epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline.	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	≤ 1.5 × ULN	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 1 (ULN to 1.5 × ULN)	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 2 (1.5 × to 3 × ULN) *Note: If > 2 × ULN, meets Hy's Law[a]	Hold epacadostat and nivolumab and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Consider steroids if AST/ALT and/or bilirubin do not resolve within 2 weeks of dose. Resume at previous dose if recovers within 12 weeks. If AE does not resolve within 12 weeks or if unable to reduce corticosteroids to ≤ 10 mg prednisone or equivalent within 12 weeks, study treatment with both study drugs should be discontinued.	Continue same dose	Continue same dose
ANY Grade 3 or Grade 4		Permanently discontinue study treatment.		
Hy's Law[a]		Permanently discontinue study treatment.		

LFT = liver chemistry test.

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) > 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

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APPENDIX L. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Date of Protocol:	15 AUG 2014
Date of Amendment (Version) 1:	01 OCT 2014
Date of Amendment (Version) 2:	03 APR 2015
Date of Amendment (Version) 3:	16 JUL 2015
Date of Amendment (Version) 4:	12 FEB 2016
Date of Amendment (Version) 5:	13 JUL 2016
Date of Amendment (Version) 6:	05 JUL 2017
Date of Amendment (Version) 7:	29 SEP 2017
Date of Amendment (Version) 8:	31 MAY 2018

Amendment (Version) 8

The primary purpose of this amendment is to update the Introduction and investigational agent background, to revise the Schedule of Assessments, to remove the post-treatment disease status and survival follow-up periods, to clarify the maximum duration of nivolumab and epacadostat treatment, to update the subject management guidelines for disease status, to revise the chemotherapy pre-medication guidelines and to update the toxicity management guidelines for subjects in the chemo-immunotherapy cohorts.

1. **Synopsis; Section 5.8, Criteria for Permanent Discontinuation of Study Drug(s); Section 5.9.1, Study Completion Criteria; Section 6, Study Assessments; Section 7.3.4, Post-Treatment Anticancer Therapy Status; Section 7.5.2, Tumor Imaging During the Study; Section 7.5.3, Assessment of Disease According to Modified RECIST for Solid Tumors; Section 7.8.7, Withdrawal or Discontinuation**

   Description of change: The post-treatment disease status and survival follow-up periods have been removed from the Protocol.

   Rationale for change: The sponsor has determined that post-treatment disease status and survival follow-up data are no longer needed.

2. **Synopsis; Section 1.4.1, Rationale for 2-Year Duration of Treatment, Section 5.5, Duration of Treatment and Subject Participation; Section 5.8, Criteria for Permanent Discontinuation of Study Drug(s); Section 6.2, Treatment Period**

   Description of change: A maximum treatment duration for nivolumab and epacadostat was updated to 2 years.

   Rationale for change: Accumulating data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

Incyte Document Number IC-DEV-PROT-AMEND-0350.

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3. **Synopsis; Section 5.2.1, Paclitaxel/Platinum (Carboplatin or Cisplatin); Section 5.2.2, Pemetrexed/Platinum (Carboplatin or Cisplatin); Section 5.2.3, Platinum (Carboplatin or Cisplatin)/5-Fluorouracil**

   Description of change: The Protocol was updated to clarify that premedications, including corticosteroids, may be given based on institutional guidelines and study investigator practice.

   Rationale for change: To allow for greater flexibility and Investigator discretion in prechemotherapy prophylaxis.

4. **Synopsis; Section 6, Study Assessments; Section 6.4.2, Disease Status Follow-Up; Section 7.5.2, Tumor Imaging During the Study**

   Description of change: Imaging schedule was updated to specify that subjects in the combination chemo-immunotherapy cohorts (Phase 1 Part 2) should be assessed at 8 and 16 weeks after the start of treatment and then every 12 weeks thereafter. The imaging schedule for all other subjects (Phase 1 Part 1 and Phase 2) was updated to every 12 weeks. The imaging schedule for all subjects was also updated to indicate that no additional imaging is required after end of treatment.

   Rationale for change: To perform fewer, less frequent imaging assessments for subject convenience and to relieve site staff burden while still evaluating disease status at clinically appropriate intervals.

5. **Synopsis; Section 6, Study Assessments; Section 7.4.6, Laboratory Assessments; Section 7.4.6.3, Liver Chemistry Tests**

   Description of change: The requirements for liver chemistry testing for subjects in the combination chemo-immunotherapy cohorts was updated to Day 1 of each cycle, starting with Cycle 4.

   Rationale for change: To clarify the requirement and to implement clinically acceptable monitoring of liver function.

6. **Section 1.2.1, Rationale for Combining PD-1 Inhibitor and IDO1 Inhibito** [redacted]

   Description of change: Additional background was added pertaining to the results of a Phase 3 randomized study of pembrolizumab plus epacadostat versus pembrolizumab versus placebo in unresectable or metastatic melanoma.

   Rationale for change: To provide relevant background information pertaining to epacadostat.

7. **Synopsis; Section 6, Study Assessments; Section 7.8, Tumor Biopsy Collection and Analysis**

   Description of change: The requirement for tumor biopsy (screening or on-treatment) has been removed from the Protocol.

   Rationale for change: Biopsy tissue is no longer needed for translational or correlative analysis, and thus the biopsy requirement was removed.

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8. **Appendix I, Dose Modifications for Paclitaxel/Platinum (Carboplatin or Cisplatin); Appendix J, Dose Modifications for Pemetrexed/Platinum (Carboplatin or Cisplatin); Appendix K, Dose Modifications for Platinum (Carboplatin or Cisplatin)/5-Fluorouracil**

   Description of change: Updated the dose hold and dose reduction criteria for specified toxicities.

   Rationale for change: To clarify the dose hold and dose reduction criteria for each of the chemoimmunotherapy combinations.

9. **Synopsis; Section 5.8, Criteria for Permanent Discontinuation of Study Drug(s); Section 6, Study Assessments; Section 7.3.4, Post-Treatment Anticancer Therapy Status**

   Description of change: Removed the 60-day post-treatment safety follow-up visit.

   Rationale for change: Standard follow-up timepoints for nivolumab combinations has changed to 30- and 100-day post-treatment only; 60-day follow-up was removed to relieve subject burden.

10. **Synopsis; Section 5.7.4, Treatment After Initial Evidence of Radiologic Disease Progression; Section 5.8, Criteria for Permanent Discontinuation of Study Drug(s); Section 6, Study Assessments; Section 7.5.3, Assessment of Disease According to Modified RECIST for Solid Tumors**

    Description of change: The option to treat clinically stable subjects beyond initial disease progression using modified assessment criteria (RECIST, Cheson, RANO) was removed from the Protocol.

    Rationale for change: Given the lack of evidence that epacadostat augments the activity of nivolumab (as described in Section 1.2.1), it is unnecessary to evaluate subjects for pseudoprogression.

11. **Section 1.1.1, Inhibition of PD-1 as a Target for Cancer; Section 1.1.6, Overview of Platinum-Based Doublet Chemotherapy Compared With Immunotherapy in Squamous and Nonsquamous Non–Small Cell Lung Cancer; Section 1.3.10, Risks From Combining a PD-1 Inhibitor With Chemotherapy; Section 1.4, Justification of Treatment Regimens**

    Description of change: The background information for nivolumab was updated; current safety and efficacy data for recent studies evaluating chemo-immunotherapy combinations was added.

    Rationale for change: To reflect the current approval status in nivolumab and recently updated data regarding anti-PD-1/chemotherapy combinations.

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12. **Section 1.3.1, Risks From Epacadostat; Section 5.7.4, Procedures for Subjects Exhibiting Serotonin Syndrome**

    Description of change: The epacadostat risk language and serotonin syndrome management guidelines were updated to reflect current language.

    Rationale for change: To incorporate updated information regarding the risk and management of serotonin syndrome.

13. **Section 6, Study Assessments (Table 20, Schedule of Assessments End of Treatment Through Safety Follow-Up [Combination Immunotherapy Cohorts With Both Q2W and Q4W Nivolumab Dosing Schedules]; Table 24, Schedule of Assessments for Phase 1 Part 2 Subjects Treated With Epacadostat + Nivolumab [Q3W] + Platinum/Paclitaxel or Epacadostat + Nivolumab + Platinum/Pemetrexed or Epacadostat + Nivolumab + Platinum/5-FU [Combination Chemo Immunotherapy Cohorts])**

    Description of change: The physical exam requirement at EOT was updated from a complete physical exam to a targeted physical exam.

    Rationale for change: Targeted physical exam at the EOT is sufficient to monitor subject safety.

[redacted]

15. **Section 6, Study Assessments (Table 26, Laboratory Tests: Required Analytes)**

    Description of change: Urea was added as an acceptable alternative to blood urea nitrogen, plasma lipase was added as an acceptable alternative to serum lipase, and reticulocyte count was deleted.

    Rationale for change: To clarify the required laboratory analytes.

16. **Section 6, Study Assessments; Section 7.5.2, Tumor Imaging During the Study**

    Description of change: Deleted text regarding collection of radiographic tumor assessments for independent review.

    Rationale for change: Independent review is no longer planned.

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17. **Incorporation of administrative changes.** Other minor administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment (Version) 7

This amendment has 2 main purposes:

- To provide separate schedule of assessment tables for the Q2W and Q4W nivolumab dosing schedules in order to clarify the clinical visit schedules for study and laboratory assessments.

This amendment includes the changes to Protocol INCB 24360-204 Amendment 6 (05 JUL 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 4.1.2, Phase 2 Combination Immunotherapy Cohort Expansions**

   Description of change: The I/O relapsed MEL cohort definition was deleted as the definitions for both I/O relapsed and refractory melanoma cohorts are included in the eligibility section.

   Rationale for change: To remove redundant information.

2. **Synopsis**

   Description of change: In the Combination Immunotherapy and Chemo-Immunotherapy, Regimen and Mode of Administration section, the last paragraph of the Nivolumab subsection was removed as it was repeating the same information it was included in the previous paragraph.

   Rationale for change: To remove the redundant information.

3. **Synopsis; Section 3.2, Subject Inclusion Criteria (Criterion 4b)**

   Description of change: Added the requirement that subjects must not have ocular melanoma.

   Rationale for change: This requirement was inadvertently removed in Amendment 6 and has been added back.

4. **Synopsis; Section 3.2, Subject Inclusion Criteria (Criterion 4b)**

   Description of change: A new criterion was added to indicate that subjects with immunotherapy (I/O) refractory melanoma (MEL) must have no more than 2 prior lines of therapy for advanced/metastatic disease, only 1 of which can be a prior anti–PD-1/PD-L1 therapy, with or without anti–CTLA-4 therapy. Prior anti–CTLA-4 monotherapy is not permitted.

   Rationale for change: To clarify prior therapy requirements for subjects with I/O-refractory MEL.

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5. **Synopsis; Section 3.2, Subject Inclusion Criteria (Criterion 4d)**

   Description of change: The prior systemic therapy requirement for subjects with squamous cell carcinoma of the head and neck (SCCHN) was separated into 2 criteria, one for Phase 1 Part 1 and Phase 2 cohorts, and one for Phase 1 Part 2 cohorts.

   Rationale for change: To clarify the prior systemic therapy requirement for combination immunotherapy and combination chemo-immunotherapy SCCHN cohorts.

6. **Synopsis**

   Description of change: The estimated study duration section, which included study timelines, was removed.

   Rationale for change: This section is no longer required as the information is included in the ClinicalTrials.gov posting for the study.

[redacted]

8. **Section 6, Study Assessments (Table 24); Section 7.4.5, Twelve-Lead Electrocardiogram**

   Description of change: Revised to indicate 1) continuous concomitant medication review and adverse events assessment, 2) 12-lead ECG during the treatment period on C1D1 and C2D1 only; 3) administration of IV chemotherapy doublet (platinum/paclitaxel or platinum/pemetrexed) will be minimum 4 cycles and up to 6 cycles (to align with the dosing schedule in Table 3), and 4) epacadostat will be administered before the start of nivolumab infusion.

   Rationale for change: To clarify that concomitant medication review and adverse events review will occur throughout the study up to 100 days safety follow-up visit, and to clarify the chemotherapy regimen duration in the study as well as the epacadostat administration order on the days when chemotherapy is being administered.

9. **Section 6, Study Assessments (Table 25)**

   Description of change: Coagulation panel and endocrine function tests should be performed at the same clinic visit; the table was updated to adjust the test schedules and to state that both tests will take place every third cycle after the first 3 cycles.

   Rationale for change: To clarify assessment schedules for coagulation panel and endocrine function tests.

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10. **Section 6, Study Assessments (Tables 25 and Table 26)**

    Description of change: Clarification regarding hepatitis B surface antigen testing was removed from the table body and added as a footnote to Table 26, stating that hepatitis B surface antigen testing will only include antigen testing (not antibody testing).

    Rationale for change: To clarify the serological marker for hepatitis B testing.

11. **Section 5.13, Prohibited Medications and Measures**

    Description of change: UGT1A9 list of medications was updated.

    Rationale for change: To align with compound level revised list.

12. **Incorporation of administrative changes.** Other minor administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment (Version) 6

This amendment has 2 purposes:

- Addition of new immunotherapy/chemotherapy combination cohorts in Phase 1 to evaluate the safety and tolerability of and to determine the recommended Phase 2 dose for epacadostat (INCB24360) and nivolumab in combination with standard-of-care (SOC) chemotherapy regimens in subjects with advanced or metastatic squamous cell carcinoma of the head and neck (SCCHN) and non–small lung cancer (NSCLC). Phase 1 is now divided into 2 parts: Part 1 is the original combination immunotherapy regimen, and Part 2 describes the new combination immunotherapy and chemotherapy regimens.
- Addition of 2 new melanoma (MEL) cohorts in Phase 2 to evaluate the safety and efficacy of epacadostat in combination with nivolumab in subjects who relapsed or are refractory to programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) therapy.

This amendment includes the following additional changes to Protocol INCB 24360-204 Amendment 5 (13 JUL 2016) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1, Introduction; Section 2, Study Objectives and Purpose; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment of Subjects; Section 6, Study Assessments; Section 7, Conduct of Study Assessments and Procedures; Section 8.8, Safety Monitoring Committee; Section 9, Statistics; Section 16, References; Appendices J, K, and L (Dose Modifications for Paclitaxel/Platinum, Pemetrexed/Platinum, and Platinum/5-Fluourouracil, respectively)**

   Description of change: Three new cohorts have been added to the study as Phase 1 Part 2, in which subjects will receive the following regimens:

   - 5-Flurouracil + carboplatin or cisplatin in combination with nivolumab and epacadostat in subjects with SCCHN as first-line therapy.
   - Pemetrexed + cisplatin or carboplatin with nivolumab and epacadostat in subjects with nonsquamous NSCLC as first-line therapy.
   - Paclitaxel + cisplatin or carboplatin with nivolumab and epacadostat in subjects with NSCLC as first-line therapy.

   Safety and tolerability have been added as primary objectives, with efficacy was added as secondary objective. The study design has been revised to include chemo-immunotherapy combination dose-finding and safety expansion cohorts. All relevant Protocol sections, including tables and figures, have been revised and updated accordingly.

   Rationale for change: To provide background, study and dose rationale, study design, study objectives and endpoints, inclusion and exclusion criteria, study treatment details, study schedule and assessments, and statistical considerations to evaluate epacadostat and nivolumab (immunotherapy combinations) in combination with SOC chemotherapy

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regimens for advanced cancers. Emerging data from other clinical studies indicate that immunotherapy combinations with chemotherapy may increase response rates and survival in certain tumor types. Further, safety will be monitored with the study team, site investigators, and a safety monitoring committee.

2. **Synopsis; Section 1, Introduction; Section 2, Study Objectives and Purpose; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment of Subjects; Section 6, Study Assessments; Section 7, Conduct of Study Assessments and Procedures; Section 8.8, Safety Monitoring Committee; Section 9, Statistics; Section 16, References**

   Description of change: Two new MEL cohorts have been added in Phase 2 to evaluate subjects with disease that has relapsed after or is refractory to anti–PD-1/PD-L1 therapy. Subjects will receive epacadostat 100 mg twice daily (BID) in combination with 480 mg nivolumab intravenously (IV) every 4 weeks (q4w). Objectives for the safety and tolerability as well as efficacy of the combination immunotherapy for these cohorts have been added. Applicable information regarding the role and rationale for use of immunotherapy combinations in relapsed and refractory solid tumors has also been added. All relevant Protocol sections, including tables and figures, have been updated accordingly.

   Rationale for change: Patients with MEL who have failed prior PD-1 or PD-L1 immunotherapies have high unmet need. Preliminary objective responses were observed in subjects who had prior anti–PD-1/PD-L1 therapies in this study. The safety data to date (Perez et al 2017) demonstrated that there were fewer dose holds and dose reductions in patients treated with epacadostat 100 mg BID compared to 300 mg BID in combination with nivolumab; therefore, the epacadostat dose will initially be 100 mg BID in these new cohorts.

3. **Synopsis; Section 1.4, Justification for Treatment Regimen; Section 4.1, Overall Study Design; Section 4.2, Study Endpoints; Section 5.1.2, Nivolumab**

   Description of change: The dose of nivolumab for the relapsed/refractory MEL cohorts will be 480 mg via 30-minute IV infusion q4w. The dose of nivolumab for Phase 1 Part 2 (new chemo-immunotherapy cohorts) will be 360 mg via 30-minute IV infusion every 3 weeks (q3w). Corresponding pharmacokinetic (PK) justification for these 2 new dosing schedules as well as supportive safety data have been added to Section 1.4. All relevant Protocol sections, including tables and figures, have been updated accordingly.

   Rationale for change: A pooled analysis derived from a comprehensive population pharmacokinetics (PPK) analysis for nivolumab demonstrated that nivolumab PK was linear, with dose-proportional exposures over a dose range of 0.1 to 10 mg/kg and similar across tumor types. Using the PPK model, the exposures following the administration of nivolumab 360 mg q3w and 480 mg q4w were simulated. Based on this analysis, it is predicted that both 360 mg q3w and 480 mg q4w doses are similar to 240 mg every 2 weeks (q2w) or 3 mg/kg q2w following the administration in subjects who have an approximately median weight of 80 kg. Thus, the 360 mg q3w and 480 mg q4w doses and schedules are supported by exposure-response analyses and will be used in this study

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in the chemo-immunotherapy combination cohorts and in the new relapsed and refractory MEL cohorts, respectively.

4. **Synopsis; Section 3.1, Study Population; Section 3.2, Subject Inclusion Criteria (Criteria 4 and 4g)**

   Description of change: The definition of glioblastoma has been revised as relapsed or refractory.

   Rationale for change: To provide a clarification for the definition of eligible glioblastoma subjects in the study.

5. **Synopsis, Section 3.2, Subject Inclusion Criteria (Criterion 7); Section 7.8, Tumor Biopsy Collection and Analysis**

   Description of change: For the new cohorts in Phase 1 Part 2 (chemo-immunotherapy cohorts) and Phase 2 (immuno-oncology relapsed and refractory MEL cohorts), it is required that biopsies must be confirmed to contain adequate tumor tissue by local pathology review. Inclusion criterion 7 was also revised to emphasize that the collection of archived tumor tissue is an alternative to fresh baseline tumor biopsies with medical monitor approval. A minimum required number of blocks for archived biopsies will be 20 slides (instead of 20-25 slides).

   Rationale for change: To clarify the Protocol text and to ensure that it is clear that confirmation of tumor tissue presence in biopsy samples is a requirement.

6. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   a. **Description of change:** Exclusion criteria 1, 1d, 1e, and 1.f have been revised. The greater than symbol was updated to greater than or equal to for serum creatinine in 1d; also, the option for glomerular filtration rate in place of creatinine was removed. Alkaline phosphatase was removed from criterion 1e, and criterion 1f was revised for bilirubin restriction based on the updated safety information at the program level.
      Rationale for change: Accumulating data from the epacadostat program and lower risks for the development of liver events, alkaline phosphatase will no longer be evaluated as an eligibility criterion in conjunction with ALT/AST. Exclusion criterion 1d has been updated to allow subjects with serum creatinine < 1.5 × ULN or measured or calculated creatinine clearance ≥ 50 mL/min to be enrolled in the study. Exclusion criterion 1f has been revised to allow subjects with total bilirubin < 1.5 × ULN or conjugated (direct) bilirubin < 40% of total bilirubin to be enrolled in the study.
   b. **Description of change:** Exclusion criterion 5 has been revised to specify that any prior immune-related adverse events (irAEs) must be resolved to ≤ Grade 1 before the first dose of epacadostat and nivolumab. Subjects with any ≥ Grade 3 irAEs (except lymphopenia or asymptomatic amylase/lipase elevations) from prior immunotherapies, including cytotoxic T-lymphocyte-associated antigen-4 treatment, are excluded. Subjects with history of ≥ Grade 3 endocrinopathies must be discussed with the medical monitor to determine eligibility.
      Rationale for change: To provide clarification about pre-existing irAEs that subjects may have had due to prior treatment before starting to this study and to provide guidance to the investigators in evaluation of these subjects during screening.

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c. **Description of change:** Exclusion criterion 6 was revised to specify that steroid use as a concomitant medication for glioblastoma subjects will be permitted when applied for systemic use or for physiological replacement doses of steroids.
Rationale for change: To provide clarification that there is an exception for glioblastoma subjects in steroid use due to its permitted use as a part of the SOC.

d. **Description of change:** Exclusion criterion 17 has been revised to specify that hepatitis C virus (HCV) Ab testing is required for screening purposes in countries where HCV RNA is not part of the SOC. In these cases, HCV antibody–positive subjects will be excluded. Subjects who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening visit. Table 24 has been revised accordingly.
Rationale for change: To clarify the exclusion of subjects identified as at risk for viral reactivation and to add country-specific hepatitis screening information.

e. **Description of change:** Exclusion criterion 22 has been updated to specify the acceptable QTc interval calculation formulas.
Rationale for change: To provide clarification and flexibility in calculation of QTc interval.

f. **Description of change:** Exclusion criterion 29 has been added to exclude subjects with bleeding associated with tumors that invade or are adjacent to major blood vessels, as shown unequivocally by imaging studies, or history of bleeding related to disease under study within 3 months of Cycle 1 Day 1.
Rationale for change: Although there is no evidence that epacadostat and/or other immunotherapies may pose an increased risk for bleeding in subjects whose tumor adjacent to major blood vessels, this exclusion criterion was added for the subject safety.

7. **Synopsis; Section 4.2.1.2, Phase 2; Section 4.2.2, Secondary Endpoints; Section 4.3, Measures Taken to Avoid Bias; Section 9.4, Statistical Analyses**

Description of change: The primary response criteria for the efficacy evaluation of solid tumors, lymphoma, and glioblastoma have been corrected, as they were included "modified" prefixes. The sections were revised to indicate that secondary endpoint efficacy analysis will be performed based on the traditional response criteria (Response Evaluation Criteria In Solid Tumors Version 1.1 [RECIST v1.1], Cheson, and Response Assessment in Neuro-Oncology [RANO]) as well as modified versions as described in the protocol (modified RECIST, modified Cheson, and modified RANO).

Rationale for change: To clarify the primary and secondary endpoint analysis response criteria for solid tumors, lymphoma, and glioblastoma.

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8. **Synopsis; Section 4.4, Number of Subjects; Section 9, Statistics**

   Description of change: The anticipated number of subjects participating in the study and selection of sample sizes/statistical methods have been updated. Per this amendment, there will be approximately 207 subjects enrolled in Phase 1 of the study (instead of approximately up to 63) and approximately 278 subjects enrolled in Phase 2 (instead of approximately up to 228), for a total of approximately 485 subjects enrolled (instead of approximately up to 291).

   Rationale for change: To account for changes in study design due to the new cohorts added as Part 2 of Phase 1 and Phase 2 of the study.

9. **Synopsis; Section 5.1, Administration of Study Drugs; Section 5.2, Background Therapies**

   Description of change: Information has been added regarding epacadostat administration and nivolumab administration in Phase 1 and Phase 2; for combination chemo-immunotherapy cohorts, timing after epacadostat and before premedications or chemotherapy and the timing of administration of new chemotherapy regimens has been included.

   Rationale for change: To clarify timing and administration of study drugs and premedications in Phase 1 and Phase 2.

10. **Synopsis; Section 6, Study Assessments (Tables 18-20); Section 6.4.2, Disease Status Follow-Up**

    Description of change: Disease status follow-up window in Phase 1 Part 1 and Phase 2 (combination immunotherapy cohorts) has been revised from every 8 weeks ± 5 days to every 8 weeks ± 7 days.

    Rationale for change: To define the follow-up period for disease status and make it consistent throughout the Protocol.

[redacted]

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12. **Synopsis; Section 8.8, Safety Monitoring Committee; Section 9.5, Analyses for the Safety Monitoring Committee**

    Description of change: New section and text added for the establishment of a sponsor-led Safety Monitoring Committee (SMC) for the new cohorts in Phase 1 Part 2 (combination chemo-immunotherapy cohorts) and Phase 2 (immuno-oncology relapsed and refractory MEL cohorts).

    Rationale for change: To describe the SMC and its function to closely monitor the safety of subjects enrolled in the new cohorts added to Phase 1 Part 2 (chemo-immunotherapy cohorts) and Phase 2 (immuno-oncology relapsed and refractory MEL cohorts).

13. **Section 1.3.1, Risks from Epacadostat; Section 5.7.5, Procedures for Subjects Exhibiting Serotonin Syndrome (Table 16)**

    Description of change: Added data on serotonin syndrome across the epacadostat program and revised the serotonin syndrome monitoring instructions.

    Rationale for change: There have been 2 separate events in 2 ongoing clinical studies (not in this study to date) reported across the epacadostat program as serotonin syndrome (each event was Grade 1). Although serotonin syndrome is uncommon, the monitoring of this event will continue in this program. The related Protocol sections have been updated accordingly.

14. **Section 1.3.1, Risks From Epacadostat; Section 5.7.5, Procedures for Subjects Exhibiting Serotonin Syndrome; Section 8.9, Adverse Events of Special Interest; Section 16, References; Appendix K, Publication on Serotonin Syndrome**

    Description of change: The Boyer and Shannon 2005 publication was removed from Appendix K. This was an administrative update.

    Rationale for change: To cite the published article as a reference rather than including it in full as an appendix.

15. **Section 5.7.2, Criteria and Procedures for Interruption (Table 8); Section 5.7.3.1, Procedures and Guidelines for Pneumonitis (Table 10)**

    Description of change: The following note has been added to the relevant sections of Table 8 and Table 10 based on the severity of events: "In case nivolumab is discontinued permanently, epacadostat should be discontinued as well."

    Rationale for change: To provide guidance and clarification for restarting study treatment or permanent discontinuation.

16. **Section 5.8, Criteria for Permanent Discontinuation of Study Drug(s)**

    Description of change: Additional criteria have been added to determine possible subject discontinuation from study treatment.

    Rationale for change: To provide investigators with additional options for decision-making for the enrolled subjects found ineligible during the study and for the subjects noncompliant with study drug administration and/or assessments.

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17. **Section 5.11.3, Management of Infusion Reactions From Nivolumab**

    Description of change: Added the management guidance for severe hypersensitivity reactions caused by infusions under Grade 3 and Grade 4 symptoms.

    Rationale for change: To provide more guidance about how to manage Grade 3 and Grade 4 hypersensitivity events that may develop after the infusion.

18. **Section 6, Study Assessments (Tables 18-21)**

    Description of change: Revised the table titles and reordered the laboratory assessments. Table 20 has been revised to include whole blood and plasma sample collection timings.

    Rationale for change: To provide clarity due to the addition of new cohorts and timings for whole blood and plasma sample collections.

19. **Section 6, Study Assessments (Tables 18 and 19); Section 7.4.6.4, Pulse Oximetry (O_2 Saturation)**

    Description of change: Section 7.4.6.4 has been removed, and Tables 18 and 19 have been revised, as pulse oximetry is no longer a required assessment in this study.

    Rationale for change: Pulse oximetry changes are not sensitive or specific for the diagnosis of pneumonitis that is suspected based on clinical signs and symptoms and confirmed with radiographic evaluations. Treatment decisions do not depend on changes in pulse oximetry parameters.

20. **Section 8.1.2, Reporting; Appendix F, Common Terminology Criteria For Adverse Events v4.0**

    Description of change: Revised adverse event reporting requirements. Additionally, Appendix F has been removed.

    Rationale for change: To align with the updated Protocol template language and to add adverse event grading definitions per National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

21. **Section 8.9, Adverse Events of Special Interest**

    Description of change: Revised the definition for adverse events of special interest further based on emerging data at the program level. The first definition now specifies that an elevated AST or ALT laboratory value that is $\geq 3 \times$ ULN and an elevated total bilirubin laboratory value that is $\geq 2 \times$ ULN as determined by way of Protocol-specified laboratory testing or unscheduled laboratory testing is considered an adverse event of special interest. The second definition now has 2 additional criteria: $\geq$ Grade 3 rash or dermatitis and Grade 4 laboratory abnormality. Some paragraphs were reordered.

    Rationale for change: To provide clarification about the adverse events of special interest to guide investigators to identify and to report these types of events.

Incyte Document Number IC-DEV-PROT-AMEND-0350.

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22. **Section 10.2, Accountability, Handling, and Disposal of Study Drug**

    Description of change: Updated study drug compliance, accountability, and destruction requirements at the investigational sites.

    Rationale for change: To align with the revised compound-level updates and requirements.

23. **Incorporation of administrative changes.** Other minor administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment (Version) 5

The primary purpose of this amendment is to modify the Protocol to enable European (EU) sites to participate in this study.

This amendment includes the changes to the Protocol INCB 24360-204 Amendment 4 (12 FEB 2016) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Title Page**

   Description of change: EudraCT number was included on the title page.

   Rationale for change: EudraCT Number was obtained.

2. **Section 1, Introduction; Section 1.2.2, Preclinical and Clinical Study Data for Epacadostat and Nivolumab; Section 1.3.2, Risks for Nivolumab; Section 10.1.2.2, Nivolumab; Section 16, References**

   Description of change: The reference for the nivolumab Investigator's Brochure was replaced with references to the nivolumab Summary of Product Characteristics (SmPC) and United States Package Insert (USPI). In Section 1.3.2, cross-references to Section 5.6.3, Table 7, and Appendix C were added for details regarding immune-related toxicities, and the paragraph regarding the overall safety experience with nivolumab was deleted.

   Rationale for change: References to the SmPC and USPI added to provide nivolumab approved product information and background for nonclinical and clinical data in the EU and US, respectively. Cross-references to Section 5.6.3, Table 7, and Appendix C were added to provide adequate details for immune-related toxicities.

3. **Section 1.1.1, Inhibition of PD-1 as a Target for Cancer**

   Description of change: Information about nivolumab marketing approval in the US and EU was updated.

   Rationale for change: To include up-to-date US and EU marketing approval information for nivolumab.

4. **Synopsis; Section 3.2, Subject Inclusion Criteria; Section 8.5, Pregnancy**

   Description of change: Duration of contraception requirement in inclusion criterion #8 was increased from 125 days to 150 days after the last dose of study treatment. In Section 8.5, the window for pregnancy was also updated to pregnancy occurring during the study or within 150 days (instead of 125 days) of completing the study.

   Rationale for change: To comply with the SmPC recommendations.

5. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of change: A note was added to inclusion criterion 4a for subjects with Stage IIIB, Stage IV, or recurrent NSCLC who have tumors with driver mutations treated with a tyrosine kinase inhibitor therapy.

   Rationale for change: To clarify that tyrosine kinase inhibitor therapy alone is not considered a second systemic chemotherapy regimen.

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6. **Section 5.9, Beginning and End of the Study**

   Description of change: "Any remaining subjects may continue to receive study medication and be seen by the investigator per usual standard of care for this subject population. In addition, the investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 8.3 (Serious Adverse Events)." was revised as "Any remaining subjects may continue to receive study medication per Protocol."

   Rationale for change: Subjects continuing to receive study medication will remain on study and be followed per Protocol.

7. **Section 1.1.1. Inhibition of PD-1 as a Target for Cancer; Section 3.3, Subject Exclusion Criteria; Section 5.11, Restricted Medications and Measures; Section 5.12, Prohibited Medications and Measures; Section 5.6.5, Procedures for Subjects Exhibiting Serotonin Syndrome; Section 8.9, Adverse Events of Special Interest**

   Description of change: In Section 1.1.1, the brand name Opdivo was deleted. In Section 5.11 the brand name "Coumadin" was deleted and replaced with the generic drug name "warfarin." In Sections 3.3 and 5.12, the brand name "FluMist" was deleted. In Sections 5.6.5 and 8.9, the brand name Demerol was deleted and replaced with the generic drug names meperidine/pethidine.

   Rationale for change: To provide generic drug names only.

8. **Synopsis; Section 6, Study Assessments (Tables 15 and Table 17)**

   Description of change: Table 15 notes that there will be laboratory assessments and reminder card distribution on Cycle 1 Day 8, and laboratory assessments on Cycle 1 Days 22, 36, and 50.

   Per Protocol Amendment 4 (dated 12 FEB 2016), [redacted]. In addition, in Section 7.4.6.3 (Liver Chemistry Tests), the frequency of liver chemistry tests was changed to every cycle rather than every week. Therefore, there will be no laboratory assessments on Cycle 1 Day 8 or Cycle 1 Days 22, 36, and 50.

   Since there will be no scheduled clinical visit on Cycle 1 Day 8, the reminder card distribution will not occur as marked in Table 15. Adverse events and concomitant medication assessments for Cycle 1 Day 8 will be collected by phone call (new footnote "a" has been added to Table 15).

   Rationale for change: To align Tables 15 and 17 with changes made in Protocol Amendment 4 to Sections 7.7.1 and 7.4.6.3.

9. **Section 7.5.1, Initial Tumor Imaging**

   Description of change: Subjects with glioblastoma are no longer required to have a chest and abdominal CT scan.

   Rationale for change: To exempt subjects with glioblastoma from the baseline chest and abdominal CT scan because extracranial metastases are rare in these subjects.

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10. **Section 10.1.1.1, Epacadostat; Section 10.1.1.2, Nivolumab**

    Description of change: Epacadostat packaging and labeling statement was revised as "All bottles of Incyte investigational product will be labeled to comply with regulatory requirements of each country." Nivolumab labeling statement was revised as "Clinical supplies will be labeled in accordance with local regulatory requirements."

    Rationale for change: To acknowledge compliance with labeling requirements in all countries.

11. **Section 13.3, Ethics Review**

    Description of change: The word "IEC" (independent ethics committee) was added to the fifth paragraph.

    Rationale for change: To include EU terminology.

12. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Appendix A was updated with Clinical Trial Facilitation Group recommendations related to contraception in clinical trials being conducted in European countries.

    Rationale for change: The clinical study will be conducted in ex-US centers; therefore, the contraception language was updated for EU compliance.

13. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment (Version) 4

The primary purpose of this amendment is to include epacadostat updates at the program level as well as clarify Phase 1 and Phase 2 cohort enrollments.

This amendment includes the changes to the Protocol INCB 24360-204 Amendment 3 (16 JUL 2015) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Section 1.3.1, Risks From Epacadostat**

   Description of change: Updated to report that 253 unique subjects have been exposed to epacadostat as monotherapy and/or in combination with checkpoint inhibitors as of 29 OCT 2015.

   Rationale for change: Updated with information contained in the recently revised epacadostat Investigator Brochure.

2. **Section 1.4, Justification for Treatment Regimen**

   Description of change: Updated the dose justification paragraph, which included INCB 24360-201 data supporting the doses of epacadostat used in this study.

   Rationale for change: The section was updated with the most recent data included in the epacadostat Investigator's Brochure.

3. **Synopsis; Section 2.1, Primary Objectives**

   Description of change: Clarification was included to state that "objective" response rate is going to be used as one of the criteria for response measurement analysis, not "overall" response rate.

   Rationale for change: To be consistent with the statistical analysis section of the Protocol (Section 9).

4. **Synopsis; Section 2.2, Secondary Objectives; Section 3.2, Subject Inclusion Criteria (Inclusion Criterion 5); Section 4.1, Overall Study Design; 4.2.2, Secondary Endpoints**

   Description of change: Clarification to specify that diffuse large B-cell lymphoma (DLBCL) is included as NHL not HL.

   Rationale for change: To correct the category of DLBCL as it belongs to NHL type not HL type of lymphoma.

5. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of change: Inclusion criterion 4g note was updated to indicate that relapse is defined as progression following initial line of therapy and if the participant had a surgical resection for relapsed disease and no antitumor therapy was instituted for up to 12 weeks, this is considered 1 relapse or recurrence.

   Rationale for change: Revised for clarity.

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6. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criterion 1f was updated to indicate that total bilirubin above the institutional upper limit of normal or conjugated bilirubin ≥ 1.2 × upper limit of normal (ULN) is excluded. If no institutional ULN for conjugated bilirubin is provided, conjugated bilirubin > 40% of total bilirubin is excluded.

   Rationale for change: Revised to be consistent with other epacadostat Protocols. In cases where a benign cause of elevated bilirubin may be present (eg, Gilbert's syndrome), an exception is clarified to indicate that conjugated (direct) bilirubin > 40% of total bilirubin is excluded. Conjugated bilirubin need only be tested if total bilirubin is elevated.

7. **Synopsis; Section 3.3, Subject Exclusion Criteria; Section 6, Study Assessments (Table 17, Laboratory Assessments for Screening Through Treatment Phase; Table 19, Laboratory Tests: Required Analytes)**

   Description of change: Exclusion criterion 17 was updated to specify that subjects with a known history of or who are positive for hepatitis B (HBsAg reactive) or hepatitis C (HCV RNA [qualitative] is detected) will be excluded. Hepatitis B surface antigen antibody, hepatitis B virus DNA, and hepatitis C virus antibody will not be tested in the study. Table 17 and Table 19 were revised accordingly.

   Rationale for change: The purpose of this change is to clarify the exclusion of patients who are identified as at risk for viral reactivation. The previous criteria excluded patients who were vaccinated for hepatitis B and could not provide documentation of prior vaccination; such patients are not at risk for viral reactivation.

8. **Synopsis; Section 3.3, Subject Exclusion Criteria; Section 5.11, Restricted Medications and Measures; Section 5.12, Prohibited Medications and Measures**

   Description of change: Exclusion criterion 6 was revised to specify subjects who use the systemic steroid or prednisone in doses that are equivalent to ≥ 10 mg/day within 7 days (instead of ≥ 7.5 mg within 14 days) prior to the first dose of treatment will not be eligible. The threshold for systemic steroids was also changed to 10 mg/day in Sections 5.11 and 5.12.

   Rationale for change: Updated to be consistent with other immunotherapy agents that use 10 mg as a cutoff since it is considered the physiologic replacement dose.

9. **Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criterion 9 was revised to clarify if a subject with glioblastoma had a major surgery; it must be ≥ 21 days since the surgery performed prior to enrollment.

   Rationale for change: This criterion was aligned with inclusion criterion 4g.

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10. **Synopsis; Section 3.3, Subject Exclusion Criteria**

    Description of change: Exclusion criterion 22 was updated to indicate that subjects with a screening QTc interval > 480 milliseconds (instead of 470 milliseconds) will be excluded.

    Rationale for change: Based on the QTc interval analysis conducted in Phase 1 and Phase 2 epacadostat studies, no clinically meaningful changes or trends were observed in QTc interval prolongation and the relationship between epacadostat plasma concentration and QTc intervals.

11. **Synopsis; Section 3.3, Subject Exclusion Criteria**

    Description of change: Exclusion criterion 27b was removed as it was indicating that if subjects with unresectable or Stage IV melanoma received prior anti-CTLA-4 treatment, they will not be eligible for the study.

    Rationale for change: This criterion was inconsistent with exclusion criterion 4a, indicating that anti-CTLA-4 therapy is permitted for subjects with metastatic melanoma as first-line treatment.

12. **Synopsis; Section 4.1 Overall Study Design**

    Description of change: The text was revised to allow subjects with colorectal cancer (CRC) to be enrolled in 300 mg cohort in Phase 1.

    Rationale for change: This change will allow CRC subjects to be enrolled in Phase 1 300 mg cohort as it was initially planned and approved in the original study design. There was no safety concern when the previous Protocol was amended to exclude CRC subjects from the 300 mg Phase 1 cohort.

13. **Synopsis; Section 4.1.1, Phase 1 Dose-Escalation Design**

    Description of change: The text was revised to specify that additional Phase 2 cohorts in the other tumor types may be opened to test 100 mg epacadostat BID. In addition, if additional cohorts are opened for other tumor types to test 100 mg BID, and 300 mg is elected as RP2D, then the remaining subjects enrolled in these cohorts may be treated with epacadostat 300 mg BID. The study design schematic (Figure 1) was updated accordingly.

    Rationale for change: The additional tumor types may be added in the Phase 2 100 mg BID cohorts, which will be conducted in parallel to the Phase 1 300 mg BID cohort. This will allow further safety and efficacy data to be obtained in other tumor types before determining the recommended dose for Phase 2 expansion.

Incyte Document Number IC-DEV-PROT-AMEND-0350.

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14. **Synopsis; Section 4.1.1, Phase 1 Dose-Escalation Design**

    Description of change: The text was revised to specify if MTD is not determined based on the Phase 1 and ongoing Phase 2 data, then the remaining Phase 2 cohorts may be opened at the pharmacologically active dose (eg, 100 mg BID).

    Rationale for change: Revised to specify what action will be taken for Phase 2 dosing if MTD cannot be determined.

15. **Synopsis; Section 4.2.1. Primary Endpoint, Section 4.2.2. Secondary Endpoints**

    Description of change: First primary endpoint for Phase 1 and secondary endpoint safety for Phase 2 texts were revised to specify that safety will be assessed by monitoring the frequency and severity of AEs, SAEs, and deaths.

    Rationale for change: Revised for clarity.

16. **Synopsis; Section 4.2.2. Secondary Endpoints**

    Description of change: Efficacy endpoint was revised to clarify that progression-free survival (PFS) will be assessed at 6 months. Also, the last sentence has been removed.

    Rationale for change: Revised for clarity and to specify the timepoints for PFS assessment.

[redacted]

18. **Synopsis; Section 4.4 Number of Subjects**

    Description of change: Total number of subjects to be enrolled in the entire study was updated as approximately 291 (previously 303).

    Rationale for change: Updated for clarity.

19. **Synopsis; Section 5.11, Restricted Medications and Measures**

    Description of change: Guidelines for coumarin-based anticoagulants were updated and a table recommending a warfarin dose adjustment based on various epacadostat doses was included.

    Rationale for change: Based on the observed magnitude of epacadostat/warfarin PK interaction and PK/PD modeling results from a completed drug-drug interaction study, for an epacadostat dose of 300 mg BID, the dose of warfarin should be reduced by approximately one-third after initiation of epacadostat administration based on approximately 30% to 40% reduction in S- and R- warfarin oral clearance values. Close INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat. Based on this PK/PD modeling, a table of recommendations for warfarin dose modifications for subjects was added.

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20. **Section 1.3.1, Risks from Epacadostat; Section 6, Study Assessments; Section 7.4.4, Assessment of Serotonin Syndrome Symptoms**

    Description of change: Serotonin syndrome assessment was removed from the schedule of assessments (Table 15 and Table 16) and corresponding sections.

    Rationale for change: Of the 253 subjects administered epacadostat to date, none have exhibited serotonin syndrome. Subjects and sites are being informed of the signs and symptoms associated with serotonin syndrome; however, the scheduled serotonin syndrome assessment was removed from the Protocol.

21. **Section 6, Study Assessments; Section 7.9.3, Administration of Epacadostat and Compliance**

    Description of change: Epacadostat administration at the clinic on Cycle 1 Day 8 was removed from Table 15.

    Rationale for change: To remove the inconsistency between footnote and the schedule on the table as well as with the other relevant sections in the Protocol.

22. **Section 6, Study Assessments; Section 7.4.6.3 Liver Function Tests**

    Description of change: The test name was revised to liver chemistry test to be consistent with the program level wording. In addition, the frequency of liver chemistry test monitoring was changed to every 8 weeks rather than weekly monitoring.

    Rationale for change: Because of the low occurrences of Grade 3 or greater ALT and AST elevations seen on the study, weekly monitoring of liver chemistry test is not required.

[redacted]

24. **Section 8.9, Adverse Events of Special Interest**

    Description of change: Electronic media and paper as reporting devices were removed.

    Rationale for change: Either electronic media or paper will not be used as a reporting devices to report both adverse events of special interest and immune-related adverse events.

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25. **Synopsis; Section 9.2.2, Sample Size for the Dose-Expansion Portion (Phase 2) of the Study; Section 9.4.1, Primary Analyses**

    Description of change: The durations entered as weeks were converted to months. In addition, the text related to time-to-event data analysis was revised to clarify when the data are censored.

    Rationale for change: Updates done for further clarification.

26. **Section 9.1, Study Populations**

    Description of change: Definition for safety evaluable subjects was revised. Definition for Phase 1 population was removed as it was not applicable for this study.

    Rationale for change: Updated for clarity.

27. **Section 9.4.2, Secondary Analyses**

    Description of change: Definition and the method of analysis for duration of disease control was revised.

    Rationale for change: Revised for clarity.

28. **Incorporation of administrative changes.** INCB024360 was replaced with the generic name epacadostat throughout the Protocol, and other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment (Version) 3

The primary purpose of this amendment is to change the dose for nivolumab for Phase 2 to a flat dose (240 mg) and to update the study design to allow the Phase 2 NSCLC and melanoma expansion cohorts to open with the 100 mg BID dose of INCB024360 once 100 mg BID is determined to be safe in Phase 1.

This amendment includes the changes to the Protocol INCB 24360-204 Amendment 2 (03 APR 2015) summarized below. A red-line version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1.4, Justification for Treatment Regimen; Section 2.2, Secondary Objectives; Section 4.1.2, Overall Study Design; Section 5.1.2, Nivolumab**

   Description of change: The dose of nivolumab for the Phase 2 expansion cohorts was changed to from 3 mg/kg via 60-minute IV infusion to 240 mg via 30-minute IV infusion. [redacted] safety data have been added to Section 4.1 to support this dose change.

   Rationale for change: Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg and similar across tumor types. Further preliminary data indicate that nivolumab PK are similar in nonsolid and solid tumors. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a milligram per kilogram dose represents an overadjustment for the effect of body weight on nivolumab PK. Conversely, given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier subjects, relative to the exposures in lighter subjects. It should be noted that a dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of subjects in the 3 Phase 2 and 3 clinical studies of nivolumab monotherapy. Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Thus, the 240 mg every-2-weeks dose and schedule is supported by safety, efficacy, and exposure-response analyses results.

2. **Synopsis; Section 4.1.1, Phase 1 Dose-Escalation Design**

   Description of change: For the dose-escalation portion of the study (Phase 1), the number of subjects was reduced from 15 to 9 subjects per cohort (total N = 63), and no subjects with colorectal cancer (CRC) will be enrolled in the 300 mg cohort. The design has been revised so that if INCB024360 100 mg BID in combination with nivolumab is deemed tolerable in Phase 1, the Phase 2 melanoma and NSCLC expansion cohorts will open with INCB024360 100 mg BID in combination with nivolumab. The 300 mg BID dose will be tested in parallel to the Phase 2 melanoma and NSCLC cohorts, and if it is deemed tolerable, the remaining Phase 2 cohorts may be opened with 300 mg BID as the recommended Phase 2 dose (RP2D). In Phase 2, if either melanoma or NSCLC cohorts at 100 mg BID enroll < 50% (≤ 25 subjects), the remaining enrollment in either of these cohorts may be treated with INCB024360 300 mg BID at the sponsor's discretion, in lieu of opening cohorts of melanoma and NSCLC with 300 mg BID. If 300 mg BID is not

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tolerated, an intermediate dose of 200 mg BID may be tested or 100 mg BID may be selected as the RP2D. A new figure depicting the revised study design has been added.

Rationale for change: The Phase 1 safety expansion cohort size has been reduced since the emerging safety profile of the combination is well tolerated. The exposure for INCB024360 100 mg BID based on PK measurements is in the range of active levels in nonclinical models; therefore, expansion cohorts may be further evaluated at this dose while a final dose escalation is completed. Depending on the enrollment rates, these cohorts may complete enrollment at the initial dose or proceed with the higher dose if that is determined to be safe.

3. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   a. **Description of change:** The inclusion criterion #4a for subjects with non–small cell lung cancer (NSCLC) has been revised to specify Stage III**B** (vs Stage III) and that subjects must have received only 1 prior systemic regimen for Stage IIIB, Stage IV, or recurrent NSCLC.

      Rationale for change: Subjects with Stage IIIA disease may be candidates for surgery and therefore not candidates for this study. The number of prior regimens for subjects with NSCLC has been revised to be consistent with current practice for use of nivolumab in this setting.

   b. **Description of change:** The inclusion criterion #4b for subjects with melanoma has been revised to indicate that subjects may be treatment-naïve or have received only 1 prior treatment for advanced or metastatic disease.

      Rationale for change: Based on recent NCCN guidelines, this criteria was revised to be consistent with current practice for use of nivolumab in this setting.

   c. **Description of change:** The inclusion criterion #7 for baseline tumor biopsy has been updated to indicate that for archived tumor tissue, unstained slides must have been prepared from a formalin fixed paraffin-embedded block obtained within 6 months before screening.

      Rationale for change: Additional clarification regarding acceptable archived tissue specimens permitted for inclusion in this study.

4. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   a. **Description of change:** The exclusion criterion #22 for abnormal electrocardiogram (ECG) has been revised to indicate that in the event that a single QTc is > 470 milliseconds, a subject may be enrolled if the average QTc for the 3 ECGs is < 470 milliseconds. In addition, the JTc must be < 340 milliseconds if JTc is used in place of the QTc, and subjects with left bundle branch block are excluded.

      Rationale for change: These criteria have been updated to be consistent with Incyte's current standard language across clinical programs for ECG requirements.

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b. **Description of change:** Use of any prohibited medication listed in Section 5.12 was added to the list of exclusion criteria as #28.

   Rationale for change: Prohibited medications are now included in the exclusion criteria so that these are considered and assessed during the subject screening process for enrollment to the study.

c. **Description of change:** Two exclusion criteria for subjects with unresectable or Stage IV melanoma that were previously included in the inclusion criteria section were moved to the exclusion criteria section (subjects with ocular melanoma and subjects treated with prior anti–CTLA-4).

   Rationale for change: Given these 2 criteria are exclusions they were moved to appropriate section of the Protocol for ease of reference.

5. **Section 5.6.3.1, Procedures and Guidelines for Pneumonitis; Section 6, Study Assessments (Tables 14, 15, and 18); Section 7.4.7, Pulmonary Function Tests**

   Description of change: Pulmonary function testing was removed from the screening assessments and from the subject evaluation recommended for symptomatic pneumonitis.

   Rationale for change: All subjects are required to have baseline CT scans of the chest at baseline, which provides reasonable baseline assessment for a subject's pulmonary status. Oxygen saturation is also assessed at baseline as well as on-study treatment in order to continually assess the subject's pulmonary status.

6. **Section 6, Study Assessments (Tables 14 and 18)**

   Description of change: In Table 14, targeted physical examination was added to Cycle 2, Days 15, 29, and 43. In Table 18, HPV (for subjects with SCCHN only) and MSI (for subjects with CRC only) were added to the table of required analytes for laboratory tests.

   Rationale for change: Targeted physical examination was omitted from table for these visits. HPV and MSI were added for consistency to match table with text in other relevant sections.

[redacted]

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8. **Section 6, Study Assessments (Table 16); Section 7.4.7, Laboratory Assessments**

   Description of change: Revised to indicate that screening laboratory tests should be performed within 7 days before the first dose of treatment instead of within 10 days. If the screening laboratory tests were performed more than 7 days before treatment initiation, they must be repeated before study treatment initiation (Cycle 1 Day 1).

   Rationale for change: Guidance for timing of screening laboratory tests has been updated for consistency with exclusion criteria, which notes that laboratory assessments performed within 7 days do not need to be repeated on Cycle 1 Day 1 before dosing.

9. **Section 7.4.7.5, Pregnancy Testing**

   Description of change: Updated to indicate that urine pregnancy tests will be conducted on Day 1 of each cycle or as required by local regulations.

   Rationale for change: Text has been updated to match Table 16, Laboratory Assessments for Screening Through Treatment Phase.

10. **Section 7.5, Efficacy Assessments**

    Description of change: Section 7.5.1 was updated to indicate that brain MRI at baseline should also be considered when disease burden due to any targeted tumor types is extensive (ie, when ≥ 3 metastatic disease sites are involved), and that for selection of target lesions, RECIST v1.1, Cheson, or RANO criteria should be followed. In Section 7.5.3, a table of guidelines for imaging and treatment after first radiographic evidence of disease progression was added.

    Rationale for change: Guidance for consideration of baseline brain MRIs has been added, and guidance for imaging and treatment after first evidence of progressive disease has been added.

11. **Section 7.8, Tumor Biopsy Collection and Analysis**

    Description of change: The number of required archival unstained slides has been updated to 20 to 25 slides (instead of 15 to 25).

    Rationale for change: Based on current sample analyses plan, 20 to 25 slides would be needed to complete all planned testing.

12. **Section 8.8, Data Monitoring Committee; Section 9.5, Data Monitoring Committee; Section 9.6, Interim Analysis**

    Description of change: Details have been added regarding data monitoring specific to Phase 1 and Phase 2 of the study and regarding an interim safety analysis for Phase 2.

    Rationale for change: Details for safety oversight for Phase 1 and Phase 2 have been included.

13. **Appendix E, Prohibited Monoamine Oxidase Inhibitors and Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity**

    Description of change: List of prohibited MAOIs has been updated.

    Rationale for change: The list has been updated after review of current literature.

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14. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the protocol and are noted in the red-line/strike-out version of the amendment.

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Amendment (Version) 2

The primary purpose of Amendment 2 is to include an additional expansion cohort in subjects with glioblastoma.

1. **Synopsis, Primary Objectives/Endpoints (also Sections 2.1 and 4.2.1), Secondary Objectives/Endpoints (also Sections 2.2 and 4.2.2), Overall Study Design (Section 4.1, 4.3), Statistical Methods (Sections 9.2.2, 9.3, 9.4.1, and 9.4.2); Study Population (Section 3), Study Schedule/Procedures (Section 7.5 and 7.5.5); Section 5.12, Prohibited Medications and Measures; Appendix K, Response Criteria for Glioblastoma**

   Description: An additional expansion cohort has been added for subjects with glioblastoma.

   Rationale: This cohort has been added to obtain further safety and efficacy data, particularly in the subset of subjects with glioblastoma.

2. **Synopsis, Planned Number of Subjects; Section 4.4, Number of Subjects**

   Description: The planned number of subjects has been updated to reflect the addition of the glioblastoma expansion cohort of 28 subjects.

   Rationale: An additional cohort has been added to further explore the safety and efficacy of this combination in subjects with glioblastoma.

3. **Section 1.1.1, Inhibition of PD-1 as a Target for Cancer; Section 1.1.4 Rationale for Studying Immunotherapy in Advanced or Metastatic Cancers; Section 1.2.1, Rationale for Combining PD-1 and IDO1 inhibitor in Advanced or Metastatic Cancers, Including Melanoma, NSCLC, SCCHN, Ovarian Cancer, Colorectal Cancer, DLBCL, and Glioblastoma**

   Description: Information regarding the approval of nivolumab by the FDA has been added to the background and rationale. In addition, background data to support the combination of a PD-1 and IDO1 inhibitor in glioblastoma has been added.

   Rationale: Nivolumab has been approved for treatment of subjects with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Nivolumab was also approved on 04 MAR 2015 to treat patients with advanced (metastatic) squamous NSCLC with progression on or after platinum-based chemotherapy.

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4. **Synopsis, Key Inclusion Criteria; Section 3.2, Subject Inclusion Criteria #4a, b, c, d, and f**

   Description: The inclusion criteria for subjects with NSCLC, melanoma, CRC, SCCHN, and B cell NHL or HL have been updated.

   Rationale: The inclusion criteria for subjects with NSCLC, melanoma, CRC, SCCHN, and B cell NHL or HL have been updated to clarify patient population and prior therapy requirements.

5. **Synopsis, Key Exclusion Criteria; Section 3.3, Subject Exclusion Criteria #1e and 22**

   Description: Exclusions for alkaline phosphatase values and QTc requirements for subjects with pacemakers have been updated.

   Rationale: These exclusion criteria have been updated to clarify requirements for alkaline phosphatase in the context of bone metastases and QTc requirements for subjects with pacemakers.

6. **Synopsis, Phase 1 Dose Escalation; Section 4.1.1, Phase 1 Dose Escalation**

   Description: The 300 mg BID dose cohort was clarified as an optional dose level that may be tested in parallel to opening the expansion cohorts.

   Rationale: To provide to option to further escalate INCB024360 if a lower dose is selected as the PAD.

7. **Section 5.5.1, Definition of Dose-Limiting Toxicities (Table 3, Criteria for Defining Dose-Limiting Toxicities); Section 5.6.2, Criteria and Procedures Interruption (Table 4, Dose Modification Guidelines for Drug-Related Adverse Events)**

   Description: Clarification has been added to the DLT criteria for the Grade 3 rash to specify steroid use means systemic steroids.

   Rationale: Use of topical steroids only would not warrant an event to be considered a DLT.

8. **Section 5.11, Restricted Medications and Measures**

   Description: Updated guidance was added for use of coumarin-based anticoagulants.

   Rationale: A study was conducted (Study INCB 24360-102) that investigated the potential drug-drug interaction between INCB024360 and warfarin. Results from the preliminary PK and PD analyses concluded that multiple dosing of INCB024360 300 mg BID increased S-warfarin and R warfarin geomean plasma AUCs by 43% and 68%, respectively, accompanied by mild but statistically significant INR and PT increases. Modeling showed that, with the same degree of warfarin PK interaction, the magnitude of INR increase may be significantly greater in patients on stable warfarin regimen targeting a typical INR range of 2 to 3 (which is higher than the INR observed in this study following a single warfarin dose). Therefore, we recommend an approximate one-third reduction of warfarin dose for subjects who also receive INCB024360, along with close INR monitoring. No clinically relevant interaction was observed on INCB024360 PK with concomitant warfarin.

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9. **Section 5.11, Restricted Medications and Measures**

   Description: Restrictions for the use of the anticonvulsant carbamazepine has been added to the list of restricted study medications.

   Rationale: Restrictions for the use of the anticonvulsant carbamazepine has been added to the list of restricted study medications with the addition of the glioblastoma cohort.

10. **Section 5.12, Prohibited Medications and Measures**

    Description: The following has been added or clarified in the prohibited medications section: administration of an injectable flu vaccine is prohibited during the DLT observation period, clarification has been added that live attenuated vaccines are prohibited, the list of prohibited UGT1A9 inhibitors has been updated, and guidance regarding corticosteroid use for subjects with glioblastoma has been added.

    Rationale: Updates have been made to address questions related to vaccine use and UGT1A9 inhibitors, and to address corticosteroid use in the new expansion cohort of subjects with glioblastoma.

11. **Section 6.0 , Study Assessments (Table 12, Schedule of Assessments – Screening Through Treatment Phase; Table 13, Schedule of Assessments End of Treatment through Survival Follow-Up); Section 7.4.7, Chest Radiograph**

    Description of change: Chest radiograph has been removed from the required screening assessments

    Rationale for change: All subjects will have a CT of the chest performed during screening; therefore, no additional chest radiograph needs to be performed.

12. **Section 6.0, Study Assessments (Table 12, Schedule of Assessments for Screening Through Treatment Phase); Section 7.4.7, Pulmonary Function Tests**

    Description: Pulmonary function testing may be omitted for subjects with stomas due to laryngectomies.

    Rationale: Subjects with stomas are unable to perform pulmonary function testing and are therefore permitted to omit this testing at screening.

13. **Section 7.4.8.3, Liver Function Tests**

    Description: Text has been added to clarify LFT monitoring requirements for subjects with persistent low-grade abnormalities.

    Rationale: Liver function test monitoring for persistent low-grade abnormalities does not need to be monitored twice a week indefinitely. Appropriate LFT monitoring intervals should be discussed with the medical monitor for these circumstances.

14. **Section 8.1.1, Adverse Events, Definitions and Reporting**

    Description of change: Guidance has been added for reporting of adverse events due to disease progression.

    Rationale for change: Additional guidance has been added to assist sites in determining when it is and is not appropriate to report adverse events related to disease progression.

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15. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the red-line/strike-out version of the amendment.

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Amendment (Version) 1

The primary purpose of the amendment is to address FDA queries, including clarifications and requested changes to the inclusion criteria, updates to the definition of dose-limiting toxicities, ECG monitoring and to add regularly scheduled urine pregnancy testing for females of childbearing potential.

This amendment includes the changes to Protocol INCB 24360-204 (dated 15 AUG 2014) summarized below. A red-line version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis, Phase 1 Dose Escalation; Section 4.1.1 Phase 1 Dose-Escalation Design; Section 5.5.1, Definition of Dose-Limiting Toxicities**

   Description of change: A dose-limiting toxicity (DLT) reporting period of 6 weeks has been added to the Phase 1 dose-escalation portion of the study.

   Rationale for change: This revision to increase the DLT reporting period to at least 6 weeks was requested by FDA.

2. **Synopsis, Study Population; Section 3.1, Study Population, Section 3.2, Subject Inclusion Criteria (Criterion #4)**

   Description of change: Inclusion criteria for selected cancers for this study have been revised to allow only subjects with refractory or relapsed disease after standard of care therapy.

   Rationale for change: FDA requested that the Protocol be revised to only include subjects who have refractory or relapsed disease after standard of care therapy.

3. **Synopsis, Key Inclusion Criteria; Section 3.2, Subject Inclusion Criteria (Criterion #4a, NSCLC)**

   Description of change: An inclusion criterion for subjects with NSCLC has been revised to require EFGR and ALK mutation status testing as well as treatment with TKI if mutation status is mutant.

   Rationale for change: FDA requested that the Protocol be revised to state that all subjects must be screened for EGFR and ALK mutations. Also, FDA agrees that if the subject has a driver mutation such as EGFR or ALK, he/she must have received a tyrosine-kinase inhibitor (TKI).

4. **Synopsis, Key Inclusion Criteria; Section 3.2, Subject Inclusion Criteria (Criterion #4b, Melanoma)**

   Description of change: The text has been revised to provide clarity for required documentation of BRAF mutation status for subject with metastatic melanoma.

   Rationale for change: The text has been revised to provide clarity that only V600E BRAF mutation <u>testing</u> is required. It is <u>not required</u> for subjects to have the BRAF activating mutation.

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5. **Section 5.5.1, Definition of Dose-Limiting Toxicities (Table 3, Criteria for Defining Dose-Limiting Toxicities)**

   Description of change: The following has been added to the criteria for defining a DLT: Febrile neutropenia ≥ Grade 3 for 72 hours, ≥ Grade 3 hemolysis, Grade 4 anemia not explained by underlying disease, ≥ Grade 3 thrombocytopenia with clinically significant bleeding or requirement for transfusion, Grade 2 AST or ALT with symptomatic liver inflammation, AST or ALT > 3 × ULN and concurrent total bilirubin > 2 × ULN without initial findings of cholestasis.

   Rationale for change: The FDA has requested the above criteria be added to the criteria for defining DLTs.

6. **Section 6, Study Assessments for Screening through Treatment Phase (Table 12); Section 7.4.6, Twelve-Lead Electrocardiograms**

   Description of change: A predose ECG assessment has been added to Cycle 1 Day 15.

   Rationale for change: FDA suggested ECG monitoring be performed at expected steady state for INCB024360.

7. **Section 6, Study Assessments (Tables 14 and Table 16); Section 7.4.9.5, Pregnancy Testing**

   Description of change: Urine pregnancy tests have been added to Day 1 of each treatment cycle for women of childbearing potential.

   Rationale for change: The FDA has requested the Protocol be revised to include a urine pregnancy test at the start of each cycle for women of childbearing potential.

   Description of change: Serum IgM assessments have been added for subjects with Waldenström's macroglobulinemia [redacted]

   Rationale for change: These laboratory assessments had been omitted from the schedule of assessments.

8. **Section 6, Study Assessments (Tables 12-15); Section 7.8, Tumor Biopsy Collection and Analysis**

   Description of change: Administrative clarifications have been made to the schedules of assessments and laboratory assessments to be consistent with other sections of the Protocol, including but not limited to: adding bone marrow examination for subjects with disease subtypes that utilize bone marrow histology as part of objective criteria for disease staging and response as noted in Appendix H (Cheson criteria), [redacted] with optional tumor biopsy that is described in the Synopsis and Section 7.8.

   Rationale for change: Inconsistencies or omissions between Protocol text and schedule of assessment tables have been corrected.

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[redacted]

11. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol including updating the abbreviations table and are noted in the attached red-line/strike-out version of the amendment.