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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: July 1, 2017
E-mailed Date: June 28, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements
(√) No review required

MEMORANDUM

This memorandum serves as notification to sites as an update on the safety of vemurafenib. New risks have been associated with the study drug as noted in the attached letter. A revision with these new risks is forthcoming.

Please inform patients and exercise caution as outlined in the attached letter and according to guidance from your IRB.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

CLOSED EFFECTIVE 04/01/2016

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Genentech
A Member of the Roche Group

June, 2017

IMPORTANT DRUG WARNING

Subject: Risk of Dupuytren's Contracture and Plantar Fascial Fibromatosis with Zelboraf® (vemurafenib)

Dear Health Care Provider:

The purpose of this letter is to inform you of new important safety information for Zelboraf, indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Zelboraf is not indicated for treatment of patients with wild-type BRAF melanoma.

Serious Risks with Use of Zelboraf

- Cases of new onset, as well as worsening of pre-existing, Dupuytren's contracture and plantar fascial fibromatosis have been reported with Zelboraf use.
- The majority of cases were mild or moderate in severity. However, severe, disabling cases of Dupuytren's contracture have also been reported.
- Dupuytren's contracture and plantar fascial fibromatosis should be managed using temporary interruption or treatment discontinuation of Zelboraf, as outlined in the current Zelboraf label (see Section 2.3, Dose Modifications).

Genentech is working closely with the U.S. Food and Drug Administration (FDA) to update the product label to reflect the risk of Dupuytren's contracture and plantar fascial fibromatosis.

Additional Information on the Serious Risks

The reported cases of Dupuytren's contracture seen with Zelboraf were characterized by thickening or appearance of visible cords in the palm of one or both hands. The median time to onset was 224 days from the initial dose of Zelboraf. In the majority of patients, the event persisted when Zelboraf treatment was maintained, while in other cases where Zelboraf was either interrupted or discontinued, the majority of patients had improvement of symptoms or resolution of the event. One patient with pre-existing Dupuytren's contracture experienced an exacerbation of the condition after Zelboraf use. In addition to Dupuytren's contracture, rare cases of mild and moderate plantar fascial fibromatosis were also reported with Zelboraf use. Sequential involvement of the hands and feet was observed in one case.

Prescriber Action

Health Care Providers should inform patients about these risks and should exercise caution when

prescribing Zelboraf to treat patients with pre-existing Dupuytren's contracture and plantar fascial fibromatosis. Health Care Providers are advised to follow the dose modification guidance for adverse events as outlined in the current Zelboraf label (see Section 2.3, Dose Modifications).

Reporting Adverse Events

Health Care Providers and patients are encouraged to report adverse events in patients taking Zelboraf to: Genentech at 1-888-835-2555. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/) or by mail, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

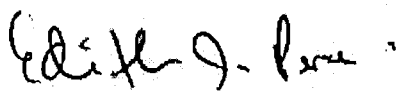
Company Contact

Should you have any questions about the information in this letter or the safe and effective use of Zelboraf, please feel free to contact us at: Genentech Medical Information/Communications Department at 1-800-821-8590.

This letter is not intended as a complete description of the benefits and risks related to the use of Zelboraf. Please refer to the enclosed full Prescribing Information, including Medication Guide, for additional Important Safety Information.

This letter is being sent in agreement with the FDA pursuant to requirements set forth in 21 CFR 200.5.

Sincerely,



Edith A Perez, M.D.
VP, Head of BioOncology, U.S. Medical Affairs

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
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STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1[illegible] FAX

1100 Fairview Ave N
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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March 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1406 Gastrointestinal	Jan. 05, 2017	AER1425062
	Jan. 10, 2017	AER1871130
	Jan. 23, 2017	AER1882493

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local

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policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

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Distribution Date: March 1, 2017
E-mail Date February 16, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
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Seattle, WA 98101
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206-667-4623
206-667-4408 FAX

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Change in e-mail address for Biologics, Inc.

MEMORANDUM

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

MEMORANDUM

The purpose of this memorandum is to alert sites to a change in email address for Biologics, Inc., the drug distributor for the following studies:

S1014
S1216
S1304
S1313
S1403
S1406
S1602

Beginning **February 20th, 2017**, the email address clinicaltrials@biologicsinc.com will no longer be valid and clinicalresearchservices@biologicsinc.com will no longer be accepting drug order submissions.

Please ensure all clinical trial drug order submissions that are emailed are being addressed to CRSorders@biologicsinc.com; all other communication outside of drug order submissions may continue to be addressed to clinicalresearchservices@biologicsinc.com.

Please note CRSorders@biologicsinc.com will only allow for inbound submission. If you require a response to an inquiry regarding an order please ensure it is addressed to clinicalresearchservices@biologicsinc.com.

Drug orders submitted via fax to 919-256-0794 will still be processed as usual.

cc: PROTOCOL & INFORMATION OFFICE

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

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1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
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1100 Fairview Ave North
M3-C102
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Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

February 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

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( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to document that the drug Vemurafenib distributed under lots M1074 and M1076 will expire at the end of February 2017.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
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STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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December 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

STATUS NOTICE

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements
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PERMANENT CLOSURE OF REGISTRATION STEP 2 AND REGISTRATION STEP 3

The purpose of this memorandum is to document that Registration Step 2 was effectively permanently closed on April 22, 2016, subsequent to the permanent closure of Registration Step 1 on April 1, 2016 (distributed on March 15, 2016), however a notice was never distributed.

Registration Step 3 will also be **permanently closed, effective December 29, 2016 at 11:59pm PT.**

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
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OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
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1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1[illegible] FAX

1100 Fairview Ave N
M3-C102
PO Box 19024
Seattle, WA 98109
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December 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements
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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1406 Gastrointestinal	Nov. 28, 2016 Mfr Rpt #1610430 FU Nov. 30, 2016 Mfr Rpt #1840684 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
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503-494-5586
503-346-8038 FAX

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4201 Medical Dr
Suite 250
San Antonio, TX 78229
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M3-C102
PO Box 19024
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206-667-4408 FAX

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December 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1406 Gastrointestinal	Jul. 15, 2016 Mfr Rpt #1781618
	Jul. 26, 2016 Mfr Rpt #1793468
	Sep. 26, 2016 Mfr Rpt #1170815 FU
	Oct. 13, 2016 Mfr Rpt #1840684

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local

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Charles D. Blanke, MD
CHAIR
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MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: December 1, 2016
CTEP Submission Date: November 10, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

REVISION #4

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
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Protocol changes
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( ) Other:

REVISION #4

Updates for the translational medicine component of the above-noted study have been made as follows:

1. **Title Page, Page 1:** The version date of the protocol and model consent form have been updated.

2. **Section 1.4g, Page 7:** The text in the parentheses "(KRAS, NRAS mutations)" was removed.

3. **Section 11.5f, Page 47:** A sentence was added to indicate that analysis of plasma samples at baseline, during therapy, and at the time of progression will be done across all arms (including Arm 3). Subsequent points were renumbered.

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4. **Section 11.5g, Page 47:** A sentence was added to indicate that analysis of plasma samples at baseline and at the time of progression will be done on all arms (including progression on Arm 3). Subsequent points were renumbered.

5. **Section 18.2b.4, Page 77:** Paragraph one was revised to indicate that Foundation Medicine will perform the gene sequencing.

   Paragraph 2, first sentence: The number of FFPE slides to be used for DNA analysis was changed from 3 to 6 and "300 ng DNA" was changed to "600 ng DNA".

   Paragraph 2, second sentence: The text "might be examined" was changed to "will be examined", MSI status and mutation load was added and "FoundationOne® Next Generation" referenced as the sequencing panel to be used.

   Paragraph 2, third sentence: The sentence outlining potential plans regarding genes that will be examined and technologies to be used was deleted.

   Paragraph 3: The sentence referring to retrospective Cobas version 2.0 testing to validate IHC was deleted.

   Paragraph 5, first sentence: The sentence was updated to reflect "NGS assay" will be used instead of "BEAMing assay", digital droplet PCR will be performed and MD Anderson and Guardant Health listed as potential labs to conduct the plasma analysis.

6. **Section 18.2c, Page 77:** The following changes were made in the first paragraph:
   Second bullet: "hMLH1" was added prior to "IHC".
   Third bullet: Guardant Health (Redwood City, CA) was added as a potential lab to perform circulating cell-free DNA analysis.
   Fourth bullet: FoundationOne® NGS multigene panel" replaces "Cobas sequencing" and "Foundation Medicine" replaces "Genentech/Roche Molecular Diagnostics".

   Second paragraph: Number of slides and amount of DNA needed for various studies was updated.

   Third paragraph: "Cobas 2.0 analysis" was removed from list of tests to be conducted.

Model Informed Consent

The screening and accrual goals referenced in the consent form for Step 1 and Step 2 were inadvertently not updated when Section 11.1 was changed (see Revision #3, distributed 1/15/16). Therefore, the consent forms are being updated at this time.

Consent Form – Step 1, page 3: Under, "Why is this study being done?", the second paragraph was changed from "We expect that about 440 patients will get this screening for this study and expect that about 78 patients will go on to the treatment part of the study" was changed to "We expect that about 163 patients will get this screening for this study and expect that about 105 patients will go on to the treatment part of the study."

Consent Form – Step 2, page 11: Under, "Why is this study being done?", the last sentence of the first paragraph was changed from "There will be about 78 people taking part in this study" to "There will be about 105 people taking part in this study."

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

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206-342-1[illegible] FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
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206-667-4408 FAX

swog.org

August 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
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These safety reports pertain to the following study:	Reports:	
S1406 Gastrointestinal	Mar. 29, 2012	Mfr Rpt #802100
	Jun. 03, 2016	Mfr Rpt #1523326 FU
	Jun. 13,2016	Mfr Rpt #1444937 FU
	Jun. 29, 2016	Mfr Rpt #1610430 FU
	Jun. 29, 2016	Mfr Rpt #1611016 FU
	Jul. 04, 2016	Mfr Rpt #1730135 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol

SWOG Authorized Document

and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee – Biologics
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210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

July 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites that the shelf life of vemurafenib batch M1076 has been extended. Please see attached notice for additional information.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

CLOSED EFFECTIVE 04/01/2016

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CERTIFICATE OF ANALYSIS

Roche

Product:	Zelboraf Film Coated Tablets 240mg
Bulk Batch no:	M1076
Manufacturer:	Roche S.p.A. Segrate
Analysis performed by:	Roche S.p.A. Segrate
Manufacturing Date:	19 Feb. 2013
Expiry date:	Feb. 2017
Analysis n°:	51035702
According to Analysis Method code:	10122165 of 05-Jan-2012

TEST	RESULTS
Description	
Shape	oval biconvex film-coated tablet
Color	pinkish white to orange white
Imprint	ROCHE engraved on one side
Width	9.7mm
Tickness	7.3mm
Length	19.0mm
Hardness	
min.	282N
max.	340N
average	310N
Average mass	874.7mg
Disintegration	
Highest value	49 sec.
Identification of RO5185426-000	
by HPLC	same RT as reference
by UV	maxima at same wavelengths as reference
Content per Tablet of RO5185426-000	
by HPLC	239.2mg
Degradation Products by HPLC	
Impurity B	<0.05%
Impurity C	<0.05%
RO6800726-000	<0.05%
Unspecified, each	<0.05%
Total of all	<0.05%
Water Content	
Karl Fisher	1.3%
Modification (Physical Form)	
Amorphous (Crystalline Form II < LOD)	corresponds
Dissolution after 30 min	
Q=80%	corresponds
min	91%
max	92%
average	91%
Uniformity of Dosage Units	
Ph.Eur./USP/JP, Mass/Weight Variation	corresponds
Ph.Eur./USP/JP, Content Uniformity	corresponds
Microbial Limits	
Ph.Eur./USP/JP, non-aqueous oral	not performed for this batch

Roberto Rossi
Quality Assurance

Francesca Maienza
Quality Control

Segrate, March 10th, 2016

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1[illegible] FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

June 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

CLOSED EFFECTIVE 04/01/2016

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1406 Gastrointestinal	Mar. 28, 2016	Mfr Rpt #1730135
	May 04, 2016	Mfr Rpt #1546842
	May 18, 2016	Mfr Rpt #1697226 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

SWOG Authorized Document

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

CLOSED EFFECTIVE 04/01/2016

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Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1[illegible] FAX

1100 Fairview Ave N
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

May 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1406 Gastrointestinal	Jan. 06, 2016	Mfr Rpt #1468479 FU
	Jan. 12, 2016	Mfr Rpt #1655508 FU
	Jan. 13, 2016	Mfr Rpt #1683112
	Jan. 14, 2016	Mfr Rpt #1689416
	Feb. 03, 2016	Mfr Rpt #1683112 FU
	Feb. 05, 2016	Mfr Rpt #1485799 FU
	Feb. 17, 2016	Mfr Rpt #1697226
	Feb. 22, 2016	Mfr Rpt #1426019 FU

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Feb. 23, 2016	Mfr Rpt #1709035
Mar. 01, 2016	Mfr Rpt #1605498 FU
Mar. 16, 2016	Mfr Rpt #1697226 FU
Mar. 18, 2016	Mfr Rpt #1560245 FU
Mar. 18, 2016	Mfr Rpt #1709035 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

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April 1, 2016

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that the shelf life of vemurafenib batch M1074 has been extended. Please see attached notice for additional information.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

CLOSED EFFECTIVE 04/01/2016

SWOG Authorized Document

Roche

To Whom It May Concern

Information to study management team

Date: 3/14/2016

Statement Study: BRAFISTUS
Ro 518-5426/F17 & Ro 518-5426/F20 – Shelf Life Extension
Zelfboraf 240 mg film coated tablets (Formulation)

Dear Sir or Madam,

We, on behalf of F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, CH-4070 Basel, Switzerland, hereby give you the following information regarding shelf life extensions of Ro 518-5426/F17 & Ro 518-5426/F20 Zelboraf 240 mg film coated tablets for the clinical study BRAFISTUS.

Material	Manufacturing batch/ lot	SAP Batch	Mfg Date Drug Product	Old Use-by	New Use-by
39007428	M1074	1137855	18.02.2013	29.02.2016	28.02.2017

The shelf life of the manufacturing batch M1074was extended from 29.02.2016to 28.02.2017 (as indicated above) in Kaiseraugst.

(Supporting document: CoA number 51035700)

Sincerely,
F. Hoffmann-La Roche Ltd

Dr. Michael Richter
IMP Quality Kaiseraugst
Responsible Person Deputy

F. Hoffmann-La Roche Ltd CH-4303 Kaiseraugst PTDQEK Bldg/Room 204/ 1.172 Tel. +41-61-68 83024 michael.richter.mr1@roche.com

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

March 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

STATUS NOTICE

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

PERMANENT CLOSURE

The above-referenced study has met its accrual goal and will permanently close to accrual (Step 1) **effective April 1, 2016 at 11:59 p.m. Pacific.**

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Jacqueline Scurlock
Christine McLeod
Brian Zeller
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

CLOSED EFFECTIVE 04/01/2016

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

February 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1406 Gastrointestinal	Dec. 3, 2015 Mfr Rpt #1668082
	Dec. 10, 2015 Mfr Rpt #1668082 FU
	Dec. 14, 2015 Mfr Rpt #1655508 FU
	Jan. 4, 2016 Mfr Rpt #1605498
	Jan. 4, 2016 Mfr Rpt # 1311143 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
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OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

January 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1406 Gastrointestinal	Nov. 19, 2015 Mfr Rpt #1649528 FU Nov. 25, 2015 Mfr Rpt #1655508 Nov. 26, 2015 Mfr Rpt #1426019

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
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Jacqueline Scurlock
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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: January 15, 2016
E-mailed Date: January 8, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

STATUS NOTICE

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

RE-ACTIVATION

The above-referenced study is open to accrual **effective January 8, 2016** at 2:00 p.m. Eastern.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Brian Zeller
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: January 15, 2016
E-mailed Date: January 8, 2016
CTEP Submission Date: November 19, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

REVISION #3

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #3

The above-noted protocol document has been revised as follows:

1. Title Page, Page 1: The version date of the protocol and model consent form has been updated. There have been no additional changes to the model consent form.

2. Table of Contents, Pages 3-4: The Table of Contents have been updated.

3. Section 2.0, Page 11: The Inclusion Women and Minorities table has been updated to reflect the increased sample size.

4. Section 3.3g.1b.4, Page 19: A note has been added regarding the drug labeling and alternative acceptable compound names that may be included on the label. Information has been displaced to Page 20.

CLOSED EFFECTIVE 04/01/2016

SWOG Authorized Document

5. Section 5.2a.2, Page 23: The first sentence has been revised from "Patients must have measurable or non-measurable metastatic disease…" to "Patients must have measurable or non-measurable disease that is either metastatic or locally advanced and unresectable…" in order to match eligibility in Step 1.

6. Sections 9.1-9.3, Pages 36-38: An "X" has been added for blood submission in the "FU prior to prog" column.

7. Section 11.0, Pages 44-46: This section has been updated to include an increased sample size for the study in order to obtain more robust results for this trial, both clinical and translational. The original sample size was lower than the usual randomized Phase II design as it was predicted that there would be a much higher demand for centralized BRAF screening than has been realized. The following changes have been made:

   a. Section 11.1, Page 44: The following has been added as the third sentence in the first paragraph: "The observed rate of accrual over the first 10 months was more than 4 patients per month.". The last sentence of the first paragraph has been revised from "We anticipate enrolling 78 patients to have 72 eligible patients randomized in Step 2, and thus expect 26 months of accrual." to "Thus, we anticipate enrolling 105 patients to have 94 eligible patients randomized in Step 2, and still expect 26 months of accrual." In the second paragraph, "Prior to opening the protocol," has been added to the beginning of the third sentence. The following sentences have been added to the end of the second paragraph: "Forty-five of the first 70 screened patients were randomized. Of these 70 patients screened in 10 months of accrual, 43 had already been tested for the $BRAF^{V600E}$ mutation and 27 needed central review. Based on these observed proportions, in total we will need to screen approximately 163 to randomize 105 patients, including about 63 patients needing central review."

   b. Section 11.2, Pages 44-45: In the first paragraph, the first sentence has been revised from "…observation of 63 progression events." to "…observation of 88 PFS events.". In the first paragraph, the last sentence has been revised from "…in this population (HR 2.0, for results to be considered clinically worthwhile for a subsequent Phase III study), we will need 72 eligible patients, based on six months of follow-up, a two-sided type 1 error of 2.5% and 81% power." to "…in this population (HR 2.0), we will need 94 eligible patients, based on six months of follow-up, a two-sided type 1 error of 5% and 90% power." In the second paragraph, "32 PFS failures" has been revised to "44 PFS failures".

   c. Section 11.3, Page 45: In the first paragraph, the last sentence has been revised from "Assuming 90% (n=32 per arm) of patients will present with measurable disease, response rate can be estimated to within 18% (95% confidence interval)." to "Assuming 90% (n=42 per arm) of patients will present with measurable disease, response rate can be estimated to within 16% (95% confidence interval).". In the second paragraph, the 6th sentence has been revised from "Thirty-six eligible patients in each arm…toxicity to within 17% (95% confidence interval)." to "Forty-seven patients in each arm…toxicity to within 15% (95% confidence interval).". In the last sentence of the second paragraph, "10%" has been changed to "8%".

   d. Section 11.5, Page 45: In the second sentence, "32" has been changed to "42".

   e. Section 11.5a.2, Page 46: "64 patients" has been changed to "84 patients" and "63% power" has been changed to "74% power".

CLOSED EFFECTIVE 01/01/2016

SWOG Authorized Document

f. Section 11.5b.2, Page 46: “64 patients” has been changed to “84 patients” and “73% power” has been changed to “80% power”.

g. Section 11.5c.1, Page 46: $BRAF^{WT}$ “n=326” has been changed to “n=52” and $BRAF^{V600E}$ “n=64” has been changed to “n=84”.

h. Section 11.5d.1, Page 46: “Screened patients (n=440)” has been changed to “screened patients (n=163)”.

8. Section 14.4d, 14.4h, and 14.4k, Pages 53-55: The locations within Rave for submission of radiology, pathology, and molecular testing reports have been added to Section 14.4d, and the Rave location of radiology report form has been added to Sections 14.4 and 14.4k.

9. Section 18.2b, Page 75: Information regarding the scoring for $BRAF^{V600E}$ positivity and negativity has been added to the first paragraph as the 5th and 6th sentences. Information has been displaced through Page 77.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Jacqueline Scurlock
Christine McLeod
Brian Zeller
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

December 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The **S1406** Master Forms Set has been updated and is available on the protocol abstract page on the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: December 15, 2015
E-mailed Date: December 9, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

STATUS NOTICE

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

TEMPORARY CLOSURE

The above-referenced study is fast-approaching its accrual target and will temporarily close to accrual, pending CTEP review of revision to increase the accrual target in order to increase power in the study. Registration to STEP 1 will be temporarily closed effective **December 23, 2015** at 11:59 p.m. Pacific Time. Please contact Kimberly Kaberle at kkaberle@swog.org for questions pertaining to the temporary closure.

This memorandum serves to notify the NCI, CTSU, and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Jacqueline Scurlock
Brian Zeller

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

December 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1406 Gastrointestinal	Nov. 5, 2015	Mfr Rpt #1649528
	Nov. 6, 2015	Mfr Rpt #1296240 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Jacqueline Scurlock
Brian Zeller
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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November 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Offices

RE: Holiday Closure

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

Biologics, Inc. Clinical Trials Services will be closed Thursday, November 26, 2015 and Friday November 27, 2015 (in observance of Thanksgiving), Thursday December 24, 2015 and Friday December 25, 2015 (in observance of Christmas), and Friday January 1, 2016 (in celebration of the New Year).

Biologics, Inc. Clinical Trials Services will be open on New Year's Eve (Thursday December 31, 2015).

Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern. Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

S0635 Lung
S1014 Genitourinary
S1202 Cancer Control
S1216 Genitourinary
S1300 Lung
S1304 Myeloma
S1313 Gastrointestinal
S1403 Lung
S1406 Gastrointestinal

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Amy Johnson
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye
Monica Yee
Stephanie Edwards
Vicki Green
Destin Carlisle – Alliance
Elliott Lee, Biologics, Inc.
Becky Fillingham – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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October 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1406 Gastrointestinal	Aug. 21, 2015 Mfr Rpt #1057897 FU Sep. 4, 2015 Mfr Rpt #1628206 Sep. 25, 2015 Mfr Rpt #1589636 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Jacqueline Scurlock
Brian Zeller
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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September 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:

S1406 Gastrointestinal

Reports:

July 2, 2015	Mfr Rpt #1074521 FU
July 10, 2015	Mfr Rpt #1315730 FU
July 24, 2015	Mfr Rpt #1589636
July 24, 2015	Mfr Rpt #1611016
July 28, 2015	Mfr Rpt #1610430
Aug. 3, 2015	Mfr Rpt #1585605 FU
Aug. 5, 2015	Mfr Rpt #1613313
Aug. 10, 2015	Mfr Rpt #1613313 FU
Aug. 13, 2015	Mfr Rpt #1583941

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
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Christine McLeod
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Brian Zeller
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

September 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The funding memorandum for the above-referenced study has been updated and is located on the protocol abstract page of the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Jacqueline Scurlock
Brian Zeller
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

August 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Updated Drug Order Form and Holiday Closure

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. has developed a new form for sites to designate non-prescribers to order investigational agent. Please note this is an optional form and submission of the form will apply to all studies the treating investigator has registered patients on that utilize Biologics Inc. as a distributor. This form is available on the protocol abstract page on the SWOG website (www.swog.org). The drug order forms for the studies listed below have been updated to include this option.

The Primary Shipping Address and Designee Form pertains to the following studies:

S0635 Lung
S1014 Genitourinary
S1216 Genitourinary
S1300 Lung
S1304 Myeloma
S1313 Gastrointestinal
S1403 Lung
S1406 Gastrointestinal

Please also note that Biologics, Inc. Clinical Trials Services will be closed Monday, September 7, 2015 in observance of Labor Day.

Regular business hours will resume on Tuesday, September 8, 2015. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

S0635 Lung
S1014 Genitourinary
S1202 Cancer Control
S1216 Genitourinary
S1300 Lung
S1304 Myeloma
S1313 Gastrointestinal
S1403 Lung
S1406 Gastrointestinal

CLOSED EFFECTIVE 04/01/2016

SWOG Authorized Document

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Amy Johnson
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye
Monica Yee
Stephanie Edwards
Vicki Green
Destin Carlisle – Alliance
Elliott Lee, Biologics, Inc.
Becky Fillingham – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN

CLOSED EFFECTIVE 04/01/2016

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

August 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:

S1406 Gastrointestinal

Reports:

June 11, 2015 Mfr Rpt #1325191 FU
June 15, 2015 Mfr Rpt #1547565
June 26, 2015 Mfr Rpt #1069575 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Brian Zeller
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
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Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: August 1, 2015
CTEP Submission Date: June 9, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

REVISION #2

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #2

The above-noted protocol document has been revised as follows:

1. Title Page, Page 1: The version date of the protocol and model consent form has been updated.

2. Table of Contents, Pages 3-4: The Table of Contents have been updated.

3. Schema, Page 6: Below "PROGRESSION" on Arm 1, "(optional)" was added before "STEP 3 CROSSOVER REGISTRATION". "Optional cross over to" has been removed and "Vemurafenib +" was moved to before "Cetuximab + Irinotecan" for clarification. In the section below, "ANY OTHER REASON**" was added after "SYMPTOMATIC DETERIORATION,".

4. Section 1.4, Page 7: Subsections "1.4h" and "1.4i" have been added. Subsequent text has been displaced to Pages 8-10 and subsequent pages have been repaginated.

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5. Section 2.0, Page 8: Bolded headings have been added above paragraphs 1-3.

6. Section 2.0, Page 10: Two new paragraphs have been added regarding "Patient-derived xerographs (PDXs) as improved models for studying human malignancy".

7. Section 3.3e.2, Page 18: "supply of" has been replaced with "grade product labeled for investigational use" for clarification.

8. Section 5.1a.5, Page 22: "Step 2 Randomization" has been corrected to "Step 1 Initial Registration".

9. Section 5.2, Page 23: The following sentence has been added as the first sentence of the paragraph for clarification, "Patients with known BRAF mutation must be registered to Step 2 Randomization immediately following Step 1 Initial Registration." In the second sentence, "SpecTrac" has been replaced with "SWOG Specimen Tracking".

10. Section 5.2a.3, Page 23: This eligibility criterion has been moved from Section 5.1a.6 (subsequent sections have been renumbered accordingly). References to "Step 1 Initial Registration" have been changed to "Step 2 Randomization" for consistency. Subsequent sections have been renumbered accordingly.

11. Section 5.2c, Page 25: This subsection has been added for institutions participating in the optional **S1406** Co-Clinical PDX Model Trial.

12. Section 5.3a, Page 25: In the first sentence, the reference to "Section 10.0" has been corrected to "Section 10.2d".

13. Section 7.5a, Page 27: In the first sentence, the reference to "Section 10.0" has been corrected to "Section 10.2d".

14. Sections 9.1, 9.2, and 9.0 Footnotes, Pages 36-37 and 39: Under "SPECIMEN SUBMISSION" on the calendars, a new row for "Fresh Tissue Biopsy ƹ" has been added with an X under the "Step 2 Rand" column. On Page 39, the following changes have been made:
    - In the "◇" footnote, "2 months" has been replaced with "8 weeks".
    - In the "†" footnote, "To evaluate for non-cutaneous SCC" has been moved from the beginning of the sentence to the end. The following text was added after "Performed", "at Step 2 Randomization or Step 3 Crossover Registration," and "treatment" has been replaced with "vemurafenib".
    - The "ƹ" footnote has been added to clarify this biopsy is only for sites listed in Section 15.4.

15. Sections 9.2 and 9.3, Pages 37-38: The "X" has been removed for an ECG performed during Week 15 of treatment.

16. Section 11.2, Page 45: In the first sentence, "35" has been replaced with "32".

17. Section 11.5, Pages 47-48: Subsections 11.5h and 11.5i have been added. Subsequent text has been displaced to Page 48 and subsequent pages have been repaginated.

18. Section 13.1a, Page 48: In the first sentence, "may" has been replaced with "must" for clarification and consistency.

19. Section 13.1c, Page 48: The following text has been added to the end of the parentheses: "and within 28 days of discontinuation of Arm 1 protocol treatment".

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20. Section 14.4c, Page 53: “WITHIN 60 DAYS OF STEP 1 REGISTRATION” has been moved to the end of the heading and all CAPS has been removed from “For patient who will not be randomized to a treatment arm,”. The reference to “Section 15.2” has been updated to “Section 15.3”.

21. Section 14.4d, Page 53: “Fresh tissue for PDX (optional for patients at select institutions, see Section 15.4)” has been added to the end of this section.

22. Section 15.0, Page 56: A table has been added to this section for clarification of the purpose, specimens needed, timepoints, applicable patients, and shipping method. Subsequent pages have been repaginated.

23. Section 15.1, Page 57: The previous Section 15.1 has been moved to Section 15.2. Section 15.1 now contains the first five paragraphs of the previous Section 15.1g. In the first sentence of the first paragraph, “(STS)” was added. In the third paragraph, “SpecTrack” has been replaced with “STS” in the first sentence and the following sentence has been removed; “Under “Specimen Specific Question”, sites must enter the contact information for the people who will receive the BRAF V600 testing results.”

24. Section 15.2, Pages 57-58: “All patients must submit specimens for central BRAF V600 testing” has been added above 15.2a. In Section 15.2a, references to “Section 15.1e” and “Section 15.1g” have been updated to “Section 15.2e” and “Section 15.2g”, respectively. Section 15.2b.2 has been reformatted for clarification. In Section 15.2c, the second sentence regarding tissue handling for registrations completed on a Friday has been added. In Section 15.2e, the reference to “Section 15.1g.1” has been updated to “Section 15.2g”. In Section 15.2g.1, “submit tissue Monday – Thursday to” has been added to the heading. In Section 15.2g.2, “Solid Tissue, Myeloma, and Lymphoma Division” has been added following “SWOG Specimen Repository”.

25. Section 15.3, Pages 58-59: The section heading has been revised from “Translational Medicine” to “Specimens for translational medicine and correlative studies (required for patients)”. In Section 15.3a.1, the reference to “Section 15.1b” has been updated to “Section 15.2”. In Section 15.3a.2, the first sentence has been revised from “2 tubes (lavender top EDTA tube) each of 10 mL blood on the day of Step 1 registration, each restaging (including restaging during treatment on crossover arm), and off treatment.” to “2 tubes (lavender top EDTA tube) each of 10 mL blood on the day of Step 1 registration, each restaging, and off treatment.” and the following sentence has been added “Patients crossing over to Step 3 registration following disease progression on Arm 1 must also submit blood on day of Step 3 registration, each restaging, and off treatment.”. The reference to “Section 15.2b” has been updated to “Section 15.3b”. The NOTE regarding banking with additional patient consent has been added below Section 15.3a.2. Section 15.3d has been added for clarification.

26. Section 15.4, Pages 59-60: This section has been added for specimen submission for the optional **S1406** Co-Clinical PDX Model Trial. Only sites listed in this section may participate in this part of the study.

27. Section 16.1f.2, Page 64: The heading text has been changed from “The adverse events listed below also require expedited monitoring for patients on this trial:” to “The adverse events listed below also require expedited monitoring for patients assigned to Arm 2 or Arm 3 of this trial that includes the administration of vemurafenib:”.

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28. Section 17.0, Page 71: References 40-49 have been added. Subsequent pages have been repaginated.

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice. SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. Patients currently on treatment need not be informed of these changes unless required by the local IRB.

29. Model Consent Form, Page 13: Under "What extra tests and procedures will I have if I take part in this study?", in the 4th sentence of the 4th paragraph, "will" has been replaced with "may, with your consent".

30. Model Consent Form, Page 14: In the bullet under "During the study", the following text was added to the end of the sentence: "through 6 months after ending treatment".

31. Model Consent Form, Page 19: The 3rd paragraph has been revised from "The initial electrocardiogram will be paid for by the study." to "The initial electrocardiogram will be paid for by the study for all patients. Up to an additional 5 electrocardiograms will be paid for by the study for patients receiving vemurafenib."

32. Model Consent Form, Pages 21-25: On Pages 21-22, "Information for Selected Sites Participating in Co-Clinical PDX Model Study" has been added and caused repagination through Page 25. Under "WHAT IS INVOLVED?", the following text was added to item 1: "*If your site is participating in the co-clinical PDX study include:* A sample of tissue will be collected from the optional biopsy." and item 1.b was added for additional information regarding the optional biopsy. On Pages 22-23 under "WHAT ARE THE POSSIBLE RISKS?", item #1 regarding possible risks associated with the optional biopsy has been added.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Brian Zeller
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

CLOSED EFFECTIVE 04/01/2015

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

July 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:

S1406 Gastrointestinal

Reports:

Dec. 29, 2014	Mfr Rpt #1100027 FU
Jan. 13, 2015	Mfr Rpt #1100027 FU
Jan. 22, 2015	Mfr Rpt #1523326
Jan. 30, 2015	Mfr Rpt #1523326 FU
Feb. 2, 2015	Mfr Rpt #1315730 FU
Feb. 3, 2015	Mfr Rpt #1153303 FU
Feb. 10, 2015	Mfr Rpt #1040118
Feb. 11, 2015	Mfr Rpt #1534093
Feb. 18, 2015	Mfr Rpt #1076892 FU
Feb. 27, 2015	Mfr Rpt #1000308 FU
Mar. 6, 2015	Mfr Rpt #1402776
Mar. 10, 2015	Mfr Rpt #1160539
Mar. 20, 2015	Mfr Rpt #1468479 FU
Apr. 7, 2015	Mfr Rpt #1560245
Apr. 8, 2015	Mfr Rpt #1043227 FU
Apr. 10, 2015	Mfr Rpt #1322129 FU
Apr. 13, 2015	Mfr Rpt #1562590
Apr. 23, 2015	Mfr Rpt #1040030 FU
May 8, 2015	Mfr Rpt #1571821
May 9, 2015	Mfr Rpt #1276488 FU
May 12, 2015	Mfr Rpt #1322129 FU
May 12, 2015	Mfr Rpt #1523326 FU

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May 19, 2015	Mfr Rpt #1573729
May 20, 2015	Mfr Rpt #1154452 FU
May 20, 2015	Mfr Rpt #1575449
May 22, 2015	Mfr Rpt #1009730 FU
May 25, 2015	Mfr Rpt #1174105
May 27, 2015	Mfr Rpt #1153303 FU
May 27, 2015	Mfr Rpt #1580690
May 28, 2015	Mfr Rpt #1571821 FU
June 2, 2015	Mfr Rpt #1575449 FU
June 3, 2015	Mfr Rpt #1585605
June 4, 2015	Mfr Rpt #1087105 FU
June 8, 2015	Mfr Rpt #1585605 FU
June 9, 2015	Mfr Rpt #1037944 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Brian Zeller
Elliott Lee – Biologics
NCI Coop Coverage – Genentech

CLOSED EFFECTIVE 03/01/2016

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

July 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Updated Drug Order Form and Holiday Closure

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc has updated all SWOG Drug Order Forms to clarify that the prescriber's signature is required.

The updated Drug Order Form pertains to the following studies:

S1313 (Gastrointestinal)	**S0635** (Lung
S1406 (Gastrointestinal)	**S1300** (Lung)
S1014 (Genitourinary)	**S1403** (Lung)
S1216 (Genitourinary)	**S1304** (Myeloma)

Please also note that Biologics, Inc will be closed Friday, July 3, 2015 in observance of Independence Day. Biologics, Inc. will resume regular business hours (M-F, 9-6 ET) on Monday July 6, 2015.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

CLOSED EFFECTIVE 04/01/2016

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This Holiday Closure pertains to the following studies:

S1202 (Cancer Control – Symptomatic)
S1313 (Gastrointestinal)
S1406 (Gastrointestinal)
S1014 (Genitourinary)
S1216 (Genitourinary)
S0535 (Leukemia)
S0635 (Lung)
S0709 (Lung)
S1300 (Lung)
S1403 (Lung)
S1304 (Myeloma)

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Amy Johnson
Austin Hamm.
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye
Louise Highleyman
Monica Yee
Stephanie Edwards
Vicki Green
Guadalupe Aquino – Alliance
Samantha Sublett – Alliance
Elliott Lee, Biologics, Inc.
Mary Alice Norrison - Boehringer Ingelheim
Linda Fischer - Bristol-Myers Squibb
Becky Fillingham – ECOG-ACRIN
Laura Gagnon – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN
April Noska – Genentech
NCI Coop Coverage - Genentech
Leta Truett, Ph.D., M.N. – Janssen Services, LLC
Mohan Chelladurai, Ph.D. M.S.A. – Janssen Services, LLC
Royce-Ann Adkins, Janssen Services, LLC
William Heckman - Lilly
Theresa Bucher, R.N., Millennium
Mark Showers – Onyx
Kellis Snodgrass – Pfizer
Afrouz Bazmi – Quintiles, Inc.
Steve Shuey – Halozyme Therapeutics

CLOSED EFFECTIVE 03/03/2016

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: June 1, 2015
E-Mailed Date: May 19, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Holiday Closure for Monday, May 25, 2015 in Observance of Memorial Day

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, May 25, 2015 in observance of Memorial Day.

Regular business hours will resume on Tuesday, May 26, 2015. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

S1202 (Cancer Control – Symptomatic)
S1313 (Gastrointestinal)
S1406 (Gastrointestinal)
S1014 (Genitourinary)
S1216 (Genitourinary)
S0535 (Leukemia)
S0635 (Lung)
S0709 (Lung)
S1300 (Lung)
S1403 (Lung)
S1304 (Myeloma - Active)

This memorandum serves to notify the NCI and the SWOG Statistical Center.

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cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Amy Johnson
Austin Hamm.
Brian Zeller
Christine McLeod
Jean Barce
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CLOSED EFFECTIVE 04/01/2016

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: February 15, 2015
CTEP Submission Date: January 30, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

REVISION #1

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #1

The above-noted protocol document has been revised as follows:

1. Title Page, Page 1: The version date of the protocol and model consent form has been updated.

2. Schema, Page 6: Under "STEP 2 RANDOMIZATION" on Arm 2, "ANY OTHER REASON**" was added to the section following Arm 2 treatment.

3. Section 3.3g.2a, Pages 18-19: References to "NCI Drug Accountability Record Form (DARF)" have been corrected to "NCI Oral Drug Accountability Record Form (NCI Oral DARF)" in this section.

4. Section 5.1a.1, Page 20: The following note was added for clarification: "Note: In the event that both cecal and appendiceal primaries are considered, patient is eligible if it is concluded by the treating oncologist to most likely be cecal based on pathological, surgical, and clinical interpretation. Clinical diagnosis must be clearly documented in the "Comments" section on the **S1406** Onstudy Form."

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5. Section 7.1, Page 25: "5-HT_3 antagonist 16 mg intravenously, given once 30 minutes prior to iriontecan. Ondansetron is not allowed as it may induce QTc prolongation and Torsades de Pointes." has been removed and replaced with the following: "Patients on Arm 1 may receive institutional recommended management for nausea. Patients on Arms 2 and 3 may receive maximum doses of the following drugs: ondansetron 8 mg IV; dolasetron 12.5 mg IV; granisetron 1 mg IV; any oral form of 5-HT_3 inhibition."

6. Section 7.2, Page 25: The "**" footnote has been added to the table regarding subsequent doses for cetuximab.

7. Section 7.3, Page 26: The "***" footnote has been added to the table regarding subsequent doses for cetuximab.

8. Section 7.5b, Page 27: In the table, the route for cetuximab has been revised from "IV over 120 min for initial dose and over 60 min for subsequent doses" to "IV over 60 min" as patients on this arm would not be receiving cetuximab for the first time.

9. Section 8.3b, Page 28: In the second sentence, "for patients receiving vemurafenib may include maximum doses of the following drugs: ondansetron 8 mg IV, dolasetron 12.5 mg IV, and granisetron 1 mg IV; oral 5-Ht_3 antagonist drug can be used" was added after "management". The second paragraph was added to clarify management for patients not receiving vemurafenib.

10. Section 8.3p, Page 33: The words "by their treating physician" was added after "examination" in the first sentence of this section.

11. Section 9.1, Page 35: The schedule for Cycle 4 has been added for clarification. Under "PHYSICAL" the "Head and Neck Exam" row has been removed. An "X" has been added under Weeks 11, 13, and 15 for both cetuximab and irinotecan treatment.

12. Section 9.2, Page 36: The schedule for Cycle 4 has been added for clarification. The "X"s for Dermatologic evaluation and Head and Neck Exam have been moved from Week 4 to Week 5 and from Week 12 to Week 13. These changes have also been made to Section 9.3 (Page 37).

13. Section 9.0 Footnotes, Page 38: "See Section 8.3p" has been added to the "~" footnote for additional reference information. The "†" footnote has been revised as follows:
- "…and performed after 4 weeks and every 2 months through 6 months after discontinuation of treatment (see Section 8.3p)." has been added to the end of the first sentence.
- "The minimum criteria should be visual inspection of the oral mucosa and lymph node palpation performed by the treating physician." has also been added to the end of this footnote.

14. Section 14.4a, Page 51: The following sentence has been removed from this section: "Submit the following: Pre-study plasma specimens (including pathology report) for Translational medicine as described in Section 15.2."

15. Section 14.4c, Page 51: This section was added to include the submission of pre-study plasma specimens for patients who register to Step 1, but do not register to Step 2. Subsequent sections have been renumbered accordingly.

16. Section 14.4h (previously Section 14.4g) and 14.4i (previously Section 14.4h), Page 52: "Plasma specimen (see Section 15.2)" has been removed from these sections.

CLOSED EFFECTIVE 04/01/2016

SWOG Authorized Document

17. Section 14.4j (previously Section 14.4i), Page 52: "Plasma specimen (see Section 15.2)" has been replaced with "Batch shipment of frozen plasma specimens (including pathology reports) for Translational Medicine as described in Section 15.2.".

18. Section 15.1a, Page 53: Section references to "Section 15.1d" and "Section 15.1f" have been corrected to "Section 15.1e" and "Section 15.1g", respectively.

19. Section 15.1d, Page 54: This section (previously 15.1e) and subsequent sections have been renumbered as they were errantly misnumbered.

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice. SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. Patients currently on protocol treatment and patients who sign a consent form prior to local implementation of the consent form changes **must** be informed of the following changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

20. Model Consent Form, Page 5: The following sentence was added to the beginning of the paragraph for clarification: "The study will pay for the cost of the BRAF testing which will be completed at a central laboratory using your tissue sample from a previous biopsy or surgery."

21. Model Consent Form, Page 6: Under "Who will see my medical information?", Alliance, ECOG-ACRIN, and NRG have been added as bullets to the list. This change has also been made to Page 19 of the Model Consent Form.

22. Model Consent Form, Page 12: Under "What are the study groups?", in the second sentence of the second paragraph, "14" was corrected to "15".

23. Model Consent Form, Page 14: Under "During the study", "you will be seen by a dermatologist" has been replaced with "your doctor will examine your head and neck…".

24. Model Consent Form, Page 19: In the third paragraph of the page, "echocardiogram" was corrected to "electrocardiogram".

25. Model Consent Form, Pages 21-23: The numbered lists have been renumbered throughout these pages.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter
Elliott Lee - Biologics Inc.
NCI Coop Coverage - Genentech

CLOSED EFFECTIVE 09/01/2016

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

January 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
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- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1406 Gastrointestinal	Dec. 18, 2014 AE #1507363 Dec. 19, 2014 AE #CID000000003453185 Dec. 19, 2014 AE #1076892 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Stephanie Edwards
Christine McLeod
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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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January 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that a signature line for the registering investigator has been added to affirm eligibility on the **S1406** Registration Worksheets for Step 2 and Step 3. The forms can be accessed from the Master Forms Set link on the **S1406** protocol abstract page of the SWOG website (http://swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter
Elliott Lee – Biologics
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210-614-0006 FAX

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Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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January 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Vemurafenib

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug vemurafenib. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:

S1406 Gastrointestinal

Reports:

Nov. 17, 2014	Mfr Rpt #1466404
Nov. 17, 2014	Mfr Rpt #1485799
Nov. 19, 2014	Mfr Rpt #1231190
Dec. 9, 2014	Mfr Rpt #1043227
Dec. 9, 2014	Mfr Rpt #1057897
Dec. 10, 2014	Mfr Rpt #800984

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter
Elliott Lee – Biologics
Andrew Dorr, M.D. – Halozyme Therapeutics
Steve Shuey – Halozyme Therapeutics

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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December 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Wednesday, December 24, 2014, Thursday, December 25, 2014, and Thursday, January 1, 2015, in observance of the seasonal holidays.

Regular business hours will continue on December 26 and January 2 from 9:00 a.m. – 6:00 p.m. Eastern.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Research Services team at 800/693-4906 or via e-mail at clinicaltrials@biologicsinc.com.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
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STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: November 15, 2014
E-mailed Date: November 13, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

STATUS NOTICE

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed (for sites that have received full board review)

( ) No review required

ACTIVATION

The study referenced above is open for participation **effective November 13, 2014 at 2:00 p.m. Eastern Time**.

This study has been approved by the NCI's Central Institutional Review Board.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter
Elliott Lee – Biologics, Inc.
Steve Shuey – Halozyme Therapeutics

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: October 1, 2014
E-mailed Date: September 24, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1406**, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer." Study Chairs: S. Kopetz, H-J. Lenz, and A. Magliocco.

MEMORANDUM

Study Chair: Scott Kopetz, M.D., Ph.D.
Phone number: 713/792-2828
E-mail: skopetz@mdanderson.org

IRB Review Requirements

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- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

MEMORANDUM

This protocol is being distributed at this time **for Institutional Review Board (IRB) review only.** Institutions will be notified when the study is activated for patient registration.

This study has been approved by NCI's Central Institutional Review Board.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter

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Activated November 13, 2014

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RANDOMIZED PHASE II STUDY OF IRINOTECAN AND CETUXIMAB WITH OR WITHOUT VEMURAFENIB IN BRAF MUTANT METASTATIC COLORECTAL CANCER

NCT #02164916

STUDY CHAIRS:

Scott Kopetz, M.D., Ph.D. (Medical Oncology)
UT MD Anderson Cancer Center
1515 Holcombe Blvd
Department of GI Med Onc, Unit 426
Houston, TX 77030
Phone: 713/792-2828
FAX: 713/745-1163
E-mail: skopetz@mdanderson.org

Heinz-Josef Lenz, M.D. (Translational Medicine)
University of Southern California
Norris Comprehensive Cancer Center
1441 Eastlake Avenue
Los Angeles, CA 90033
Phone: 323/865-3955
FAX: 323/865-0061
E-mail: lenz@usc.edu

Anthony Magliocco (Translational Medicine)
H Lee Moffitt Cancer Center
Department of Pathology
12902 Magnolia Dr.
Tampa, FL 33612
Phone: 813/745-3980
FAX: 813/745-2689
E-mail: anthony.magliocco@moffitt.org

BIOSTATISTICIANS:

Shannon McDonough, M.S.
Katherine A. Guthrie, Ph.D.
SWOG Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M3-C102
P.O. Box 19024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: smcdonou@fhcrc.org
E-mail: kguthrie@fhcrc.org

AGENTS:

IND-Exempt Agents:
Cetuximab (NSC-714692)
Irinotecan (Camptosar®)(NSC-616348)

SWOG-Held IND Agents:
Vemurafenib (NSC-761431) (IND-122167)

NCTN INVESTIGATORS:

Luis Diaz, M.D. (ECOG-ACRIN)
Ludwig Center for Genetics and Therapeutics
1650 Orleans St., Rm 590
Baltimore, MD 21231
Phone: 410/95-8878
FAX: 410/955-0548
E-mail: ldiaz1@jhmi.edu

Chloe Atreya (ALLIANCE)
UC San Francisco
1600 Divisadero St, 4th Floor
San Francisco, CA 94115
Phone: 415/353-9888
FAX: 415/353-9636
E-mail: chloe.atreya@ucsf.edu

Carmen Allegra (NRG)
University of Florida, Cancer Pavilion
2000 SW Archer Rd.
Gainesville, FL 32608
Phone: 352/265-0725
FAX: 352/273-5006
E-mail: carmen.allegra@medicine.ufl.edu

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PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology

ECOG-ACRIN/ECOG-ACRIN Cancer Research Group

NRG/NRG Oncology

SWOG/SWOG

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section for instructions on using the OPEN system.	Online Data Submission: This protocol will use Medidata Rave® for electronic data submission. Access Rave® using your active CTEP-IAM userid and password at the following url: https://login.imedidata.com/selectlogin Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility questions contact the SWOG Data Operations Center by phone or email: 206-652-2267 giquestion@crab.org **For treatment or toxicity related questions** contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: 888-823-5923 ctsucontact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website: https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

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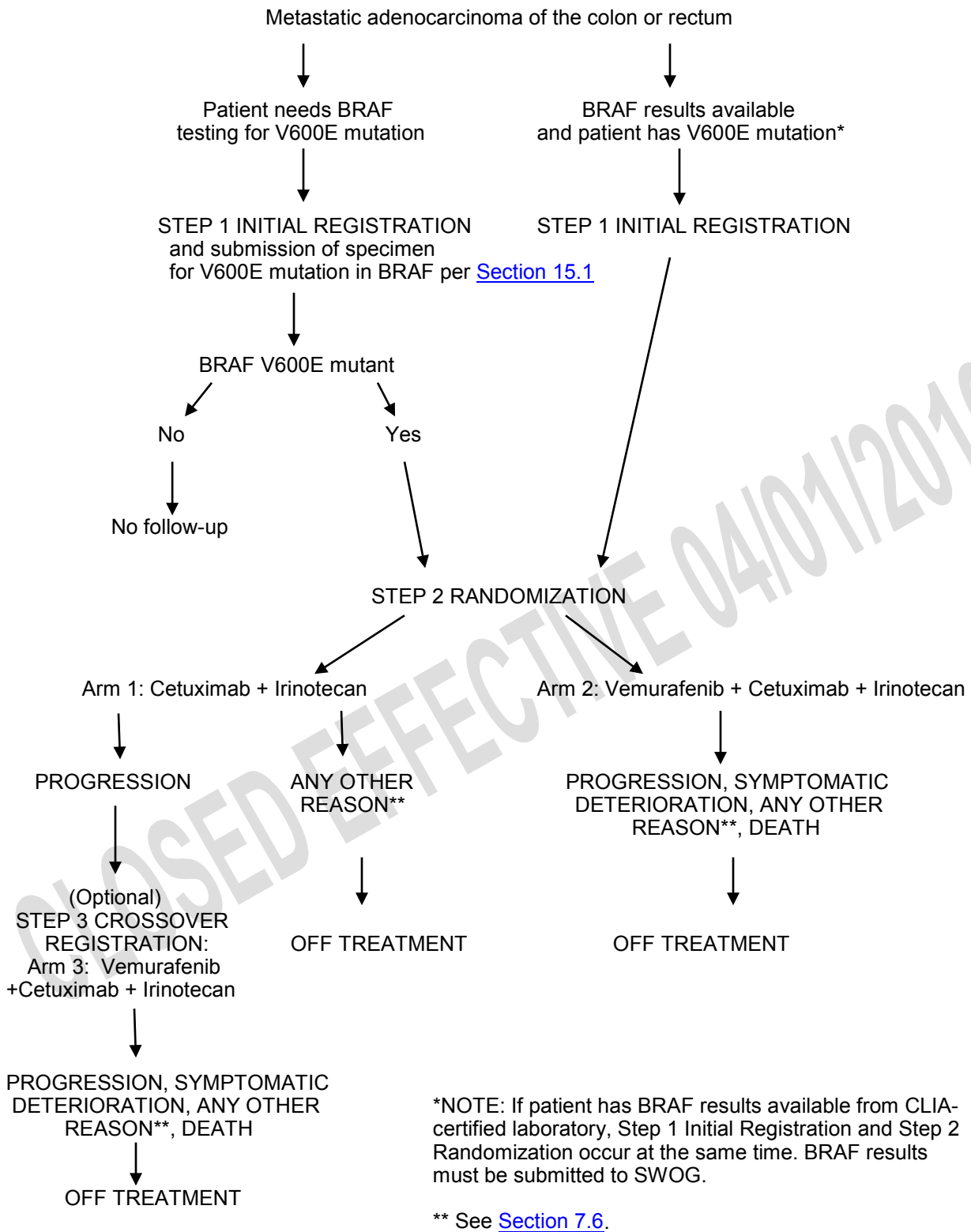
SCHEMA



*NOTE: If patient has BRAF results available from CLIA-certified laboratory, Step 1 Initial Registration and Step 2 Randomization occur at the same time. BRAF results must be submitted to SWOG.

** See Section 7.6.

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1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the progression-free survival (PFS) of BRAF mutant metastatic colorectal cancer patients treated with irinotecan, cetuximab, and vemurafenib, compared to a control arm of irinotecan and cetuximab.

1.2 Secondary Objectives

a. To evaluate the frequency and severity of toxicity associated with each of the treatment arms in this patient population.

1.3 Other Objectives

a. To evaluate overall survival (OS) in treatment Arms 1 and 2.

b. To evaluate the overall response rate (ORR), including confirmed and unconfirmed, complete and partial response, in treatment Arms 1 and 2 in the subset of patients with measurable disease.

c. To estimate rates of OS, ORR, and PFS in patients who register to Arm 3 after disease progression on Arm 1.

1.4 Translational Objectives

a. To evaluate genetic alterations, including low-frequency *KRAS* or *NRAS* mutations (definitive list of genes to be finalized after completion of enrollment based on latest scientific knowledge) as detected by high-depth sequencing as predictive biomarkers of efficacy.

b. To evaluate PIK3CA pathway activation through PIK3CA mutations or PTEN protein loss as a predictive biomarker of innate resistance to this regimen.

c. To evaluate gene expression signatures from screened patients with $BRAF^{WT}$ and $BRAF^{V600E}$ tumors.

d. To provide validation of BRAF IHC using complementary sequencing methodology from screened patients with $BRAF^{WT}$ and $BRAF^{V600E}$ tumors.

e. To confirm the estimated sensitivity of detectable BRAF V600E circulating cell-free DNA as a non-invasive biomarker for BRAF V600E mutation as detected by IHC in the primary tumor.

f. To correlate radiographic tumor response with change in quantification of BRAF V600E alleles in circulating cell-free DNA.

g. To monitor for known mechanism of acquired resistance to EGFR inhibition in circulating cell-free DNA.

h. To assess the correlation of treatment efficacy between the patients and the matched patient-derived xenograft (PDX) models.

i. To assess the correlation between PDX mechanisms for resistance and circulating free DNA (cfDNA) in plasma samples of matched patients following progression of disease.

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2.0 BACKGROUND

***BRAF*-mutations in metastatic colorectal cancer**: Mutations in the *BRAF* oncogene are present in 5-10% of all human cancers and occur most frequently in melanoma (approximately 50%), colorectal cancer (7-10%), papillary thyroid cancer (45-50%), non-small cell lung cancer (3%), and serous ovarian cancers (30%). *(1-8)* Throughout all tumor types, the *BRAF* mutation manifests itself in over approximately 90% of cases as a valine-to-glutamic acid substitution in amino acid 600 of the kinase (V600E), which leads to a BRAF kinase domain ten-times more active than its *BRAF* wild-type counterpart and promotes tumor formation and growth via constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway. *(1)* Colorectal cancer remains the second leading cause of cancer mortality in the United States, with over 50,000 estimated deaths in 2012. *(9)* As stated above, *BRAF* mutations occur in fewer than 10% of all these tumors. These mutations are typically associated with older age at the time of diagnosis, female gender, right-sided primary location, gene hypermethylation, and microsatellite instability. *(10,11)* Additionally, the presence of a *BRAF* mutation is widely accepted as a poor prognostic marker in patients with metastatic colorectal cancer. *(12-16)* Multiple retrospective reviews have reported that, for patients with Stage II and III *BRAF*-mutated tumors, recurrence-free survival and overall survival following surgical resection are historically worse than for their *BRAF* wild-type counterparts. *(17,18)* One retrospective study reported a median overall survival of 10 months for patients with Stage IV disease with *BRAF*-mutated tumors, significantly worse than the 34.7 months for patients with metastatic, *BRAF* wild-type colorectal cancer. *(19)*

Inefficacy of *BRAF* inhibitors as monotherapy in *BRAF*-mutated colorectal cancer: Vemurafenib is a selective kinase inhibitor of the mutated V600E BRAF kinase that has no activity against the wild-type BRAF kinase domain. In a Phase I trial of patients with *BRAF*-mutated metastatic colorectal cancer, a partial response was noted in a single patient among 21 patients treated with the BRAF inhibitor (response rate < 5%). *(20)* Therefore, there is a dire need to introduce novel, effective treatment options for patients with *BRAF*-mutated metastatic colorectal cancer.

Blockade of *BRAF* and EGFR as a novel approach in *BRAF*-mutated colorectal cancer: Two papers have provided important insight into the mechanisms driving innate resistance to vemurafenib in *BRAF*-mutated metastatic colorectal cancer. Prahallad and colleagues used short hairpin RNA (shRNA) sequences on a kinase library screen in *BRAF*-mutated colorectal cancer cell lines treated with vemurafenib and found that the shRNA vectors targeting the epidermal growth factor receptor (EGFR) resulted in a synergistic inhibition of cell growth. *(21)* Based on these findings, the group next treated three different *BRAF*-mutated colorectal cell lines with a combination of vemurafenib and one of two classes of available anti-EGFR therapies – cetuximab, a monoclonal antibody against EGFR, or gefitinib, a small molecule tyrosine kinase inhibitor of EGFR – and found a strong synergistic interaction between the two therapies. Of note, a low response was seen when either vemurafenib or anti-EGFR therapy (cetuximab or gefitinib) was used as a single-agent therapy. Interestingly, a drastic increase in expression of phosphorylated EGFR was detected when cells were treated with vemurafenib alone, a finding which generated the hypothesis that treatment with a BRAF inhibitor may induce a reflexive activation of EGFR needed to maintain activity of the MAPK signaling cascade and hinder cytotoxicity from vemurafenib monotherapy. Concomitant BRAF inhibition and EGFR blockade resulted in a more complete suppression of Akt, MEK, and ERK phosphorylation relative to vemurafenib alone.

In a second study, levels of phosphorylated ERK, a downstream kinase in the MAPK pathway, were initially decreased in *BRAF*-mutated colorectal cancer cell lines when treated with vemurafenib, but that re-expression of phospho-ERK could be detected within 24 hours of treatment with vemurafenib. *(22)* Levels of phosphorylated CRAF also increased within 24 hours of BRAF inhibition, a finding suggesting that activated CRAF may bypass the blockade of BRAF by vemurafenib to maintain MAPK activity needed to perpetuate cell growth in vitro. Treating

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different BRAF-mutated colorectal cell lines with vemurafenib and gefitinib suppressed expression not only of phospho-EGFR but also of phospho-CRAF. As phospho-EGFR was also expressed after treatment with vemurafenib alone, these experiments corroborate the idea that *BRAF*-mutated colorectal cells harbor resistance to vemurafenib by immediate upregulation of the MAPK pathway by activating EGFR.

It has been shown that resistance to single-agent vemurafenib is associated with activated receptor tyrosine kinases, including EGFR, which may be responsible for initial resistance. In addition, exposing colon cancer cell lines to increasing and prolonged BRAF inhibition leads to acquired EGFR overexpression and acquired high level. Murine studies that included BRAF + EGFR inhibition demonstrated that the combination of BRAF + EGFR inhibition led to tumor regression in 5 of 10 mice. *(23)* The addition of irinotecan to the combination resulted in tumor regression in 10 of 10 mice, compared to no regression (0/10 mice) with irinotecan and EGFR inhibition without BRAF inhibition. Collectively, this data supports a combination approach of irinotecan with BRAF plus EGFR inhibition in colorectal cancer.

In this study, the control arm of irinotecan plus cetuximab is utilized as a standard subsequent therapy for patients previously treated with a 5-FU combination of FOLFOX/XELOX, FOLFOXIRI, or FOLFIRI, commonly administered with bevacizumab. Despite prior cohort studies suggesting lack of benefit of EGFR monoclonal antibodies in patients with BRAF mutant tumors, subsequent randomized studies demonstrated the poor prognosis of this cohort, but suggested maintained incremental benefit from EGFR inhibition. *(24,25)* These and other studies have also shown that addition of anti-EGFR therapies to standard chemotherapy regimens does not improve survival in patients with BRAF-mutated metastatic colorectal cancer, and thus this biomarker is not predictive for a survival benefit. *(26,27)*

A Phase I trial is currently underway in which patients with advanced BRAF-mutated solid tumors are being treated with the combination of vemurafenib, cetuximab, and irinotecan. As of 1/31/2014, ten patients had been enrolled. Nine of these patients had a diagnosis of colorectal cancer (the other with appendiceal adenocarcinoma and no neuroendocrine features). Seven patients had been treated at dose level 1 (vemurafenib 480 mg by mouth twice daily, cetuximab 500 mg/m^2 every 14 days, and irinotecan 180 mg/m^2 every 14 days), and three at dose level 2 (vemurafenib increased to 720 mg by mouth twice daily). At dose level 1, only one Grade 3 adverse event has been observed (arthralgia) and resolved with dose reduction. Of the five patients with metastatic CRC who have thus far been evaluated, responses have been detected in 4, with a reduction of tumor size of -44% (range 0-70%) as the median best response. The durations of response in these patients have been 5, 5+, 8+, 12+, and 14+ cycles (data unpublished). These results, although early, suggest that the combination of vemurafenib with irinotecan and cetuximab is well tolerated and may cause a biological response in patients with these tumors.

In summary, patients with *BRAF*-mutated metastatic colorectal cancer have poor prognoses and demonstrate poor responses both to traditional chemotherapy combinations for colorectal cancer and to BRAF inhibitors which have demonstrated efficacy in other malignancies driven by *BRAF* mutations. In vitro work has suggested that upregulation of EGFR in the presence of BRAF inhibition may generate a bypass mechanism through which these tumors may continue to survive and proliferate. The addition of cetuximab in order to block EGFR has been shown in cell lines and in mice models to overcome EGFR activation and restore sensitivity to vemurafenib. Furthermore, adding the cytotoxic chemotherapeutic agent irinotecan generates added cytotoxicity with this combination, as seen with in vivo models. Very preliminary Phase I results of the vemurafenib, cetuximab, and irinotecan combination intimate that these three drugs are safe for patients and may lead to promising results not seen before in this cohort of patients with colorectal cancer.

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Patient-derived xenografts (PDXs) as improved models for studying human malignancy: PDXs serve as biologically relevant models for studying metastatic cancer which utilize immunosuppressed mice that are subcutaneously implanted with biopsied human tumor specimens. *(40,41)* This model maintains a higher degree of intratumoral heterogeneity and incorporates human stroma from the implanted tumor that recapitulates a tumor microenvironment. In contrast, these attributes are not provided by tumor cells in culture or through homogenous cell-line derived xenografts. Additionally, the PDX platform also maintains slower doubling times for tumor growth and higher number of available molecular subtypes. These properties enable the use of PDXs as more realistic models to investigate novel therapies and resistance mechanisms for other types of malignancies. Prior work employing a PDX model of mCRC in a mock clinical trial comparing cetuximab with placebo showed similar outcomes to clinical trials in humans which had been run in an *unmatched* set of patients. *(42-45)* In addition, other retrospective series, in colorectal cancer and in other solid malignancies, have reported similarities in outcomes between patient responses to chemotherapy and tumor shrinkage in tumor xenografts. *(46-48)* However, the number of patients whose tumors were utilized was small and limits definitive conclusions to be made.

While these examples hint that the PDX model retrospectively may be promising to recapitulate responses in humans across various types of malignancies, thus far correlations in outcomes between the PDX model and the *matched* patient are poorly understood in *prospective* analyses. If a correlation between patient response on this study and a response in the matched PDX model is observed, then these findings may serve as the initial rationale for the design of future clinical trials for patients.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Note: We estimate that approximately 440 patients will be screened for BRAF V600E mutation in order to enroll the 78 patients necessary for the study. This table represents only the patients with the BRAF mutation who register to Step 2 (randomization).

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Ethnic Category	Females	Males	Total
Hispanic or Latino	3	3	6
Not Hispanic or Latino	44	55	99
Total Ethnic	47	58	105
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	2	2	4
Black or African American	4	4	8
Native Hawaiian or other Pacific Islander	1	1	2
White	39	50	89
Racial Category: Total of all Subjects	47	58	105

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3.0 DRUG INFORMATION

Investigator's Brochures

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, cetuximab and irinotecan are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the Physician's Desk Reference (PDR), prescribing information and other resources.

For this study, vemurafenib is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Cetuximab (IMC-C225, Erbitux®) (NSC-714692)

a. PHARMACOLOGY

Mechanism of Action: Cetuximab, a chimerized antibody of the IgG_1 subclass, was originally derived from a mouse myeloma cell line. Cetuximab was genetically engineered by cloning the heavy and light chains of cetuximab and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization resulted in an antibody with binding affinity to epidermal growth factor receptors (EGFR) greater than the natural ligand epidermal growth factor (EGF). Cetuximab blocks binding of EGF and transforming growth factor alpha (TGFα) to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand.

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b. PHARMACOKINETICS

1. Absorption: When cetuximab was administered as monotherapy or in combination with chemotherapy or radiation therapy it exhibited nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while the clearance decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2. The clearance seemed to plateau at doses greater than 200 mg/m^2.

2. Distribution: The volume of distribution of cetuximab is independent of the dose and is approximately the plasma volume (2 to 3 L/m^2). When administered at the recommended dose regimen of 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly dose, the concentration of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations in the range of 168 to 235 and 41 to 85 mcg/mL, respectively.

3. Metabolism: Cetuximab is eliminated via the EGFR binding/ internalization on hepatocytes and skin in a saturable manner.

4. Elimination: At the recommended dose regimen, the mean half-life of cetuximab was approximately 112 hours (range 63–230 hours).

c. ADVERSE EFFECTS

1. Possible Side Effects of Cetuximab

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 20% to 100% of subjects treated with cetuximab include: nail changes, radiation recall, rash, itching, dry skin, acne, dehydration, weight loss, anorexia, mucositis, constipation, diarrhea, vomiting, nausea, insomnia, headache, fatigue, pain, fever, infection, cough, and dyspnea.

Adverse effects reported in 4% to 20% of subjects include: allergic reaction/hypersensitivity which may cause rash, hypotension, wheezing, shortness of breath, and swelling of the face or throat, confusion, depression, anxiety, syncope, sepsis, and pulmonary embolism.
Adverse effects that are rare and serious that occurred in 3% or less of subjects include: interstitial lung disease, renal failure, and cardiopulmonary arrest and/or sudden death.

Note: Cetuximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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Additional information on common, serious, or severe reactions includes:

Infusion Reactions: In clinical trials, severe, potentially fatal infusion reactions were reported. These events included the rapid onset of airway obstruction (bronchospasm, stridor, and hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Dermatologic Toxicity: In clinical studies of cetuximab, dermatologic toxicities, including acneiform rash, skin drying and fissuring, and inflammatory and infectious sequelae (e.g. blepharitis, conjunctivitis, keratitis, cheilitis, cellulitis, cyst), and hypertrichosis were reported. In patients with advanced colorectal cancer, acneiform rash was reported in 88% (560/633) of all treated patients, and was severe (Grade 3 or 4) in 12% (79/633) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Non-suppurative acneiform rash described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving cetuximab plus irinotecan and in 90% (10% Grade 3) of patients receiving cetuximab monotherapy. Acneiform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (e.g. blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneiform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

A related nail disorder, occurring in 14% of patients (0.3% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Hypomagnesaemia: In patients treated with cetuximab during clinical trials, hypomagnesemia occurred in 55% of 365 patients with colorectal cancer and head and neck cancer, and was severe (NCI CTC Grades 3 and 4) in 6–17%. The addition of cetuximab to cisplatin and 5-fluoruracil resulted in an increased incidence of hypomagnesemia (14% vs. 6%) and of Grade 3–4 hypomagnesemia (7% vs. 2%) compared to cisplatin and 5-fluorouracil alone. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of cetuximab.

2. Pregnancy and Lactation: Pregnancy Category C. There are no adequate and well-controlled studies of cetuximab in pregnant women. Based on animal studies, EGFR has been involved in the control of prenatal development and may be essential for normal organogenesis,

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proliferation, and differentiation in the developing embryo. Human IgG is known to cross the placental barrier; therefore, if administered to a pregnancy woman, cetuximab may be transmitted from the mother to the developing fetus and has the potential to cause fetal harm

It is not known whether cetuximab is secreted in human milk. IgG antibodies, such as cetuximab, can be excreted in human milk and has the potential to cause serious adverse reactions in the nursing infant. Based on the mean half-life of cetuximab, nursing should not resume for at least 60 days following the last dose of cetuximab.

3. Drug Interactions: There are no reports of drug interactions with cetuximab.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Cetuximab is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.2 Irinotecan (Camptosar ®) (NSC616348)

a. PHARMACOLOGY

Mechanism of Action: Irinotecan and its metabolite SN-38 inhibit topoisomerase I. Topoisomerase I relieves torsional strain in the DNA helix during replication and RNA transcription by inducing single-strand breaks. By binding with the topoisomerase I—DNA complex, irinotecan or SN-38 prevents the religation of the single-strand breaks. Irreversible DNA damage occurs when a DNA replication fork encounters the irinotecan or SN-38/topoisomerase I complexes resulting in double-strand DNA breaks. Camptothecins are highly S-phase specific in their activity due the requirement of DNA synthesis.

b. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: Protein binding of irinotecan is 30-70%, whereas SN-38 shows a higher protein binding of 95%. Both irinotecan and SN-38 are primarily bound to albumin. Volume of distribution of irinotecan is approximately 110-234 L/m^2.

3. Metabolism: Irinotecan is metabolized primarily in the liver by carboxylesterase to SN-38, and via hepatic cytochrome P450 (CYP) 3A4 to aminopentane carboxylic acid (APC). SN-38 is conjugated to form a glucuronide metabolite by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1). Genetic polymorphisms exist in the enzyme UGT1A1, leading to different levels of exposure and toxicity among patients. In addition, both irinotecan and SN-38 undergo plasma hydrolysis between their active (lactone) and inactive forms (carboxylate). Finally, a small amount of irinotecan is metabolized by the intestinal wall.

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4. Elimination: Approximately 10-25% of irinotecan is recovered unchanged in urine whereas only small amounts of SN-38 have been found. Clearance is approximately 13.5 L/hr/m^2. In addition, irinotecan has approximately 25% biliary excretion.

c. ADVERSE EFFECTS

1. Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 20% to 100% of subjects treated with irinotecan include: diarrhea and cholinergic reaction (may be severe), constipation, nausea, vomiting, asthenia, infection, leukopenia, neutropenia, alopecia, anorexia, weight loss, anemia, fatigue, fever, pain, dizziness, cough, dyspnea, mucositis, rash, thrombocytopenia.
Adverse effects reported in 4% to 20% of subjects include: gastrointestinal perforation, hypersensitivity reaction, cardiovascular events, thromboembolic events, interstitial lung disease.

2. Pregnancy and Lactation: Pregnancy Category D. It is not known whether irinotecan or its derivatives are excreted in human milk.

3. Drug Interactions: Irinotecan and its active metabolite SN-38 may be substrates for CYP3A4, CYP2B6, OATP1B1/SCLO1B1, P-glycoprotein/ABCB1 and UGT1A1. Inducers or inhibitors may affect serum concentrations of irinotecan. Drugs of strong CYP3A4 inducers should be discontinued for at least 2 weeks before starting irinotecan therapy. Drugs of strong CYP3A4 inhibitors should be discontinued at least 1 week before starting irinotecan therapy. St. John Wort and Ketoconazole are contraindicated during irinotecan therapy. Due to potential drug interactions, a complete patient medication list, including irinotecan, should be screened prior to initiation of and during treatment with irinotecan. Refer to the current FDA-approved package insert. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

Dosing – See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Irinotecan is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

3.3 Vemurafenib (Zelboraf®) (NSC-761431) (IND-122167)

a. PHARMACOLOGY

Mechanism of Action: Inhibitor of mutated forms of the BRAF serine-threonine kinase enzyme, including BRAF V600E, exhibiting anti-tumor effects in melanomas with mutated BRAF V600E. BRAF gene mutations may lead to cell proliferation in the absence of growth factors.

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b. PHARMACOKINETICS

1. Absorption: Time to peak ~3 hours

2. Distribution: V_d ~106L, >99% protein binding

3. Metabolism: Not appreciably metabolized in humans, however CYP3A4 was the primary enzyme responsible for the metabolism of vemurafenib. Unchanged vemurafenib was the major component detected in plasma samples following oral administration.

4. Elimination: Feces (94%) & urine (1%), half life elimination 57 hours (30-120 hour range)

c. ADVERSE EFFECTS

1. Adverse Effects:

Adverse Events with Possible Relationship to Vemurafenib		
Likely (>20%)	Less Likely (4 – ≤20%)	Rare but Serious (≤3%)
CARDIAC DISORDERS		
	Peripheral Edema	Atrial fibrillation Hypotension Prolonged QT interval Retinal vein occlusion Vasculitis
EYE DISORDERS		
		Photosensitivity Photophobia Blurred vision Uveitis
GASTROINTESTINAL DISORDERS		
Nausea Diarrhea Vomiting	Decreased appetite Constipation Dysgeusia	Colonic polyps
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue Headache		
HEPATOBILIARY DISORDERS		
	Increased gamma-glutamyl transferase	Increased serum alkaline phosphatase Increased serum ALT Increased serum AST Increased serum bilirubin
IMMUNE SYSTEM DISORDERS		
	Allergic Reaction	Anaphylaxis Hypersensitivity Reactions
METABOLISM AND NUTRITION DISORDERS		
		Weight loss
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
Arthralgia Myalgia	Limb pain Back pain Musculoskeletal pain weakness	Arthritis

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NERVOUS SYSTEM DISORDERS		
		Cranial nerve palsy (facial) Dizziness Peripheral neuropathy
RENAL AND URINARY DISORDERS		
		Increased serum creatinine
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia Pruritus Skin photosensitivity Rash Hyperkeratosis Skin neoplasm Squamous cell carcinoma of skin	Maculopapular rash Xeroderma Sunburn Erythema Papular rash	Malignant melanoma(new primary) Stevens-Johnson syndrome Toxic Epidermal Necrosis

QT Prolongation: Vemurafenib has been shown to increase the QT interval, leading to ventricular arrhythmias including Torsade de Pointes. Use with caution in patients who are taking concurrent QT prolonging medications or products.

2. Pregnancy and Lactation: Pregnancy Category D. Vemurafenib may cause fetal harm. Adequate contraception methods should be implemented during and at least two months after treatment. Excretion in breast milk is not known.

3. Drug Interactions: In vitro studies have demonstrated that vemurafenib is a substrate of CYP3A4 (major). Use vemurafenib with caution when administered concurrently with potent CYP3A4 inhibitors or inducers, due to possible increased or decreased plasma concentrations of vemurafenib, respectively. Concomitant use of vemurafenib with drugs of narrow therapeutic windows that are metabolized by CYP3A4, CYP1A2, or CYP2D6 are not recommended. If coadministration cannot be avoided, use caution and consider a dose reduction of CYP1A2 or CYP2D6 substrates. Use caution and monitor INR when vemurafenib is given with warfarin.

   Use vemurafenib with caution with QT prolonging medications (e.g. antiarrhythmics, antipsychotic agents that prolong the QT interval, HIV protease inhibitors, moxifloxacin). Consider therapy modification.

   Due to potential drug interactions, a complete patient medication list, including vemurafenib, should be screened prior to initiation of and during treatment with vemurafenib. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

   See Section 7.0 Treatment Plan

e. HOW SUPPLIED

   1. Vemurafenib is available as a 240 mg oral tablet in a bottle of 120 tablets.

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2. Biologics Inc. from Genentech will supply commercial grade product labeled for investigational use vemurafenib.

f. STORAGE, PREPARATION & STABILITY

1. Tablets should be stored at room temperature (20°-25°C or 68°-77°F). Store in the original container with the lid tightly closed.

2. Sites and subjects are advised to keep vemurafenib in its original container when feasible. If a container must be opened, repackage in a secure container, dispense a sufficient supply and store the remaining product in its original container. Labeling should be done in accordance to the law and contain the statement "CAUTION: NEW DRUG – LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE."

3. Storage excursions are permitted to 15°-30°C or 59°-86°F.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering:

a. Vemurafenib may be requested by the Principal Investigator (or their authorized designee) by completing and faxing the Biologics Drug Request form for **S1406**. The form should be faxed to the number listed on the order form. Authorized and completed orders will be processed and shipped "same day" of receipt if received before 2:00 pm EST Monday through Friday. Authorized and completed orders received after 2:00 pm EST Monday through Friday will be processed and shipped the next business morning. Packages are tracked until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator for all shipments. Biologics will be closed for the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, Thanksgiving Friday, Christmas Eve, and Christmas Day.

b. Once a patient is registered, the site will fax a completed Drug Request form to Biologics at 919/256-0794. Upon receipt of faxed Drug Request form, Biologics will:

1. Place a call or email to the site confirming the Drug Request form was received, while providing the estimated day and time of arrival of the study drug.

2. Biologics will ship the requested quantity of bottles for the patient to complete their cycles of vemurafenib. During Month 5 and Month 11, biologics will place a call to the study site to arrange for the next shipment of study drug for the subsequent cycle.

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3. All study drug will be shipped in original manufacturers packaging with a patient-specific label adhered to the outer packaging. Biologics will place the manufacturer's packaging in a resealable bag. Each shipment includes a protocol label on the resealable bag with the following information:

   - The Study Number (i.e., SWOG **S1406**);
   - SWOG Patient ID#
   - IND caution statement and/or local regulatory statements
   - Drug identification
   - Lot number and Expiration date
   - Dosing instructions (i.e., "Administer as directed per Protocol SWOG **S1406**")
   - Storage instructions
   - Emergency contact instructions

4. Once study drug is received at the clinical trial site, the designated site coordinator validates the contents of package and matches the information provided on packing slip, signs off on the packing slip, and faxes completed form to Biologics to validate shipment has been received and is accurate.

   NOTE: The vemurafenib shipped is labeled either RO5185426 or PLX4032. The vemurafenib Investigator Brochure indicates that it is also known as RO5185426 and/or PLX4032. For editorial simplicity, the compound is referred to as vemurafenib in the Investigator Brochure. Labeling may also include reference to Brafistus, which is an acronym for BRAF, IST (investigator sponsored trial), US.

c. All drug orders are shipped via *FedEx for Priority Overnight* delivery for shipments to US sites.

The Biologics distribution team monitors packages throughout duration of transit via Fed Ex website and FedEx One Call Solution (live support). Real-time monitoring enables the Biologics distribution team to mitigate potential delivery delays (e.g. misrouted packages).

In the event a package cannot be delivered within the 24 hour time period (e.g., due to severe weather), Biologics' distribution team works proactively with Fed Ex One-Call, confirming the exact location of the package and providing instruction to Fed-Ex to return the package to Biologics. Upon notification of a delayed shipment, a replacement shipment will be sent to the site, as authorized. Sites are also alerted "same day" to any delays in delivery and provided estimated time for arrival of replacement package. The process for delayed deliveries including recovery strategies, are detailed in a Biologics SOP that may be provided upon approval of this proposal. All delivery exceptions will be reported via Accountability Reporting.

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2. Drug Handling and Accountability (NCI logs or other)

   a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Oral Drug Accountability Record Form (NCI Oral DARF) available at http://ctep.cancer.gov.

      Questions about drug orders, transfers, returns, or accountability should be addressed to the Clinical Research Services at Biologics, Inc. at 800-693-4906 or Clinicalresearchservices@biologicsinc.com.

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI Oral DARF.

3. Drug return and/or disposition instruction

   a. Drug Return: At the conclusion of the study, remaining inventory is documented in the accountability records and unused drug will be destroyed per local institutional guidelines..

   b. Drug expiration: If packaging does not have expiration date, check with drug ordering designee and/or PI to confirm receipt of ongoing stability testing letter. If packaging has an expiration date, indicate drug expiration date on the DARF and use the drug lots with shorter expiration date first.

4. Questions about drug orders, transfers, returns, or accountability should be addressed to the Clinical Research Services at Biologics, Inc. at 800-693-4906 or Clinicalresearchservices@biologicsinc.com.

4.0 STAGING CRITERIA

Staging criteria are not applicable to this study.

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5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Step 1 Initial Registration: BRAF^{V600E} Testing

If patient has already had BRAF testing, he or she must satisfy these eligibility criteria before being considered for Step 2 Randomization.

a. Disease Related Criteria

_____ 1. Patients must have histologically or cytologically documented adenocarcinoma of the colon or rectum that is either metastatic, or locally advanced and unresectable. NOTE: In the event that both cecal and appendiceal primaries are considered, patient is eligible if it is concluded by the treating oncologist to most likely be cecal based on pathological, surgical, and clinical interpretation. Clinical diagnosis must be clearly documented in the "Comments" section on the **S1406** Onstudy Form.

_____ 2. Patients must have BRAF^{V600E} mutant status documented by a CLIA certified laboratory on a pathology report prior to Step 2 registration. Use of an FDA-approved test is preferred although other BRAF tests at a CLIA-certified laboratory will also be accepted.

If a BRAF^{V600E} mutation is known, then the patient must be registered to Step 2 Randomization immediately following Step 1 Initial Registration.

If testing has not been performed locally, BRAF^{V600E} testing must be completed by the central lab (see Section 15.1) prior to Step 2 Randomization. If the specimen does not have a BRAF^{V600E} mutation, the patient is ineligible for Step 2 Randomization.

_____ 3. Brain metastases are allowed if they have been adequately treated with radiotherapy or surgery and stable for at least 90 days prior to Step 1 Initial Registration. Eligible patients should be neurologically asymptomatic and without corticosteroid treatment for at least 7 days prior to Step 1 Initial Registration.

_____ 4. Patients must have had one or two prior regimens of systemic chemotherapy for metastatic or locally advanced, unresectable disease. (A maintenance regimen of 5-fluorouracil or capecitabine, with or without bevacizumab, should not be counted as a separate line of treatment.) Prior treatment with irinotecan is allowed. Prior treatment for metastatic disease is not required for patients who experienced disease recurrence during or within 6 months of completion of adjuvant chemotherapy.

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SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Step 1 Initial Registration: BRAF^{V600E} Testing (contd.)

_____ 5. Patients must not have been treated with any of the following prior to Step 1 Initial Registration:

- Cetuximab, panitumumab, or any other monoclonal antibody against EGFR or inhibitor of EGFR.
- BRAF inhibitor including, but not limited to, vemurafenib or dabrafenib. Regorafenib is not considered a BRAF inhibitor for the purpose of determining trial eligibility.
- MEK inhibitor including, but not limited to, trametinib or selumetinib.

_____ 6. Known KRAS or NRAS mutations:

a. All patients must have molecular testing performed in a clinical lab which includes codon 12 and 13 of KRAS. Patients with any mutation in codon 12 and 13 of KRAS are not eligible for the protocol.

b. Testing for additional codons in KRAS or testing for NRAS is not required. However, if such testing has been performed in a clinical lab and any mutation in codons 61 or 146 in KRAS, or codons 12, 13, 61, or 146 in NRAS is detected, the patient is not eligible for the protocol.

b. Specimen Submission Criteria

_____ 1. Patients must have tumor (slides or block) available for submission for V600E BRAF testing as described in Section 15.1.

_____ 2. Patients must have additional tumor available and be willing to submit tissue and blood samples as described in Section 15.2.

c. Regulatory Criteria

_____ 1. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. For Step 1 Initial Registration of patients who have not yet submitted specimens for the central BRAF^{V600E} testing, the appropriate consent form is the Step 1 Consent Form. For both Step 1 Initial Registration and Step 2 Randomization of patients whose BRAF mutation status is already known, the appropriate consent form is the Step 2 Consent Form.

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5.2 Step 2 Randomization

Patients with known BRAF mutation must be registered to Step 2 Randomization immediately following Step 1 Initial Registration. Results of BRAF testing will be available on the SWOG Specimen Tracking Website within 10 calendar days from submission of tissue specimen to Moffitt Cancer Center and patient must be registered to Step 2 within 60 days of Step 1 Initial Registration.

a. Clinical/Laboratory Criteria

_____ 1. Patients must have $BRAF^{V600E}$ mutation.

_____ 2. Patients must have measurable or non-measurable disease that is either metastatic or locally advanced and unresectable, as defined in Section 10.1. CT scans or MRIs used to assess all disease must have been completed within 28 days prior to Step 2 Randomization. CT scans or MRIs must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

_____ 3. Previous chemotherapy, immunotherapy, or radiation therapy must have been completed at least 14 days prior to Step 2 Randomization and all toxicity must be resolved to CTCAE v4.0 Grade 1 (with the exception of CTCAE v4.0 Grade 2 neuropathy) prior to Step 2 Randomization.

_____ 4. Patients must have a Zubrod Performance Status of 0-1. (See Section 10.4.)

_____ 5. Patients must be ≥ 18 years of age.

_____ 6. Patients must have a complete physical examination and medical history within 28 days prior to Step 2 Randomization.

_____ 7. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to Step 2 registration: ANC ≥ 1,500/mcL; platelets ≥ 100,000/mcL; and hemoglobin ≥ 9 g/dL.

_____ 8. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to Step 2 registration: AST and ALT ≤ 2.5 x Institutional Upper Limit of Normal (IULN) or ≤ 5 x IULN if liver metastases are present; and total bilirubin ≤ 1.5 x IULN.

_____ 9. Patients must have adequate kidney function as evidenced by at least ONE of the following:

- Serum creatinine ≤ 1.5 x IULN within 14 days prior to Step 2 Randomization OR
- Calculated creatinine clearance > 60 ml/min. The serum creatinine value used in the calculation must have been obtained within 14 days prior to Step 2 Randomization.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times [0.85 \text{ (if female)}]}{72 \times \text{creatinine (mg/dL)}}$$

_____ 10. Patients must have an ECG within 14 days prior to Step 2 Randomization. Patients must have QTc ≤ 500 msec.

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5.2 Step 2 Randomization (contd.)

_____ 11. Patients must not have a known history of Gilbert's Syndrome or known homozygosity for the UGT1A1*28 allele.

_____ 12. Patients must not have interstitial pneumonia or extensive symptomatic interstitial fibrosis of the lung.

_____ 13. Patients must not have an uncontrolled intercurrent illness including, but not limited to, active bleeding diathesis, uncontrolled infection/disorders, nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy, or psychiatric illness/social situations which would limit compliance with study requirements.

_____ 14. Patients must be able to swallow pill/tablet and have no refractory nausea, vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate absorption.

_____ 15. Patients must not be pregnant or nursing due to risk of fetal or nursing infant harm. Women/men of reproductive potential must have agreed to use an effective contraceptive method while on study and for at least 60 days after study treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

_____ 16. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.

b. Regulatory Criteria

_____ 1. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. For all patients, the appropriate consent form for this registration is the Step 2 Consent Form.

_____ 2. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

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5.2 Step 2 Randomization (contd.)

c. Specimen Submission Criteria

_____ 1. Patients (at institutions listed in Section 15.4 only) must be offered the opportunity to participate in the optional **S1406** Co-Clinical PDX Model Trial (see Section 15.4). Participating patients must have a fresh tissue biopsy for the Co-Clinical PDX Model Trial completed within 7 days of Step 2 Randomization.

5.3 Step 3 Crossover Registration

_____ a. Patients must have documented disease progression as defined in Section 10.2d while on Arm 1 of this protocol. The Follow-up Tumor Assessment Form documenting disease progression must be submitted to SWOG prior to Step 3 Crossover Registration. Registration to Step 3 Crossover must be within 28 days of discontinuation of Arm 1 protocol treatment. Patients going off treatment for any other reason are not eligible.

_____ b. Patients must have a Zubrod Performance Status of 0-1. (See Section 10.4)

_____ c. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to Step 3 registration: ANC ≥ 1,500/mcL; platelets ≥ 100,000/mcL; and hemoglobin ≥ 9 g/dL.

_____ d. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to Step 3 registration: AST and ALT ≤ 2.5 x Institutional Upper Limit of Normal (IULN) or ≤ 5 x IULN if liver metastases are present; and total bilirubin ≤ 1.5 x IULN.

_____ e. Patients must have adequate kidney function as evidenced by at least ONE of the following:

- Serum creatinine ≤ 1.5 x IULN within 14 days prior to Step 3 registration OR
- Calculated creatinine clearance > 60 ml/min. The serum creatinine value used in the calculation must have been obtained within 14 days prior to Step 3 registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times [0.85 \text{ (if female)}]}{72 \times \text{creatinine (mg/dL)}}$$

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6.0 STRATIFICATION FACTORS

6.1 Stratification Factors

Stratification factors do not apply to Step 1 Initial Registration or Step 3 Crossover Registration.

6.2 Randomization

Patient will be randomized at Step 2 Randomization using a dynamic balancing algorithm with stratification based on prior treatment with irinotecan: yes vs. no. *(38)*

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Kopetz at 713/792-2828 or Dr. Lenz at 323/865-3955. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication *

Diphenhydramine (or other H_1-antagonist) 50 mg intravenously, given once 30-60 minutes prior to first dose of cetuximab.

Dexamethasone 10 mg intravenously, given 30-60 minutes prior to irinotecan.

Patients on Arm 1 may receive institutional recommended management for nausea. Patients on Arms 2 and 3 may receive maximum doses of the following drugs:

- ondansetron 8 mg IV,
- dolasetron 12.5 mg IV,
- granisetron 1 mg IV,
- any oral form of 5-HT_3 inhibition.

* NOTE: These may be modified at the discretion of the treating physician.

7.2 Treatment – Arm 1

Patients assigned to Arm 1 will receive the following treatment until meeting one of the criteria in Section 7.6.

Agent	Dose	Route	Day	Schedule *
Cetuximab	500 mg/m^2	IV over 120 min for initial dose and over 60 min for subsequent doses **	1, 15	Prior to irinotecan
Irinotecan	180 mg/m^2	IV over 90 min	1, 15	After cetuximab

* Note: One cycle = 28 days
** Subsequent doses may be given over 60 minutes or 120 minutes at the discretion of the treating physician.

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7.3 Treatment – Arm 2

Patients assigned to Arm 2 will receive the following treatment until meeting one of the criteria in Section 7.6.

Agent	Dose	Route	Day	Schedule *
Cetuximab	500 mg/m^2	IV over 120 min for initial dose and over 60 min for subsequent doses ***	1, 15	Prior to irinotecan
Irinotecan	180 mg/m^2	IV over 90 min	1, 15	After cetuximab
Vemurafenib	960 mg (1920 mg total daily dose) **	PO BID	1-28	Daily

* Note: One cycle = 28 days
** Patients should take 4 tablets in the morning and 4 tablets in the evening with or without a meal. A missed dose can be taken up to 4 hours prior to the next dose.
*** Subsequent doses may be given over 60 minutes or 120 minutes at the discretion of the treating physician.

7.4 Drug Compliance Documentation

Drug compliance for vemurafenib will be recorded by patients in an Intake Calendar (see **S1406** protocol abstract page on the SWOG website [www.swog.org] for an example). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.5 Crossover following disease progression on Arm 1

a. Following radiographic documentation by RECIST 1.1 (in Section 10.2d) of disease progression, patients initially randomized and treated on Arm 1 may register to Step 3 Crossover Registration to be treated with vemurafenib, irinotecan, and cetuximab per the schedule and doses listed below. Patients must be eligible and registered for Step 3 Crossover Registration per Section 5.3. Patients must be re-staged at time of progression on Arm 1 prior to registration to Step 3 Crossover Registration. Follow-up for these patients after crossover will be the same as those patients initially randomized to Arm 2.

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b. Treatment – Arm 3

Patients who are registered to Step 3 Crossover Registration will receive the following treatment until meeting one of the criteria in Section 7.6.

Agent	Dose**	Route	Day	Schedule*
Cetuximab	500 mg/m^2	IV over 60 min	1, 15	Prior to irinotecan
Irinotecan	180 mg/m^2	IV over 90 min	1, 15	After cetuximab
Vemurafenib	960 mg (1920 mg total daily dose)	PO BID	1-28	Daily

* Note: One cycle = 28 days
** If patient was on a reduced dose of cetuximab and/or irinotecan in Arm 1, he or she should begin treatment at that dose in Arm 3.

7.6 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

b. Arm 1 only: If patient progresses per RECIST 1.1 (see Section 10.2d), patient has the option to crossover to treatment Arm 3.

c. Unacceptable toxicity.

d. Treatment delay for any reason > 3 weeks.

e. The patient may withdraw from the study at any time for any reason.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.8 Follow-Up Period

All patients will be followed until death or 3 years after Step 2 Randomization, whichever occurs first.

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8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

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8.2 General Considerations

a. Where several toxicities with different grades or severity occur at the same time, the dose modification applied should be the greatest reduction applicable.

b. The maximum dose delay for any reason is 3 weeks.

c. Doses omitted during a cycle will not be made up.

d. If treating investigator feels an event is attributable to another drug, then, after conversation with the Study Chair, other modification may be considered.

e. Patient may continue protocol treatment if either cetuximab or irinotecan must be stopped. If patient must stop vemurafenib treatment, patient should be removed from all protocol treatment.

f. Advise patients to avoid sun exposure while on treatment with vemurafenib and cetuximab. Encourage patients to wear protective clothing and to use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors.

8.3 Dose Modifications

a. Dose Levels for Treatment Modifications

Agent	Starting Dose	Level -1	Level -2	Level -3
Vemurafenib	960 mg PO BID (total daily dose 1920 mg)	720 mg PO BID (total daily dose 1440 mg)	480 mg PO BID (total daily dose 960 mg)	N/A
Irinotecan	180 mg/m^2	150 mg/m^2	125 mg/m^2	100 mg/m^2
Cetuximab	500 mg/m^2	375 mg/m^2	250 mg/m^2	N/A

* Patients who require dose reductions below the values listed above will be removed from protocol treatment.

b. Nausea and/or vomiting despite optimal medical management

Institute the recommended management at first occurrence, if reoccurs despite optimal medical management, follow dose modification guidelines below. Recommended management for patients receiving vemurafenib may include maximum doses of the following drugs: ondansetron 8 mg IV, dolasetron 12.5 mg IV, and granisetron 1 mg IV; oral 5-Ht_3 antagonist drugs can be used. If symptoms do not improve, then other alternatives like aprepitant, prochlorperazine, or metoclopramide may be considered. If patient is taking vemurafenib and vomits after taking dose, do not redose vemurafenib.

Patients not receiving vemurafenib should be managed per standard practice.

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Toxicity Grade	Dose Modification Arm 1	Arm 2
2	Hold all treatment until recovery to ≤ Grade 1. Resume at same dose level.	Hold all treatment until Recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.	Hold all treatment until recovery to ≤ Grade 1. At the first occurrence, reduce irinotecan by one dose level. At second occurrence, reduce vemurafenib by one dose level. At third occurrence, reduce irinotecan by one dose level. After the fourth occurrence, the patient must be removed from protocol treatment.

c. Diarrhea despite optimal medical management

Recommended management: Loperamide 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours).

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold irinotecan until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.

d. Neutropenia

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level. Use of G-CSF (or PEGylated G-CSF) may be considered.*

* G-CSF or pegylated G-CSF may be utilized per ASCO guidelines (http://jop.ascopubs.org/cgi/content/full/2/4/196).

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e. Thrombocytopenia

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.

f. Blood Bilirubin Increased

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold irinotecan and vemurafenib until recovery to ≤ Grade 1. Reduce irinotecan and vemurafenib each by one dose level.

g. Mucositis

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.

h. Fatigue

Toxicity Grade	Dose Modification Arm 1	Arm 2
2	Hold all treatment until recovery to ≤ Grade 1. Resume at same dose level.	Hold all treatment until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.	Hold all treatment until recovery to ≤ Grade 1. At the first occurrence, reduce irinotecan by one dose level. At the second occurrence, reduce vemurafenib by one dose level. At third occurrence, reduce irinotecan by one dose level. the fourth occurrence, the patient must be removed from protocol treatment.

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i. Arthralgia

Toxicity Grade	Vemurafenib Dose Modification
2	Hold vemurafenib until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold vemurafenib until recovery to ≤ Grade 1. Reduce vemurafenib by one dose level.

j. Pneumonitis

Toxicity Grade	Cetuximab Dose Modification
2	Hold cetuximab until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold cetuximab until recovery to ≤ Grade 1 and until interstitial lung disease has been ruled out. Reduce cetuximab by one dose level. Discontinue protocol treatment if interstitial lung disease is confirmed by CT scan.

k. Rash

Toxicity Grade	Dose Modification Arm 1	Arm 2 + Arm 3
3 or 4	At the first occurrence of rash, hold cetuximab until recovery to Grade ≤ 2. If there is improvement in the rash upon holding therapy, Then resume at same dose. At second occurrence of rash, hold cetuximab until recovery to Grade ≤ 2. If there is improvement in the rash upon holding therapy, reduce cetuximab by one dose level and resume. At third occurrence, remove patient from cetuximab treatment.	At the first occurrence of rash, hold cetuximab until recovery until recovery to Grade ≤ 2. If there is improvement in the rash upon holding therapy, then resume at same dose. At second occurrence of rash, hold cetuximab and vemurafenib until recovery to Grade ≤ 2. If there is improvement in the rash upon holding therapy, reduce cetuximab by one dose level and resume. At third occurrence, hold cetuximab and vemurafenib until recovery to Grade ≤ 2 If there is improvement in the rash upon holding therapy, reduce vemurafenib and resume. At fourth occurrence, the patient must be removed from protocol treatment.

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l. Photosensitivity

Toxicity Grade	Dose Modification
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce vemurafenib by one dose level.

m. Uveitis

Toxicity Grade	Dose Modification
2	Hold vemurafenib until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold vemurafenib until recovery to ≤ Grade 1. Reduce vemurafenib by one dose level.

n. Hypersensitivity Reaction*, Cytokine Release*, Infusion Reaction

Toxicity Grade	Dose Modification
1	Decrease cetuximab infusion rate by 50% until symptoms resolve, then resume at the initial planned rate.
2	Stop cetuximab infusion. Administer H_1 and/or H_2 blockers, and/or steroids according to institutional policy. Restart the infusion at 50% lower rate when symptoms resolve and pretreat before all subsequent doses. All subsequent cetuximab doses should be administered at the lower infusion rate.
3 or 4	Stop the infusion. Discontinue cetuximab treatment.

* For reporting these events: NCI CTCAE 4.0 defines these reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the CTCAE version 4.0 for a complete list of signs and symptoms of "Cytokine release syndrome/acute infusion reaction;" and see the "Allergy/Immunology" section for a description of hypersensitivity.

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o. Electrocardiogram QT Corrected Interval Prolonged

Toxicity Grade	Dose Modification
3 or 4	Withhold vemurafenib until QTc interval ≤ 500 msec and resume therapy at one reduced dose level. Permanently remove from protocol treatment if the QTc remains > 500 msec and increased > 60 msec from pre-treatment values after controlling cardiac risk factors for QT prolongation (e.g., electrolyte imbalances, congestive heart failure, bradyarrhythmias).

p. Development of new keratoacanthomas or squamous cell carcinoma of the skin

All patients receiving vemurafenib are recommended to undergo a dermatologic evaluation and head/neck examination by their treating physician for monitoring of keratoacanthomas and squamous cell carcinomas. This evaluation should be done at baseline and every 2 months on therapy. CT imaging of the chest, which is performed at baseline and every 2 months on treatment for disease assessment, should be evaluated for any findings of concern for non-dermatologic squamous cell carcinomas. These evaluations should continue for 6 months after completion of vemurafenib, if deemed clinically appropriate by the treating physician. Any new skin lesions or head/neck/chest findings must be treated appropriately, as directed by a dermatologist or otolaryngologist as indicated, while receiving therapy on this protocol. Patients who develop keratoacanthomas or new squamous cell carcinomas of the skin while being treated on protocol should be managed by removal of the carcinomas by a dermatologist. If the lesions are unable to be removed due to the number or location, then the patient should be removed from all protocol therapy.

q. Hypomagnesemia

Toxicity Grade	Dose Modification
1 or 2	Supplementation with magnesium. Closely monitor patient for appropriate magnesium levels.
3 or 4	Institute maximal medical management with magnesium. If Grade ≥ 3 persists despite magnesium supplementation, reduce cetuximab by one dose level. At second occurrence, discontinue cetuximab therapy.

r. Other non-hematologic toxicities

Toxicity Grade	Dose Modification
3 or 4	Hold all treatment and monitor toxicity at least weekly. If toxicity resolves to ≤ Grade 1 within 3 weeks, reduce irinotecan by one dose level and resume treatment.

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8.4 Dose Modifications Contacts

For treatment or dose modification questions, please contact Dr. Kopetz at 713/792-2828 or Dr. Lenz at 323/865-3955.

8.5 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

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9.1 Arm 1: Cetuximab + Irinotecan

			Cycle 1				Cycle 2				Cycle 3				Cycle 4				Ω	% α
REQUIRED STUDIES	Step 1	Step 2	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	FU	FU
	Initial Reg	Rand	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	prior to prog	after prog
PHYSICAL ∑																				
History and Physical Exam		X ¥	X		X		X		X		X		X		X		X		X	X
Weight and Performance Status		X	X		X		X		X		X		X		X		X		X	X
Toxicity Notation					X		X		X		X		X		X		X		X	X
Disease Assessment		X									X								X	X
LABORATORY ∑																				
CBC/Differential/Platelets		X			X		X		X		X		X		X		X			
AST and ALT		X			X		X		X		X		X		X		X			
Serum creatinine/ Calculated creatinine clearance		X			X		X		X		X		X		X		X			
Total bilirubin		X			X		X		X		X		X		X		X			
Magnesium/ Potassium Calcium/Sodium/Bicarb/ Chloride		X			X		X		X		X		X		X		X			
SPECIMEN SUBMISSION																				
Tissue for BRAF Testing & Banking £	X																			
Blood £	X										X								X	X
Fresh Tissue Biopsy ʒ		X																		
X-RAYS AND SCANS																				
CT or MRI for Disease Assessment ◇		X									X								X	X
ECG		X																		
TREATMENT ∑																				
Cetuximab			X		X		X		X		X		X		X		X			
Irinotecan			X		X		X		X		X		X		X		X			

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9.2 Arm 2: Cetuximab + Irinotecan + Vemurafenib

			Cycle 1				Cycle 2				Cycle 3				Cycle 4				Ω	%
REQUIRED STUDIES	Step 1	Step 2	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	FU prior to prog	FU after prog
	Initial Reg	Rand	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
PHYSICAL ∑																				
History and Physical Exam		X ¥	X		X		X		X		X		X		X		X		X	X
Weight and Performance Status		X	X		X		X		X		X		X		X		X		X	X
Toxicity Notation					X		X		X		X		X		X		X		X	X
Disease Assessment		X									X								X	X
Dermatologic evaluation ~		X					X								X					X
Head and Neck Exam †		X					X								X					X
LABORATORY ∑																				
CBC/Differential/Platelets		X			X		X		X		X		X		X		X			
AST and ALT		X			X		X		X		X		X		X		X			
Serum creatinine/ Calculated creatinine clearance		X			X		X		X		X		X		X		X			
Total bilirubin		X			X		X		X		X		X		X		X			
Magnesium/ Potassium Calcium/Sodium/Bicarb/Chloride		X			X		X		X		X		X		X		X			
SPECIMEN SUBMISSION																				
Tissue for BRAF Testing & Banking £	X																			
Blood £	X										X								X	X
Fresh Tissue Biopsy ʒ		X																		
X-RAYS AND SCANS																				
CT or MRI ◇ ϖ		X									X								X	X
ECG ð		X			X				X				X							
TREATMENT ∑																				
Cetuximab			X		X		X		X		X		X		X		X			
Irinotecan			X		X		X		X		X		X		X		X			
Vemurafenib			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

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9.3 Arm 3: Cetuximab + Irinotecan + Vemurafenib

		Cycle 1				Cycle 2				Cycle 3				Cycle 4				Ω	%
REQUIRED STUDIES	Step 3 Cross-over Reg	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	FU prior to Prog	FU after Prog
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
PHYSICAL ∑																			
History and Physical Exam	X ¥	X		X		X		X		X		X		X		X		X	X
Weight and Performance Status	X	X		X		X		X		X		X		X		X		X	X
Toxicity Notation				X		X		X		X		X		X		X		X	X
Disease Assessment	X									X								X	X
Dermatologic evaluation ~	X					X								X					X
Head and Neck Exam †	X					X								X					X
LABORATORY ∑																			
CBC/Differential/Platelets	X			X		X		X		X		X		X		X			
AST and ALT	X			X		X		X		X		X		X		X			
Serum creatinine/ Calculated creatinine clearance	X			X		X		X		X		X		X		X			
Total bilirubin	X			X		X		X		X		X		X		X			
Magnesium/ Potassium Calcium/Sodium/Bicarb/Chloride	X			X		X		X		X		X		X		X			
SPECIMEN SUBMISSION																			
Tissue for BRAF Testing & Banking £																			
Blood £	X									X								X	X
X-RAYS AND SCANS																			
CT or MRI ◇ ϖ	X									X								X	X
ECG δ				X				X				X							
TREATMENT ∑																			
Cetuximab		X		X		X		X		X		X		X		X			
Irinotecan		X		X		X		X		X		X		X		X			
Vemurafenib		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Click here for footnotes.

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Calendar 9.1, 9.2 and 9.3 footnotes.

∑ Protocol treatment and parameters will continue at these intervals until progression of disease or until patient has met any of the guidelines in Section 7.6.

Ω After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 8 weeks until progression.

% After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 6 months for three years from the time of registration to Step 2.

¥ Must be done within 28 days prior to registration

£ Required specimen submission for patients. See Section 15.1 and 15.2 for additional information.

◇ CT or MRI for disease assessment must be performed every 8 weeks while on study treatment.

α Patients who progress on Arm 1 may crossover to Arm 3 treatment if criteria in Section 5.3 are met and patient is registered to Step 3 Crossover Registration.

δ Performed once every cycle for the first three cycles and every 3 cycles thereafter until 6 months after off treatment of vemurafenib. Anytime a dose adjustment is required for QTc changes, monitoring frequency is performed as if the patient just started treatment.

~ Performed at Step 2 Randomization or Step 3 Crossover Registration, after 4 weeks and every 2 months through 6 months after discontinuation of vemurafenib to evaluate for cutaneous malignancies (see Section 8.3p).

ϖ Chest imaging should be performed for disease assessment at baseline and with each restaging through 6 months after off treatment. This imaging will also allow for surveillance for non-cutaneous squamous cell carcinoma.

† Performed at Step 2 Randomization or Step 3 Crossover Registration, after 4 weeks and every 2 months through 6 months after discontinuation of vemurafenib to evaluate for non-cutaneous SCC. (see Section 8.3p). The minimum criteria should be visual inspection of the oral mucosa and lymph node palpation performed by the treating physician.

ʒ Only for sites listed in Section 15.4.

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10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

This study will use the RECIST 1.1 guidelines. *(39)*

10.1 Measurability of Lesions

a. **Measurable disease**

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

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5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as *non-target* lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

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e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

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b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status:

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival

a. Primary Endpoint (Arms 1 and 2): From date of Step 2 Randomization to date of first documentation of progression or symptomatic deterioration (as defined in Section 10.2), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

b. Crossover Endpoint (Arm 3 only): From date of Step 3 Crossover Registration to date of first documentation of progression or symptomatic deterioration (as defined in Section 10.2), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

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10.6 Time to Death

From date of Step 2 Randomization to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

All potentially eligible patients will be registered (step 1) and screened for BRAF, either passively (standard of care BRAF testing outside of trial in CLIA-compliant labs) or actively through consenting to be screened in this study. Patients who test positive for the V600E BRAF mutation are then eligible for randomization (step 2 registration) to treatment with irinotecan, cetuximab, and vemurafenib, or irinotecan and cetuximab. Patients randomized to the control arm (irinotecan and cetuximab) with disease progression during treatment are then eligible to cross over to treatment with vemurafenib in step 3 registration.

11.1 Accrual Goals

SWOG and the other adult oncology groups have no prior experience accruing this selected patient subset. By opening this study through CTSU, with support from ECOG-ACRIN, Alliance, and RNG, we are aiming for accrual of approximately 3 patients per month. The observed rate of accrual over the first 10 months was more than 4 patients per month. Thus, we anticipate enrolling 105 patients to have 94 eligible patients randomized in Step 2, and still expect 26 months of accrual.

The prevalence of V600E mutant BRAF is 5-7% (or 9-13% of KRAS wild-type tumors, given the mutual exclusivity of KRAS and BRAF). Some screening will be performed by sites that include BRAF in their standard of care testing, and for those pre-screened patients only retrospective confirmatory testing will be performed. Prior to opening the protocol, we estimated the screening sample size based on the following assumptions: the KRAS mutation rate is 40% and the BRAF mutation rate is 5.9% in mCRC; 60% of enrolled patients will come from sites that perform BRAF testing as part of the current standard of care; 85% of sites that do not perform BRAF testing will have KRAS testing results prior to considering a patient for study screening; the BRAF mutation rate is 9.8% in KRAS wild type patients; and 10% of screened patients will drop out and not enroll in the study. Based on these criteria, we estimated a need to perform primary central BRAF testing on approximately 440 patients. Forty-five of the first 70 screened patients were randomized. Of these 70 patients screened in 10 months of accrual, 43 had already been tested for the $BRAF^{V600E}$ mutation and 27 needed central review. Based on these observed proportions, in total we will need to screen approximately 163 to randomize 105 patients, including about 63 patients needing central review.

11.2 Primary Analysis and Power Justification

The primary analysis of PFS among patients randomized to Arm 1 or Arm 2 will be conducted in all eligible patients according to the intent-to-treat principle, using the log rank test upon the observation of 88 PFS events. Patients will be stratified by prior treatment with irinotecan. There are no randomized second or third line studies that have reported outcomes with cetuximab and irinotecan specifically for the population of patients with BRAF mutations. However, a retrospective study of 75 patients with BRAF mutant tumors demonstrated progression-free survival of 2.4 and 2.3 months for second and third line regimens, respectively. *(in press, Clinical Colorectal Cancer)* Therefore, we estimate the median Progression-Free Survival (PFS) of patients treated with Cetuximab and Irinotecan to be 2.4 months (null hypothesis) in this study population. Assuming that the targeted agent offers an increase of 2.4 months in PFS for this population (HR 2.0), we will need 94 eligible patients, based on six months of follow-up, a two-sided type 1 error of 5% and 90% power.

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An interim analysis will be performed when one-half of the events (approximately 44 PFS failures) have been observed (anticipated to occur when approximately 60% of accrual is reached). Evidence suggesting early termination would consist of a PFS hazard ratio > 1.0 comparing the experimental arm to the control arm, as estimated by a Cox regression model. This rule yields a 50% likelihood of terminating the study under the null hypothesis. Unless there are toxicity concerns, the study will not close during this interim assessment.

11.3 Other Analyses

Secondary endpoints will include overall survival, response, and toxicity. Distributions of overall survival in Arms 1 and 2 will be estimated using the method of Kaplan-Meier. The overall response rate (confirmed and unconfirmed, complete and partial) in each treatment arm will be assessed in the subset of patients with measurable disease. Assuming 90% (n=42 per arm) of patients will present with measurable disease, response rate can be estimated to within 16% (95% confidence interval).

Patients receiving at least one dose of drug on any arm will be included in the assessment of adverse events. Adverse event monitoring is conducted by the study chairs, disease committee chair, Adverse Event Coordinator and study statistician on an ongoing basis, with notification to the DSMC and CTEP should any concerns arise. Any events reported through the CTEP-AERS system are reported immediately, and reports are sent to the above group for all other AEs on a monthly basis. This trial will employ especially careful adverse event monitoring for the first 14 patients randomized to vemurafenib (Arm 2). Rates of serious toxicities will be compared between Arms 1 and 2 after 3, 6, and 14 patients are assigned to Arm 2 and have completed the first cycle, to inform discussions of protocol modification or early closure if required. Forty-seven eligible patients in each arm are sufficient to estimate the probability of a particular toxicity to within 15% (95% confidence interval). Any toxicity occurring with at least an 8% probability is likely (98% chance) to be seen at least once.

Patients progressing on Arm 1 will be provided the opportunity to cross over to vemurafenib treatment on Arm 3. Overall survival, response and PFS among patients who register to Arm 3 after disease progression will be summarized using descriptive statistics as described above.

11.4 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

11.5 Translational Medicine

The associations between each potential predictive biomarker (Objectives 11.5a and 11.5b below) and PFS will be explored via Kaplan-Meier curves and Cox regression. For each arm, it is estimated that 42 (90% of) eligible patients will have usable samples submitted for these translational studies. Statistical power to assess treatment-biomarker interactions will be low; all such power calculations assume the baseline median PFS is 2.4 months, no treatment effect in the biomarker-negative subgroup, and a two-sided alpha of 0.05.

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Objectives

a. To evaluate low-frequency *KRAS* or *NRAS* mutations as detected by high-depth sequencing as a predictive biomarker of efficacy.

   1. Preliminary data is pending for *BRAF* mutant patients, but approximately 20% of *KRAS* wild type patients by standard of care testing will have detectable *KRAS* or *NRAS* on high-depth sequencing.

   2. Assuming that detectable KRAS or NRAS is present in 20% of patients, 84 patients would provide 74% power to detect an interaction hazard ratio of 5.0 between treatment and biomarker status (corresponding to a median PFS of 12.0 months in the vemurafenib arm for the biomarker positive subgroup).

b. To evaluate PI3K pathway activation as a predictive biomarker of efficacy (PFS)

   1. Preliminary data in archival material from *BRAF* mutant, metastatic colorectal cancer tumors suggests that 60% of patients will have activation of the PI3K pathway, as defined by complete PTEN loss by IHC or PIK3CA mutation in the kinase or helical domains.

   2. Assuming that PI3K pathway activation is present in 60% of patients, 84 patients would provide 80% power to detect an interaction hazard ratio of 4.0 between treatment and biomarker status (corresponding to a median PFS of 9.6 months in the vemurafenib arm for the biomarker positive subgroup).

c. To evaluate gene expression signatures from screened patients with $BRAF^{WT}$ and $BRAF^{V600E}$ tumors.

   1. This analysis will be very exploratory in nature. Analyzed gene signatures from tumor tissue will be described separately in patients with $BRAF^{WT}$ (up to n=52, 90% of screen-negative patients) and $BRAF^{V600E}$ (n=84, 90% of eligible patients). We will explore, but not limited to, associations between gene signatures and colorectal cancer oncogenesis, angiogenesis, immune pathways, PI3K, WNT, EGF, and MEK pathway signatures, epigenetic regulators, p53, NOTCH and TGF-beta signaling. The definitive list of genes and technologies might only be finalized after complete enrollment and will be based on scientific knowledge at that time.

d. To provide validation of BRAF IHC using complementary sequencing methodology.

   1. Both BRAF and Cobas version 2.0 testing will be performed on screened patients (n=163). We will evaluate the sensitivity and specificity of BRAF IHC compared to the Cobas version 2.0 testing.

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e. To confirm the estimated sensitivity of detectable BRAF V600E circulating cell-free DNA as a non-invasive biomarker for BRAF V600E mutation as detected by IHC and Cobas in the primary tumor.

1. Unpublished results in 37 patients demonstrated 100% specificity and 78% sensitivity for the circulating cell-free DNA compared to the mutation assay on the primary tumor.

f. To correlate radiographic tumor response with the change in quantification of BRAF V600E alleles in circulating cell-free DNA.

1. Analysis of plasma samples at baseline, during therapy, and at the time of progression across all arms (including Arm 3).

2. No preliminary data are available for this aim.

3. We will assess the relationship between RECIST radiographic assessment and change in BRAF V600E allele burden in the cfDNA via logistic regression.

g. To monitor for known mechanism of acquired resistance to EGFR inhibition in circulating cell-free DNA (KRAS, NRAS mutations).

1. Analysis of plasma samples at baseline and at the time of progression on all arms (including progression on Arm 3).

2. Preliminary data are not available for the BRAF population, but in a KRAS wild-type population, our preliminary data suggest that approximately 40% of patients develop new detectable mutations in KRAS, NRAS, or EGFR after treatment with cetuximab.

3. Simple proportions with estimated 95% confidence intervals will be used to describe the observed incidence of new detectable mutations.

h. To assess the correlation of treatment efficacy between patients and matched patient-derived xenograft (PDX) models.

The correlation between radiographic response in patients and reduction in tumor size in the corresponding PDX models receiving matched treatment will be assessed. Given a 67% success rate at MD Anderson in establishing PDXs using *BRAF*-mutated tumors, it is estimated that 12 PDXs will be established from the 18 tumor biopsies collected from either arm of **S1406**. For each PDX, 24 mice will be equally randomized into one of three arms: a control arm receiving placebo (C) or one of two treatment arms, irinotecan + cetuximab or irinotecan + vemurafenib + cetuximab. For each PDX, the mice will be assessed at Day 21. The average % reduction in tumor size will be compared between the mice receiving the treatment to which the corresponding patient had been randomized and the mice in the control arm receiving placebo. The treatment/ control ratio (%T/%C) will be calculated. To evaluate the association between the patient and corresponding xenograft model results, a Pearson correlation coefficient will then be estimated between %T/%C and the RECIST response of matched patients. 12 PDXs will have 80% power to detect a correlation coefficient of 0.712 at a two-sided 0.05 significance level.

In order to investigate further the correlation in raw tumor responses between the clinical and animal studies, a secondary analysis will model $\%T_{end}/T_{start}$ in the xenograft animals as a function of radiographic response according to RECIST criteria in matched patients via a linear mixed model.

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i. To assess the correlation between PDX mechanisms for resistance and circulating free DNA (cfDNA) in plasma samples of matched patients following progression of disease.

cfDNA will be extracted from plasma taken from pre-treatment and post-progression samples of patients whose tumors were used to establish PDX models. These samples will then be analyzed by ultra-deep next-generation sequencing for the full exons of 15 genes (including KRAS, NRAS, EGFR, and MEK) and hotspot coverage for an additional 36 genes of interest. McNemar's test will be used to compare the mutation status of cfDNA before treatment and after progression for each gene of interest. We will adjust for multiple comparisons using methods described by Benjamin-Hochberg. *(49)* The concordance (i.e. proportion of the status unchanged, with 95% CI) of acquired mutation status between patient plasma samples and corresponding PDX models for each gene will be estimated. If concordance of PDX with matched patient in 6 of 12 pairs is observed, then the estimated half length of the 95% CI will be 0.25.

12.0 DISCIPLINE REVIEW

Discipline review is not applicable to this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

a. If patient has already had $BRAF^{V600}$ testing completed in a CLIA-certified laboratory and is eligible based on Section 5.1, the patient must be registered to Step 2 on the same day as Step 1. Patients must be registered for Step 2 prior to initiation of treatment (no more than five working days prior to planned start of treatment).

b. If patient has not had $BRAF^{V600}$ testing, specimens must be submitted as described in Section 15.1 on the day of Step 1 registration. If tumor is $BRAF^{V600}$ mutant, patient must be registered to Step 2 prior to initiation of treatment (no more than five working days prior to planned start of treatment and within 60 days of Step 1 registration).

c. Patients must be registered to Step 3 prior to initiation of treatment (no more than five working days prior to planned start of treatment and within 28 days of discontinuation of Arm 1 protocol treatment).

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13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (http://ctep.cancer.gov/investigatorResources/investigator_registration.htm). Questions should be directed to the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Oncology Patient Enrollment Network (OPEN) will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Cooperative Group Credit

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f. Credit Investigator

g. Patient Initials

h. Patient's Date of Birth

i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

j. Country of Residence

k. ZIP Code

l. Gender (select one):
- Female Gender
- Male Gender

m. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

n. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

o. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is a web-based application that is integrated with the CTSU Enterprise System for regulatory and roster data and, at the time of patient registration, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

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b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

- The study site is listed as “approved” in the CTSU RSS.

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site. Additional information about obtaining a CTEP-IAM account can be found at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. Questions should be directed to the CTEP Associate Registration Help Desk by e-mail at ctepreghelp@ctep.nci.nih.gov.

- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

  1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

  2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab of the CTSU members’ side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

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14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url:

https://login.imedidata.com/selectlogin

1. If prompted, select the 'CTEP-IAM IdP' link.

2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

b. Rave® may also be accessed via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using the SWOG Roster ID Number and password. After logging on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. Registering individual is entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. Registering individual is associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,

3. Sites local Web User Administrator has added registering individual as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please e-mail technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table on Page 5.

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14.4 Data Submission Overview and Timepoints

a. ON THE SAME DAY AS STEP 1 INITIAL REGISTRATION:

For patients who have not yet undergone BRAF V600 testing, submit the following:

Tissue specimens for V600 BRAF testing directly to Moffitt Cancer Center as outlined in Section 15.1.

Pathology report with specimens to Moffitt Cancer Center (see Section 15.1)

b. WITHIN 7 DAYS AFTER STEP 1 INITIAL REGISTRATION:

Submit the **S1406** Onstudy Form

c. For patients who will not be randomized to a treatment arm, WITHIN 60 DAYS OF STEP 1 REGISTRATION:

Submit the pre-study plasma specimens (including pathology report) for Translational Medicine as described in Section 15.3.

d. WITHIN 7 DAYS AFTER STEP 2 RANDOMIZATION:

Submit the following:

S1406 Randomization Eligibility Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation: Baseline form found in the Randomization Disease Assessment Folder in Rave®.)

Pathology report (NOTE: Upload reports via the Source Documentation: Baseline form found in the Randomization Eligibility Folder in Rave®. This submission is in addition to the pathology report submission to Moffitt Cancer Center that is required by Section 15.1)

Molecular testing report (NOTE: Upload reports via the Source Documentation: Baseline form found in the Randomization Eligibility Folder in Rave®.)

Fresh tissue for PDX (optional for patients at select institutions, see Section 15.4).

e. WITHIN 28 DAYS AFTER STEP 2 REGISTRATION (RANDOMIZATION):

Submit the tissue and plasma specimens (including pathology report) as described in Section 15.0 (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp).

f. WITHIN 14 DAYS AFTER EVERY CYCLE OF TREATMENT (INCLUDING BOTH ON INITIAL TREATMENT ARM AND CROSSOVER TREATMENT ARM):

Submit the following:

S1406 Treatment Form

S1406 Adverse Event Form

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g. For the first 14 patients (approximately) randomized to Arm 2, EVERY 14 DAYS WHILE ON TREATMENT:

Submit the **S1406** Adverse Event Form: In Rave, update the **date of most recent adverse event assessment** on the ***Adverse Events: Assessment Form*** at each assessment and then complete the ***Adverse Events: Report Week 3-4***, accordingly, for each cycle of treatment.

h. WITHIN 14 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION)*:

Submit the following:

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans used to assess disease (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®.)

* For patients on the control arm (Arm 1) who continue to Crossover (Arm 3), submit disease assessments (in the Crossover Disease Assessment Folder) until second progression.

i. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the following:

Follow-Up Tumor Assessment Form (RECIST 1.1)

Off Treatment Notice – if patient is still on treatment

Final **S1406** Treatment Form – if patient is still on treatment

Follow Up Form documenting date, site and method for determining progression/relapse – if patient is already off treatment

Radiology Reports (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®.)

NOTE: For patients on the Control arm (Arm 1) who continue to Crossover (Arm 3), submit disease assessments until second progression.

j. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT (INCLUDING BOTH ON INITIAL TREATMENT ARM AND CROSSOVER TREATMENT):

Submit the following:

Off Treatment Notice

S1406 Treatment Form

S1406 Adverse Event Form

Batch shipment of frozen plasma specimens (including pathology reports) for Translational Medicine as described in Section 15.2.

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k. WITHIN 7 DAYS AFTER STEP 3 CROSSOVER REGISTRATION:

Submit the following:

S1406 Crossover Eligibility Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports (NOTE: Upload reports via the Source Documentation: Baseline form found in the Crossover Disease Assessment Folder in Rave®.)

l. AFTER OFF ALL PROTOCOL TREATMENT, EVERY 6 MONTHS FOR THREE YEARS:

Submit the Follow-Up Form

NOTE: If the patient experiences any severe (Grade ≥ 3) long term toxicity that has not been previously reported, complete and submit the Late Effects Form.

m. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the following:

Notice of Death

Final **S1406** Treatment Form - if the patient was still on protocol treatment

Final **S1406** Adverse Event Form

Follow-Up Form (if the patient was off protocol treatment) documenting death information.

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15.0 SPECIAL INSTRUCTIONS

Purpose	Specimens	Timepoint	Patients	Shipping
BRAF V600 testing (see Section 15.2)	(1) 1 H&E tumor tissue slide (2) 3 unstained paraffin-embedded tissue slides -or- 1 paraffin-embedded tissue block	Day of Step 1 Initial Registration	Patients who have not yet undergone BRAF V600 testing	Lab #213: Moffitt Cancer Center
BRAF V600 testing (see Section 15.2)	(1) 1 H&E tumor tissue slide (2) 3 unstained paraffin-embedded tissue slides -or- 1 paraffin-embedded tissue block	Within 28 days of Step 2 Registration	Patients who have undergone BRAF V600 testing locally	Lab #201: SWOG Specimen Repository
Correlative Studies and Banking (see Section 15.3)	12 unstained paraffin-embedded tissue slides or block from baseline	Within 28 days of Step 2 Randomization	Required for all unless a block was submitted for BRAF testing	Lab #201: SWOG Specimen Repository
Correlative Studies and Banking (see Section 15.3)	Plasma	(1) Day of Step 1 registration (2) Each restaging (3) Off treatment	Required for all	Lab #201: SWOG Specimen Repository
Correlative Studies and Banking (see Section 15.3)	Plasma	(1) Day of Step 3 registration (2) Each restaging (3) Off treatment	Required for patients crossing over to Step 3 following progression on Arm 1	Lab #201: SWOG Specimen Repository
PDX Model (see Section 15.4)	Tumor Biopsy	Pre-treatment - within 7 days of Step 2 Randomization	Optional for patients. See Section 15.4 for a list of participating institutions.	Lab #216: The Jackson Laboratory

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15.1 SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking System (STS). SWOG members may log on to the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. First time non-SWOG users must refer to start-up instructions located at https://gill:crab.org/SpecTrack/.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

STS laboratory IDs are used to identify the laboratories to which specimens are shipped.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/667-2267 to be routed to the Data Coordinator for further assistance.

15.2 Specimens for BRAF V600 testing (required for patients)

All patients must submit specimens for central BRAF V600 testing.

a. Collection instructions are outlined in Section 15.2e and submission instructions are outlined in Section 15.2g.

b. Specimens to be submitted (see Sections 9.1 and 9.2):

1. 1 H&E tumor tissue slide

2. 3 unstained paraffin-embedded tissue slides
-or-
1 paraffin-embedded tissue block

c. For those who have not yet undergone BRAF V600 testing, specimens must be submitted to Moffitt Cancer Center, the central lab, on the day of Step 1 Initial Registration. If patient is registered on a Friday, sites should hold tissue shipment until Monday. With additional patient consent, any material remaining after BRAF testing will be forwarded to the SWOG Solid Tumor Repository for banking.

d. For those who have undergone BRAF V600 testing locally, specimens must be submitted to the bank within 28 days of Step 2 registration for future BRAF V600 mutation confirmation.

e. Paraffin-embedded tissue must be fixed per the instructions on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp) and submitted to the lab in Section 15.2g.

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f. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

g. Shipping Samples

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue for BRAF V600 testing and SWOG Repository Submission is identified as follows:

1. For those who have not yet undergone BRAF V600 testing, submit tissue Monday - Thursday to:

Lab #213: Moffitt Cancer Center, Department of Pathology
Phone: 813/745-3980
E-mail: anthony.magliocco@moffitt.org
Contact: Anthony Magliocco

2. For those who have undergone BRAF V600 testing locally:

Lab #201: SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division

h. For those who have not yet undergone BRAF V600 testing, institutions will be notified by e-mail with the patient's BRAF V600 testing results within approximately 10 calendar days after specimen submission. A formal lab report will be FAXed to the number provided in the specimen tracking system. If the patient's BRAF V600 results are NOT received by e-mail within 10 calendar days of submitting the specimen, please contact the SWOG Data Operations Center at 206/652-2267.

15.3 Specimens for translational medicine and correlative studies (required for patients)

a. Specimens must be submitted at the following times (see Sections 9.1 and 9.2):

1. 12 unstained paraffin-embedded tissue slides or block from baseline within 28 days of Step 2 registration. If tissue block is submitted for Section 15.2, these additional slides are not required.

2. 2 tubes (lavender top EDTA tube) each of 10 mL blood on the day of Step 1 registration, each restaging, and off treatment. Patients crossing over to Step 3 registration following disease progression on Arm 1 must also submit blood on day of Step 3 registration, each restaging, and off treatment. Collect plasma from samples per the link in Section 15.3b. Plasma may be frozen and batch shipped.

NOTE: With additional patient consent, any remaining material after initial testing will be forwarded to the SWOG Solid Tumor Repository for banking.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp).

1. Federal guidelines for the shipment of blood products:

a. The tube must be wrapped in an absorbent material.

b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

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c. Pack the resealable bag and tube in a Styrofoam shipping container.

d. Pack the Styrofoam shipping container in a cardboard box.

e. Mark the box "Biohazard".

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

d. Shipping Samples

In the online specimen tracking system (STS), specimens for correlative studies and banking can be submitted to:

Lab #201: SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division

15.4 Specimens for Translational Medicine: Co-Clinical PDX Model Trial (optional for patients)

Patients enrolled on study at the following institutions only may participate in this portion of the protocol:

- MD Anderson Cancer Center
- University of California, Davis
- University of California, San Francisco
- University of Colorado
- University of Southern California
- Yale University

a. With patient's consent, specimens must be submitted at the timepoints listed below. Collection instructions are outlined in Section 15.4c and submission instructions are outlined in Section 15.4f.

b. With patient's consent, the following specimen and documents must be submitted within 7 days of Step 2 Randomization (see Sections 9.1 and 9.2):

1. Tumor Biopsy: Pre-treatment
2. Requisition Form (located on the **S1406** abstract page on the SWOG website [www.swog.org])
3. History and Baseline Information Form (located on the **S1406** abstract page on the SWOG website [www.swog.org])
4. STS packing slip (see Section 15.1)

c. Fresh tumor samples should be placed in a 50 mL screw cap conical tube containing 40 mL RPMI buffer media (without fetal bovine serum) within 30 minutes of tumor removal. The cap of the tube should be sealed tightly and covered with Parafilm. Samples should be refrigerated at 4°C until packed for shipping. The sealed conical tube containing RPMI and the tumor specimen must be wrapped in absorbent material (e.g., paper towels) and placed in an airtight bag (e.g., resealable bag). The specimen should be packed into an insulated styrofoam shipper with a refrigerated (4°C) cool pack (not frozen) to protect the specimen from temperature fluctuations. All paperwork pertaining to the patient should be placed in a plastic bag, sealed tightly, and packed with the tissue shipment. Samples must be received at the Jackson Laboratory (JAX) within 24 hours of collection.

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d. The specimen should be collected following Institutional Universal Precaution SOPs for maintaining tissue integrity. Please remind all personnel that are involved in processing the sample that it will be implanted into profoundly immune deficient mice. This is the reason that it is imperative that extra care be taken in sample collection in order to minimize the risk of transferring human bacteria to mice.

e. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

f. Samples

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tumor biopsy samples for PDX models is identified as follows:

Lab #216: The Jackson Laboratory – In Vivo Services
Phone: 916/469-2609
Contact: Margaret Bundy
E-mail: margaret.bundy@jax.org

1. Federal guidelines for the shipment of blood products:

   a. The tube must be wrapped in an absorbent material.

   b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

   c. Pack the resealable bag and tube in a Styrofoam shipping container.

   d. Pack the Styrofoam shipping container in a cardboard box.

   e. Mark the box "Biohazard".

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16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. Also see Appendix 18.1 for general and background information about expedited reporting.

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b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1 or 16.2, as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in Arm 2 of this study is vemurafenib. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

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Table 16.1: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Vemurafenib (Arm 2 and Arm 3)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2) The adverse events listed below also require expedited monitoring for patients assigned to Arm 2 or Arm 3 of this trial that includes the administration of vemurafenib:

- **Cutaneous squamous cell carcinoma (cuSCC)**
- **Non-cutaneous squamous cell carcinoma (non-cuSCC)**
- **New second primary malignancy**
- **Grade ≥ 3 elevations in AST, ALT or serum bilirubin, OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice.**

g. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.2. The commercial agents used in both arms of this study are cetuximab and irinotecan. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

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Table 16.2. Expedited reporting requirements for adverse events experienced by patients on study Arm 1 who have received the commercial drug(s) listed in Section 16.1g above within 30 days of the last administration of the commercial agent(s).

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require routine reporting via CDUS and SAE reporting per Section 16.1f.2.

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For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to the SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:
   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

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*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 Translational Medicine

18.3 Inhibitors/Inducers of CYP3A4 & CYP1A2 and QTc Prolonging Medications

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18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner (*This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- ***Concurrent administration*:** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- ***Sequential administration*:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

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Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1f of the protocol.

An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

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18.2 Translational Medicine

a. Background

Loss of PTEN and activating mutations in the *PIK3CA* oncogene result in activation of PI3K/Akt signaling, a pathway implicated in anti-apoptotic activity. When compared to melanoma, *BRAF* mutant CRCs have higher PI3K pathway activity due to both genetic (PTEN, *PIK3CA, PIK3R1*) and epigenetic (hypermethylation) mechanisms. *(28)* Comparative studies between BRAF-mutated melanoma and colorectal cell lines by reverse phase protein arrays suggest that the colon cell lines have much higher rates of PI3K pathway activation, as reflected by significant differences in pAkt, pMTOR, pFoxo3A, pGSK3b, pS6, and p4EBP expression. Those lines harboring *PIK3CA* gene mutations or loss of PTEN are less sensitive to BRAF inhibition than cell lines expressing PTEN and lacking mutations in *PIK3CA.* Additionally, when cell lines with intact PTEN were introduced with siRNA against PTEN, cytotoxic activity of vemurafenib was lost. These results imply that, in the presence of BRAF inhibition, molecular aberrations like PTEN loss or activating *PI3KCA* mutations, which increase signaling of the PI3K/Akt pathway, decrease sensitivity to BRAF inhibition. Therefore, we hypothesize that patients whose tumors contain activating *PIK3CA* mutations or show loss of PTEN immunohistochemically will demonstrate no benefit in progression-free survival with the addition of vemurafenib, relative to patients whose tumors do not harbor such alterations.

NRAS mutations and *KRAS* mutations outside of codons 12 and 13 have been identified as a potential predictive biomarker of resistance to cetuximab, and we propose to include this in the testing, recognizing a potential shift in clinical practice during the course of the study.

Data on the utility of circulating DNA for monitoring treatment response and development of resistance have previously been reported. *(30-32)* Unpublished results using mice implanted with patient-derived *BRAF*-mutated colorectal tumors and treated with a BRAF inhibitor have shown that *NRAS* and *KRAS* mutations may develop as a mechanism of resistance to BRAF inhibition in *BRAF*-mutated CRC and the concurrent use of EGFR inhibitors suggests that *KRAS* mutations may likewise occur. *(33)*

b. Experimental Approach, validated assays employed and expertise of PI:

In the setting where no prior BRAF test has been conducted, a validated monoclonal antibody from Roche Ventana will be used that has been developed against the V600E *BRAF* mutation. In the event of technical failure of the immunohistochemistry staining, then DNA pyrosequencing will be performed at Moffitt Cancer Institute using DNA extracted from available tumor specimen to assess for the presence of a *BRAF* V600E mutation. If pyrosequencing reveals a *BRAF* V600E mutation, then the patient will remain eligible for participation onto the study. However, if no mutation can be detected by DNA sequencing, then the patient will become ineligible for study enrollment/participation. The $BRAF^{V600E}$ antibody product being used is a Class I IVD. Scoring will be interpreted per the package insert: Positive for $BRAF^{V600E}$ – Unequivocal cytoplasmic staining of any intensity in viable tumor cells; Negative for $BRAF^{V600E}$ – Absence of unequivocal cytoplasmic staining in viable tumor cells (nuclear staining, weak to moderate staining of isolated tumor cells/focal confluent staining of viable tumor cells should be considered negative.). All testing will be done in a CLIA-compliant facility.

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Several studies have reported on the high sensitivity and specificity of using an immunohistochemical assay to detect a *BRAF*-mutated tumor:

(1) Sinicrope and colleagues looked at 75 surgically resected, stage III primary colorectal tumors – in 50 of these tumors, a *BRAF* V600E mutation was detected using a PCR based assay from FFPE specimens in a CLIA-compliant laboratory at Mayo, whereas wild-type *BRAF* was observed in the remaining 25 tumors. *(34)*. Immnunohistochemical analyses of these tumors was performed using two different monoclonal antibodies – a pan-BRAF antibody (pBR1; Spring Biosciences, Pleasanton, CA) for total BRAF protein and a mutant *BRAF* V600E-specific antibody (VE1; Spring Biosciences, Pleasanton, California) in all tumor specimens. BRAF protein expression was measured using a DAB Detection kit (Ventana Medical Systems, Inc; Tuscon, AZ). Protein expression from the ICH results was measured by two different pathologists who were blinded to the clinical outcomes and mutation results of all patients' tumors in this study. Expression was graded as 0 (no staining), 1 (weak staining), 2 (medium staining), or 3 (strong staining). Pan-BRAF expression (pBR1) was detected in 74 of 75 tumors, with 49 of the 74 patient's tumors staining positive for the *BRAF* V600E-mutated specific VE1 antibody; this staining was not observed in all 25 of the patients in whom wild-type *BRAF* had been sequenced from their primary tumors. This represented a sensitivity of 100% (95% confidence interval [CI] of 93% to 100%), and specificity of 100% (95% CI of 86% to 100%). In all cases of mutated *BRAF* colorectal tumors, at least 70% of all tumor cells demonstrated grade 2 or 3 levels of staining; in 75% of these same cases, 100% of tumor cells had were IHC-positive at a level of 2 or 3.

(2) Another study examined the sensitivity and specificity of the VE1 antibody in 91 MSI-high colorectal tumor specimens that were tested for HNPCC [35]. Immunohistochemical results were compared with Sanger sequencing techniques. IHC results for the mutated BRAF protein were deemed "positive" when 80% or greater of all tumor cells stained for the VE1 antibody at a level higher than background. Results were scored by three separate pathologists, with 100% concordance between all pathologists on all specimens analyzed (kappa =1). Among the 11 tumors with *BRAF* V600E mutations by DNA sequencing, all 11 were positive by IHC (sensitivity 100%, 95% CI of 75% to 100%); for the 80 samples that were negative for a *BRAF* mutation by Sanger sequencing, IHC results were negative in 79 (specificity of 98.8%, with 95% CI of 93% to 100%).

(3) Long et al. tested this same VE1 antibody in 100 patients with stage IIIc unresectable or stage IV melanoma who had undergone *BRAF* mutation testing from DNA extracted from FFPE tumor specimens. *(36)* Sensitivity of this antibody in the melanoma specimens was 97.4%, and specificity was 98.3%.

(4) 505 tissue microarrays from tumors of patients with stages I-IV colorectal cancer were analyzed for *BRAF* V600E mutations and mutated proteins in a study performed by Desai and colleagues. *(37)* 476 of these tumors had tissue available sufficient to perform both Sanger sequencing and ICH using the aforementioned VE1 antibody. DNA sequencing detected a BRAF V600E mutation in 56 of 476 specimens, whereas the immunohistochemical approach stained positive for V600E BRAF in 65 of 476 tumors. Repeat evaluation of the discordant cases with alternate

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sequencing methodology confirmed the presence of the mutation in the majority of the cases.

KRAS, NRAS, and *PIK3CA* mutation by sequencing methodology will be performed by Foundation Medicine (next-generation sequencing here will include 400+ genes of interest in colorectal cancer).

DNA will be prepared from 6 FFPE slides per patient (approx. 600 ng DNA, TBC) to systematically explore genetic alterations which might be associated with response or resistance to combined therapeutic approaches. A defined set of genes potentially associated to or significantly mutated in mCRC (e.g. but not limited to *KRAS, NRAS, PIK3CA, BRAF, EGFR, AKT, FLT3, KIT, MET, ERBB2, JAK2* etc.) MSI status and mutation load will be examined on the FoundationOne® Next Generation Sequencing (NGS) panel.

RNA will be prepared from 3 FFPE slides per patients (approx 300ng RNA, TBC) to detect differential expression by methods like Nanostring or others. Analyzed genes might comprise e.g. but not limited to gene signatures related to CRC and gastric cancer oncogeneis, angiogenesis, immune pathways, PI3K, WNT, EGF and MEK pathway signatures, epigenetic regulators, p53, NOTCH and TGF-beta signaling. The definitive list of genes and technologies might only be finalized after complete enrolment and will be based on scientific knowledge at that time.

Plasma analysis of *BRAF, KRAS,* and *NRAS* will be performed using NGS assay (performed at MD Anderson or Guardant Health, Redwood City, CA) and digital droplet PCR.

Data analysis will be performed at the SWOG Statistical Center, to allow exploration of the associations of each potential predictive biomarker with patient outcomes including progression-free and overall survival.

c. Testing will be performed at the following sites:

- BRAF V600E IHC: Dr. Anthony Magliocco, Director of Pathology, Moffitt Cancer Center, Anthony.Magliocco@moffitt.org
- PTEN, hMLH1 IHC (Dako/Agilent, Carpinteria, CA): Drs. Dipen Maru, Scott Kopetz, MD Anderson Cancer Center
- Circulating cell-free DNA: Drs. Scott Kopetz , M.D. Anderson Cancer Center or Guardant Health, Redwood City, CA
- FoundationOne® NGS multigene panel, RNA expression analysis/NanoString, Foundation Medicine, Yibing Yan yan.yibing@gene.com

15 slides from FFPE tissue will be collected as follows: 1 slide for H&E, 2 slides for BRAF IHC testing, 2 slides for PTEN, hMLH1 IHC, 6 slides (or 600 ng of DNA) for FoundationOne® NGS DNA sequencing, 3 slides (or 300 ng RNA) for RNA expression/NanoString.

The priority list for these specimens will be (1) H&E, BRAF IHC (2) DNA NGS (3) PTEN IHC (4) RNA expression/NanoString (5) Banking/future studies. In addition, for plasma analysis, 20 mL blood (2x10mL) at each time point will also be collected.

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18.3 Inhibitors/Inducers of CYP3A4 & CYP1A2 and QTc Prolonging Medications

Patients on study should avoid concomitant use of vemurafenib with CYP1A2 substrates, CYP3A4 substrates and QTc prolonging medications with a narrow therapeutic window. If co-administration cannot be avoided, monitor closely for toxicities and consider a dose reduction of these subtrates and medications.

a. Inhibitors of CYP3A4:
- clarithromycin
- erythromycin
- troleandomycin
- chloramphenicol
- anti-retrovirals (delaviridine)
- protease inhibitors (ritonavir, indinavir,saquinavir, nelfinavir, amprenavir, lopinavir)
- itraconzaole
- ketoconazole
- voriconazole
- fluconazole (>150 mg daily)
- nefazodone
- fluvoxamine
- Grapefruit or its juice

b. Inducers of CYP3A4:
- efavirenz
- nevirapine
- carbamazepine
- phenytoin
- oxcarbamazepine
- rifampin (rifampicin)
- rifabutin
- rifapentene
- efavirenz
- nevirapine
- St. John's Wort
- modafinil

c. Substrates of CYP1A2:
- Amitriptyline
- Caffeine
- Clozapine
- Flutamide
- Imipramine
- Melatonin
- Mexiletine
- Mirtazapine
- Olanzapine
- Ramelteon
- Rasagiline
- Ropinirole
- Tacrine
- Theophylline
- Tizaidine
- Triamterene
- Zolmitriptan

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d. Inhibitors of CYP1A2:
- Artemisinin
- Atazanavir
- Cimetidine
- Ciprofloxacin
- Enoxacin
- Ethinyl estradiol
- Fluvoxamine
- Grapefruit juice
- Mexiletine
- Tacrine
- Thiabendazole
- Zileuton

e. Inducers of CYP1A2:
- Barbiturates
- Cruciferous vegetables
- Grilled meat
- Carbamazepine
- phenytoin
- Primidone
- Rifampin
- Smoking

f. QTc Prolonging Medications:
- amiodarone
- dofetilide
- sotalol
- procainamide
- quinidine
- disopyramide
- haloperidol
- chlorpromazine
- clarithromycin
- erythromycin
- methadone

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Informed Consent Model for S1406

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	63.9 (targeted above 55)
Flesch-Kincaid Grade Level	8.1 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

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- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

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Step 1 Consent Form

Study Title for Study Participants: Testing the addition of vemurafenib to usual chemotherapy in metastatic colorectal cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: S1406, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer"

What is the usual approach to my metastatic colorectal cancer?

You are being asked to take part in this study because you have colorectal cancer which has grown or has recurred. People who are not in a study are usually treated with drugs approved by the FDA. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have your cancer tissue tested locally
- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

The purpose of this screening step is to perform a genetic test on your colorectal cancer tumor sample to see if it has a specific genetic mutation called BRAF. BRAF is a human gene that makes a protein called B-raf. This protein is involved in sending signals to the cells which direct cell growth. BRAF tumor testing is common for this type of cancer. The performance of the test is not part of the research question in this study. If your tissue has a BRAF mutation, you will be eligible to participate in the next part of the study.

We expect that about 163 patients will get this screening for this study and expect that about 105 patients will go on to the treatment part of the study.

The purpose of the treatment part of the study is to compare any good and bad effects of using vemurafenib along with the usual chemotherapy approach alone. The addition of vemurafenib to the usual chemotherapy could shrink your cancer, but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach.

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How long will I be in this study?

This part of the study is just about the BRAF testing and submission of tissue and blood for biobanking. You will be finished with this part of the study when your specimens are submitted for testing and the result is received. Then, if you are eligible to continue on the study, you will be asked to sign another consent form for the study treatment.

What extra tests and procedures will I have if I take part in this study?

You will not have any extra tests or procedures for this part of the study. You have already had surgery or a biopsy to remove some of your cancer tissue. This tissue will be collected and sent for BRAF testing. You and your study doctor will receive the results from the test before you decide whether to join the treatment part of the study. The result of the test will be included in your health record.

You will also have 2 tubes of blood drawn (about 4 teaspoons). The samples will be tested to see if markers for the cancer returning can be detected in the blood. These results which are experimental in nature and not part of normal clinical decision making, will not be made available to you or your study doctor.

Your tissue samples will be sent to a laboratory at Moffitt Cancer Center for BRAF testing. Your blood samples will be sent to the SWOG Biobank until testing is performed.

Why is this test being done?

We are using the BRAF test to determine whether patients are eligible to continue to the treatment part of this clinical trial. We are asking that you give permission for your colorectal cancer tissue to be tested.

If your BRAF test is wild-type, then you will not be eligible to participate in the treatment part of the study. In this case, we ask that you discuss other treatment options with your study doctor.

If your BRAF test is mutant, then you will be eligible to participate in the treatment part of this study. We ask that you discuss participation in this study with your study doctor and consider joining the treatment part of the study.

What possible risks can I expect from taking part in this study?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research

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may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members. Check with your study doctor to find out what kinds of privacy protections are available to you.

What possible benefits can I expect from taking part in this study?

Taking part in this part of the study will not have any impact on your health because no treatment is given. We do know that the information from this part of the study will help doctors learn more about the use of BRAF testing. This information could help future cancer patients.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The study will pay for the cost of the BRAF testing which will be completed at a central laboratory using your tissue sample from a previous biopsy or surgery. *(added 1/30/15)*You and/or your health plan/insurance company will need to pay for all of the other costs of your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests

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are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and any drug company supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- Alliance *(added 1/30/15)*
- ECOG-ACRIN *(added 1/30/15)*
- NRG *(added 1/30/15)*

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:
This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

1. Optional Biobanking of Collected Samples for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, leftover tissue and blood that was collected for initial testing will be sent from the lab to the Biobank. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) A sample from the tissue and blood that was collected at the beginning of the study will be sent to the Biobank.

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a) Your samples and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.

2) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

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WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

Yes **No**

FUTURE CONTACT:

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

This is the end of the section about optional studies.

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My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____
(or legally authorized representative)

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

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Step 2 Consent Form

Study Title for Study Participants: Testing the addition of vemurafenib to usual chemotherapy in metastatic colorectal cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: S1406, "Randomized Phase II Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer"

What is the usual approach to my metastatic colorectal cancer?

You are being asked to take part in this study because you have colorectal cancer which has grown or has recurred. People who are not in a study are usually treated with drugs approved by the FDA. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- **you may choose to have the usual approach described above**
- **you may choose to take part in a different study, if one is available**
- **or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.**

Why is this study being done?

The purpose of this study is to compare any good and bad effects of using vemurafenib along with the usual chemotherapy, cetuximab and irinotecan, to using the usual chemotherapy approach alone. The addition of vemurafenib to the usual chemotherapy could shrink your cancer, but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. To be better, the study drug approach should extend the amount of time before your cancer gets worse by 1.6 months or more compared to the usual approach. Vemurafenib is currently FDA approved for treatment of late-stage or unresectable melanoma. There will be about 105 people taking part in this study.

Another purpose of this study is for researchers to learn if a biomarker test is helpful to decide who should be enrolled in this study. Tissue from your surgery or biopsy will be used for the BRAF biomarker test. BRAF is a human gene that makes a protein called B-raf. This protein is involved in sending signals to the cells which direct cell growth. The

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study drug, vemurafenib, blocks the activity of the B-raf protein only when a mutation is present. Therefore, in order to see how effective this drug is when given with other drugs already used in the treatment of this disease, only patients whose tumors have a BRAF mutation are eligible for this study. Researchers do not know if using the biomarker test is better, the same, or worse than if you were put in the study without using the biomarker test.

What are the study groups?

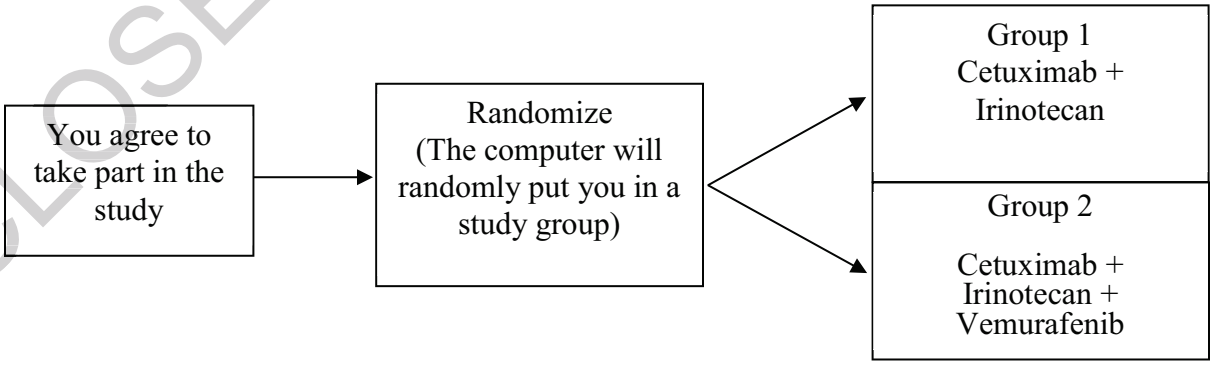
A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other.

This study has two study groups. Group 1 will receive the standard chemotherapy of cetuximab and irinotecan both given through a vein on Day 1 and 15 of every 28 day cycle. *(1/30/15)* Group 2 will receive the same chemotherapy with cetuximab and irinotecan, and will also receive the study drug vemurafenib which is taken by mouth. If your disease gets worse while in Group 1, you may have the opportunity to receive the Group 2 treatment.

If you are randomized to Group 2, you will take 4 vemurafenib tablets by mouth twice a day (a total of 8 tablets a day). Each dose can be taken with or without a meal with a whole glass of water. Do not chew or crush the tablets. If you miss a dose, it can be taken up to 4 hours prior to the next scheduled dose. Both doses should not be taken at the same time.

You will also receive an Intake Calendar when you start treatment to help you and your doctor keep track of the amount of dugs you are taking. It will be used to keep track of how much you take and to make sure you are not getting sick because of the drug. You will use the Intake Calendar until you have completed all study treatments. The Intake Calendar should be returned at each office visit *(NOTE: This section may be altered to fit the local procedure for assessing patient compliance.)*

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



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How long will I be in this study?

You will receive the study treatment until your disease gets worse or until the side effects become too serious to manage. After you finish study treatment, your doctor will continue to watch you for side effects and follow your condition for up to 3 years.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following extra test to find out if you can be in the study:

- Electrocardiogram (tracing of the heart beat)

Small pieces of cancer tissue removed by prior surgery or biopsies will be taken before you begin the study. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. The sample will be tested to see if your tumor has a specific mutation and to see if markers in your tumor tissue can indicate whether this treatment will be more effective than another treatment. Any tissue left over from the testing may, with your consent, be stored for biobanking. This will be discussed in the section on optional studies. *(6/9/15)*

Before, during, and when you go off the study:

Two tubes of blood (about 4 teaspoons total) will be taken before you begin the study, each time your disease is restaged, and when you go off study treatment. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. The samples will be tested to see if markers that may predict the cancer returning can be detected in the blood.

Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. The results of this test will not be made available to you and your study doctor.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra exams or tests. They are not part of the usual approach for your type of cancer.

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During the study:

- If in Group 2, your doctor will examine your head and neck at the start of the study, after 4 weeks, and every 2 months while on treatment through 6 months after ending treatment. *(updated 1/30/15) (updated 6/9/15)*

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- **You may lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **You may be asked sensitive or private questions which you normally do not discuss**
- **The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.**

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

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Possible side effects for all patients

Possible Side Effects of Cetuximab

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cetuximab, more than 20 and up to 100 may have:
• Change in nails • Swelling and redness of the area of where you previously had radiation • Rash, itching, dry skin, acne • Dehydration, weight loss, loss of appetite • Sores in mouth which may cause difficulty swallowing • Constipation, diarrhea, vomiting, nausea • Difficulty sleeping • Headache, tiredness • Pain • Fever • Infection, especially when white blood cell count is low • Cough, shortness of breath

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cetuximab, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Confusion, depression, worry • Fainting • Severe blood infection • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving Cetuximab, 3 or fewer may have:
• Scarring of the lungs • Kidney damage which may require dialysis • Heart stops beating

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Possible Side Effects of Irinotecan

COMMON, SOME MAY BE SERIOUS In 100 people receiving Irinotecan, more than 20 and up to 100 may have:
• Severe diarrhea • Constipation, nausea, vomiting • Weakness • Infection, especially when white blood cell count is low • Hair loss • Loss of appetite, weight loss • Anemia which may cause tiredness, or may require a blood transfusion • Fever, pain • Dizziness, tiredness • Cough, shortness of breath • Sores in mouth • Rash • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Irinotecan, from 4 to 20 may have:
• A tear or hole in internal organs that may require surgery • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to the heart • Blood clot which may cause swelling, pain, shortness of breath • Scarring of the lungs

RARE, AND SERIOUS In 100 people receiving Irinotecan, 3 or fewer may have:
• None

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In addition to the above listed side effects, patients in Group 2 may also have the following side effects.

Possible Side Effects of Vemurafenib

COMMON, SOME MAY BE SERIOUS In 100 people receiving Vemurafenib, more than 20 and up to 100 may have:
• Nausea, vomiting, diarrhea • Tiredness • Pain in joints • A new cancer resulting from treatment of earlier cancer • Hair loss, increased risk of sunburn, itching, rash • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Vemurafenib, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Change in the heart rhythm • Redness, pain or peeling of palms and soles • Severe skin rash with blisters and can involve inside of mouth and other parts of the body • Decreased appetite • Constipation

RARE, AND SERIOUS In 100 people receiving Vemurafenib, 3 or fewer may have:
• Blurred vision, increased sensitivity of your eyes to light

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

Cetuximab and vemurafenib cause sensitivity to sunlight, so while you are on this study you should avoid long periods in the sun. You should wear long sleeve shirts, pants, hat, and use sun block protection (SPF 30 or higher) when you are in the sun. Exposing your skin to sunlight while on study could cause severe damage to it.

While on the study use caution when using over the counter products, herbal medicines, or prescribed drugs. You should check with your study team before taking any of those drugs. St. John Wort and ketoconazole are not allowed during irinotecan treatment.

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Vemurafenib and irinotecan are associated with multiple drug interactions. Drug interactions may result in severe side effects. To reduce the chance of drug interactions, please tell your study doctor and his/her staff about any medications you are taking during the study. This includes prescription drugs, over-the-counter medicines, and vitamins.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the addition of the study drug is better than the usual approach so this study may or may not help you. This study will help researchers learn things that may help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The vemurafenib will be supplied at no charge while you take part in this study. It is possible that the vemurafenib may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

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You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

The initial electrocardiogram will be paid for by the study for all patients. *(1/30/15) (6/9/15)* Up to an additional 5 electrocardiograms will be paid for by the study for patients receiving vemurafenib. *(added 6/9/15)*

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and any drug company supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- Alliance
- ECOG-ACRIN
- NRG

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

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ADDITIONAL STUDIES SECTION:
This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

1. Optional Biobanking of Collected Samples for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, leftover tissue and blood that was collected for initial testing will be sent from the lab to the Biobank. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

(Section below added 6/9/15)

Information for Selected Sites Participating in Co-Clinical PDX Model Study *(If your site is not participating in this co-clinical study, this section may be removed from your consent form)*:

2. Optional Fresh Tissue Biopsy and Participation in Co-Clinical Study

If you agree to participate in this study, you will need to have a new tissue biopsy performed. The tissue collected during this procedure will be submitted to a special lab. Your tumor cells will be removed and sent to Jackson Labs where they will be used to create tumor models in animals for research. Jackson Labs is a non-profit company that does cancer research. They will also provide their tumor models for other researchers for a fee. Future research could include

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developing new treatment or drugs. You will not receive any financial benefit from the research or products, including drugs that might come from the use of your tissue. No information that could directly identify you will be available to the researchers.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the tissue sample that will be used for this study. You and your study doctor will not receive the results of any tests done on your sample.

I agree to participate in this co-clinical study and have an additional tissue biopsy performed.

Yes No

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) A sample from the tissue and blood that was collected at the beginning of the study will be sent to the Biobank. *If your site is participating in the co-clinical PDX study include*: A sample of tissue will be collected from the optional extra biopsy. *(sentenced added 6/9/15)*
   a) Your samples and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.

   If your site is participating in the co-clinical PDX study include: (section added 6/9/15) b) Your optional extra biopsy sample and some related health information will be sent to a researcher for use in the study described in "Optional Fresh Tissue Biopsy and Participation in Co-Clinical Study" above.
2) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

If your site is participating in the co-clinical PDX study include: (section updated 6/9/15)
1) The most common risks related to a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain

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medications, and bruising. You will sign a separate consent form before the biopsy is taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place.

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.

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4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

Yes **No**

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FUTURE CONTACT:

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____
(or legally authorized representative)

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

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Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

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How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

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