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**CHILDREN'S ONCOLOGY GROUP**

**ADV1522**

**A Phase 2 Study of IMG901 (Lorvotuzumab Mertansine; IND# 126953, NSC# 783609) in Children with Relapsed or Refractory Wilms Tumor, Rhabdomyosarcoma, Neuroblastoma, Pleuropulmonary Blastoma, Malignant Peripheral Nerve Sheath Tumor (MPNST) and Synovial Sarcoma**

**A Phase 2 Study**

NCI Supplied Agent: IMG901 (Lorvotuzumab Mertansine)  
IND sponsor for IMG901: Children's Oncology Group (COG)

**Open to COG Institutions within the United States**

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**STUDY COMMITTEE**

[REDACTED]

<b>AGENT</b>	<b>NSC#</b>	<b>IND#</b>
Dexamethasone	34521	
IMGN901	783609	126953
<a href="#">(IND Sponsor: COG)</a>		

[REDACTED]

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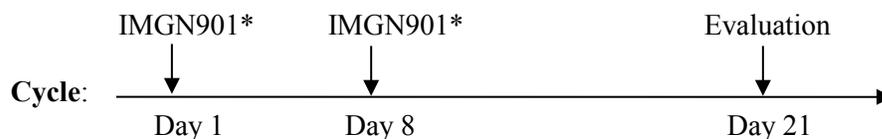
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## ABSTRACT

Novel therapeutic strategies are necessary to increase cure rates for children with relapsed or refractory Wilms tumor, rhabdomyosarcoma, neuroblastoma and other CD56-expressing tumors such as pleuropulmonary blastoma, malignant peripheral nerve sheath tumor (MPNST) and synovial sarcoma. Such cancers nearly uniformly express tumor cell surface CD56 or NCAM (neural cell adhesion molecule). Antibody drug conjugate therapies (ADCs) that target cytotoxic moieties, such as potent anti-microtubule poisons, directly to specific tumor cell receptors have been developed. IMGN901 (lorvotuzumab mertansine) is an ADC that links a potent anti-mitotic (DM1) via a disulfide linker to CD56 targeting antibodies. Pre-clinical data demonstrate potent *in vivo* effects of IMGN901 against Wilms tumor, rhabdomyosarcoma, and neuroblastoma. This trial will determine the clinical effects of IMGN901 administered on Days 1 and 8 of a 21-day cycle to pediatric and adolescent patients with Wilms tumor, rhabdomyosarcoma, neuroblastoma or other CD56-expressing tumors such as pleuropulmonary blastoma, malignant peripheral nerve sheath tumor (MPNST), and synovial sarcoma. Pharmacokinetic data, including an assessment of impact on peripheral blood CD56+ cell burden, will be obtained.

## EXPERIMENTAL DESIGN SCHEMA

### Treatment Schema:



\* IMGN901 is administered via intravenous infusion.

A cycle of therapy is 21 days. Therapy may consist of up to 17 cycles, for a total duration of therapy approximating 12 months, absent disease progression or unacceptable toxicity.

## 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

### 1.1 Primary Aims

- 1.1.1 To assess the efficacy of IMG901 in Wilms tumor, rhabdomyosarcoma, neuroblastoma and other CD56-expressing tumors such as pleuropulmonary blastoma, MPNST and synovial sarcoma.
- 1.1.2 To determine the tolerability of the adult recommended Phase 2 dose (RP2D) of IMG901 administered as an intravenous infusion, administered on Days 1 and 8 of a 21-day cycle, to children with refractory Wilms tumor, rhabdomyosarcoma, neuroblastoma, pleuropulmonary blastoma, malignant peripheral nerve sheath tumor (MPNST), or synovial sarcoma.
- 1.1.3 To define and describe the toxicities of IMG901 administered on this schedule.

### 1.2 Exploratory Aims

- 1.2.1 To correlate tumor response with tumor CD56+ expression.
- 1.2.2 To characterize the pharmacokinetics of IMG901 in children with refractory cancer, including an assessment of impact on circulating CD56+ peripheral blood cells.

## 2.0 BACKGROUND

### 2.1 Introduction/Rationale for Development

IMG901 (lorvotuzumab mertansine) is a humanized immunoglobulin (IgG1) kappa monoclonal antibody, conjugated through a disulfide linker, to the cytotoxic maytansinoid, DM1, with an average of 3.5 molecules DM1 per antibody. The monoclonal antibody is the humanized version of the murine N901 monoclonal antibody engineered to bind specifically with the CD56 antigen, a member of the family of neural cell adhesion molecules (NCAMs). The target CD56 antigen is expressed on the surface of tumor cells of neuroendocrine origin, including small cell lung cancer (SCLC), carcinoid tumors; on neuroectodermal tumors, such as astrocytomas; as well as many multiple myelomas (MM) and ovarian cancers. CD56 is also nearly universally expressed on Wilms tumors, rhabdomyosarcomas, neuroblastomas,<sup>1-12</sup> pleuropulmonary blastomas, malignant peripheral nerve sheath tumors and synovial sarcomas.<sup>13-16</sup> In Wilms tumor, CD56 has been specifically demonstrated to be a marker of the putative cancer stem cell.<sup>1,2</sup> IMG901 acts by binding to the target antigen, CD56 on tumor cells and once bound, the conjugate is internalized and DM1 released. Within the cell, DM1 disrupts microtubule assembly, leading to G2/metaphase arrest and ultimately cell death.<sup>17</sup>

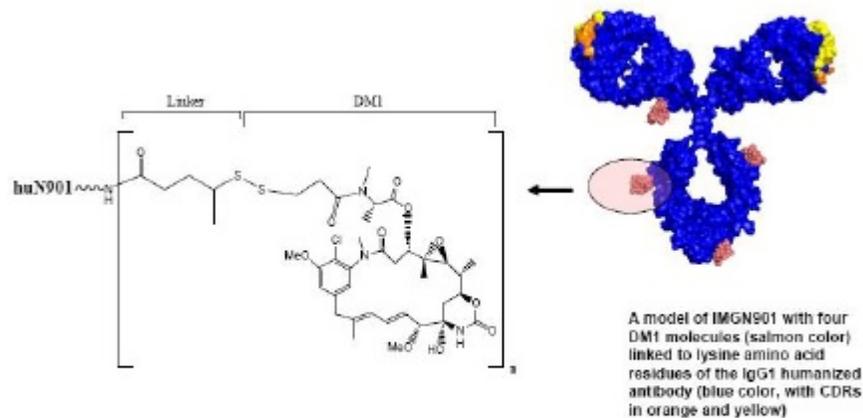
**IGMN901:****Linker**

IGMN901 was made using the reagent N-succinimidyl 4-(2-pyridyldithio) pentanoate (SPP), which forms a stable disulfide link between the huN901 antibody and DM1 (Figure 1).

**Antibody, huN901**

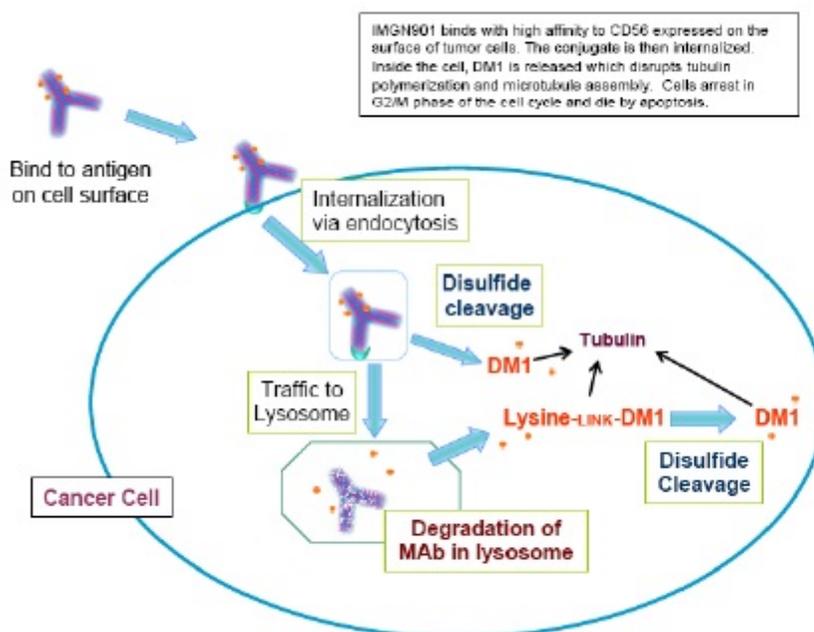
N901, a murine monoclonal antibody of the immunoglobulin G (IgG) 1 subclass, was originally generated as an antibody that binds specifically to natural killer (NK) cells and CD56-positive T-lymphocytes but is non-reactive with monocytes, B-lymphocytes, most T-lymphocytes that are CD56 negative, erythrocytes and platelets. The antibody binds to the CD56 antigen, a member of the NCAM family expressed on many tumors of neuroendocrine origin as outlined above. N901 also binds to about 70% of MMs and many ovarian cancers.

**Figure 1: Description of IGMN901**



n ~ 3.5 (DM1 is ~ 1.8% by weight of Mab)

CDR = complementarity determining regions; DM1 refers to DM1 in this figure.

**Figure 2: IMGN901 Mechanism of Action: Disruption of Tubulin Polymerization**

Mechanism of action of IMGN901 based on Erickson et al, 2006.

Of normal tissue screened, binding was seen with cardiac muscle cells; peripheral nerve tissues: neuroectodermal cells, such as astrocytes; and neuroendocrine cells of the adrenal gland, pancreas and thyroid gland. N901 did not bind to bladder, bone marrow, cervix, colon, esophagus, kidney, liver, lung, skeletal muscle, pancreatic ducts, prostate glands, skin, small intestine, or uterus. Binding was also seen on a subset of lymphocytes in lymph node, spleen, and thymus that were thought likely to be NK cells and CD56-positive T-lymphocytes. To overcome the limited effectiveness of murine antibody conjugates due to the formation of a human anti-murine antibody response in recipients, N901 was humanized by complementarity determining regions (CDR) grafting to form huN901, which retains 100% of the binding avidity of the parent murine antibody. The antibody was modified to introduce active disulfide-containing groups, which react with the thiol-containing maytansinoid, DM1, via thiol-disulfide exchange, to produce a conjugate containing, on average, 3.5 DM1 molecules per antibody molecule. The huN901 antibody component of IMGN901 was initially produced from a murine SP2/0 cell line (MS-151). Later in development, the source of the huN901 antibody component of IMGN901 was changed to a Chinese hamster ovary (CHO) cell line (HD-157 or ND-199) because antibody production by the CHO cell line is more efficient. Comparability of IMGN901 made with antibody produced from all cell lines has been demonstrated. Phase 1/2 clinical studies are being performed using IMGN901 made with antibody produced from the CHO cell lines.

#### **Cytotoxic Component, DM1**

DM1, the cytotoxic component of IMGN901, is a member of the maytansinoid family. Maytansinoids are mitotic inhibitors that kill cells by interfering with the formation of microtubules and depolymerization of already-formed microtubules (Figure 2). DM1 is an

analog of the well characterized maytansinoid, maytansine. Maytansine was studied extensively in nonclinical and clinical studies by the National Cancer Institute (NCI).

DM1 differs from maytansine in that it contains a sulfhydryl group that allows the drug to be linked to an antibody via disulfide bond formation.

*In vitro* screening showed maytansine to be 100- to 1000-fold more toxic than other cytotoxic drugs for a range of human cancer cell lines. Free maytansine had a low therapeutic index in human clinical studies because of high systemic toxicity. However, by conjugating maytansinoids with antibodies via cleavable disulfide bonds, the cytotoxicity can be targeted specifically against tumor cells. The intracellular cleavage of the disulfide bond is important for activity.

## 2.2 Preclinical Studies

### 2.2.1 Antitumor Activity

*In vitro* studies show that the cytotoxicity of IMG901 is restricted to CD56-positive cells. For example, IMG901 caused potent cytotoxicity with a concentration resulting in 50% inhibitory concentration (IC50) of approximately 60 pM in the CD56-positive neuroblastoma cells IMR32, but was inactive in CD56 negative colon cancer cells COLO205 at concentrations as high as 1.5 nM even though both cell lines show similar sensitivity to non-conjugated maytansine.<sup>15</sup> These data indicate that IMG901 specifically induces CD56-dependent cytotoxic effects in cells expressing the target CD56 antigen, while sparing cells that do not express CD56 and which, therefore, cannot bind IMG901.

The immune effector activity of huN901 antibody and IMG901 and their effect on the function and growth of CD56-positive human primary NK cells was investigated *in vitro*. It was found that huN901 fails to mediate complement dependent cytotoxicity (CDC) but induces antibody-dependent NK cell-mediated cytotoxicity (ADCC) in a dose-dependent manner against target cells expressing high levels of CD56, but not in those expressing low levels of CD56. IMG901 showed ADCC activity comparable to huN901 antibody alone, suggesting that DM1 conjugation did not alter the interaction between the Fc domain of the antibody and the Fc receptor of NK cells.<sup>17</sup>

***Adult Tumors Pre-Clinical Testing:*** Studies evaluating the *in vivo* efficacy of IMG901 were conducted in severe combined immunodeficient (SCID) mice bearing subcutaneous xenografts of adult-derived human tumor cell lines derived from SCLC, MM and ovarian cancer. In these studies, IMG901 showed marked efficacy, including complete regressions in some animals.<sup>17-21</sup>

### ***Pediatric Tumors Pre-Clinical Testing:***

CD56 is well known to be expressed in all blastemal dominant Wilms tumors (typical at relapse), the majority of epithelial Wilms tumor components as well, all rhabdomyosarcomas, all neuroblastomas and the majority of pleuropulmonary blastomas, malignant peripheral nerve sheath tumors and synovial sarcomas.<sup>4,13-16,21</sup>

The Pediatric Preclinical Testing Program tested IMG901 against a panel of solid tumor models. *In vitro* experiments demonstrated low nanomolar IC50s against both rhabdomyosarcoma and neuroblastoma models. *In vivo* experiments, using a weekly x 3 schedule of 15 mg/kg/dose, demonstrated objective responses in 9/24 (38%) models. Specifically, 2/2 Wilms tumor models (KT10 and KT11) demonstrated sustained complete remissions (2/2); 2/7 rhabdomyosarcoma models, which were both alveolar rhabdomyosarcomas, demonstrated sustained complete remissions (RH30 and RH65) with an embryonal rhabdomyosarcoma model (RH36) demonstrated growth stasis; and 3/7 neuroblastoma models demonstrated complete responses (NB-SD, NB-1643, NB-1382).<sup>3</sup> Additional investigation of a Wilms tumor cancer stem cell xenograft model, representing a CD56+ blastemal-type Wilms tumor, demonstrated complete responses to IMG901.<sup>1,2</sup>

### 2.2.2 Animal Toxicology

Nonclinical safety evaluation of IMG901 has focused on studies in cynomolgus monkey due to the lack of cross-reactivity to the antigen in non-primate species. The principal target organ for this species is the peripheral and central nervous system (spinal cord). In a single dose study, single bolus IV infusion of IMG901 (152 and 456 mg/m<sup>2</sup>) was associated with dose-dependent minimal to mild findings of axonal degeneration of peripheral nerves and spinal cord. Repeat dosing was investigated on a weekly schedule (24 to 228 mg/m<sup>2</sup> for six weeks) and daily schedule (2.4 to 114 mg/m<sup>2</sup> for five days). At the lowest weekly dose tested (24 mg/m<sup>2</sup>) minimal lesions in the spinal cord only were noted. Higher dose levels (> 24 mg/m<sup>2</sup> weekly or daily) were associated with lesions of the peripheral (sciatic and peroneal) and central (cervical, thoracic, and lumbar spinal) nerves.

The skin was also a target organ, with clinical changes relating to hyperkeratosis (peeling, flaking, cracking, etc.) after a single dose of 456 mg/m<sup>2</sup> or at repeated doses of ≥114 mg/m<sup>2</sup> weekly. Skin darkening correlated with increased amounts of melanin pigment and prominent melanocytes in the skin were observed following repeat doses of ≥ 24 mg/m<sup>2</sup> daily or ≥ 114 mg/m<sup>2</sup> weekly.

Changes in markers of hepatic function were limited to rises in transaminases and serum alkaline phosphatase (ALK) in the highest single dose tested (456 mg/m<sup>2</sup>) and transient rises in serum ALK activity with repeat daily doses of 114 mg/m<sup>2</sup>. There were no changes in markers of renal function.

Treatment-related bone marrow suppression, leading to pancytopenia, and effects on the gastrointestinal (GI) system including enteropathy, affecting the small and large intestines, characterized by loss, dilatation and epithelial regeneration of intestinal crypts were seen in animals receiving the highest repeat daily dose of (114 mg/m<sup>2</sup>).<sup>17</sup>

### 2.2.3 Preclinical Pharmacokinetic Studies

Briefly, pre-clinical pharmacokinetic studies in animals have demonstrated that the clearance of the antibody moiety of IMG901 is similar to that of “naked” humanized antibody, with a t<sub>1/2</sub> in mice of about five days for the antibody. Thus, conjugation of an average of 3.5 molecules of DM1 to huN901 does not

appreciably alter the PK properties of the huN901 antibody itself. IMGN901  $t_{1/2}$  is approximately two days (55 hours) in mice and 30 hours in monkeys. The shorter  $t_{1/2}$  in monkeys may be due to CD56 binding, since IMGN901 cross-reacts with monkey CD56, but not murine CD56. The highest percentage of injected dose is found in the blood, liver, spleen, and kidney.

In mice, clearance was biphasic: an initial rapid decline was followed, after about eight hours, by a slower rate of disappearance that followed first order kinetics (overall elimination phase) with an overall clearance rate of 2 to 3 mL/h/kg. In monkeys, the maximum concentration ( $C_{max}$ ) and the area under the curve ( $AUC_{0-inf}$ ) increased in an approximately dose proportional manner. The huN901 antibody component of IMGN901 itself had a slower clearance ( $t_{1/2}$  about three days) in monkeys than intact IMGN901, as assessed by an assay specific for total huN901 antibody, whether conjugated or not. Comparison of the clearance curves for intact conjugate and total antibody (the difference between them) allows for estimation of the  $t_{1/2}$  of the disulfide link between DM1 and the huN901 antibody, which was calculated to be about 50 hours *in vivo*.  $C_{max}$  and  $AUC_{0-inf}$  values for total huN901 antibody increased in an approximately dose proportional manner for the two doses (12.7 and 38 mg/kg) studied. The  $t_{1/2}$ , volume of distribution, and clearance values calculated for total huN901 antibody were similar at the two doses of IMGN901. The relatively short  $t_{1/2}$  for total huN901 antibody (approximately three days) in monkeys relative to that expected for a human IgG1 antibody (approximately 10 days) also suggests a contribution from CD56 mediated clearance in this species. No monkey anti-IMGN901 antibodies were detected.

The tissue distribution in mice of 125I-huN901 antibody was compared with that of 125I-labelled IMGN901 conjugate, both dosed at 10 mg/kg. The pattern of uptake was similar at all time points and in all tissues. Distribution was characterized by a higher percentage of injected dose per gram of tissue in the blood, liver, spleen, and kidney for the first eight hours post-administration. At all time points, the highest percentage of the injected dose was in the bloodstream. These results suggest that conjugation does not alter the biodistribution of the antibody *in vivo* in mice.<sup>17</sup>

## 2.3 Adult Studies

### 2.3.1 Phase 1 and 2 Studies

To date, there have been five IMGN901 studies. Studies 001, 002, and 003 evaluated IMGN901 as monotherapy; Study 0005 evaluated IMGN901 administered in combination with lenalidomide and dexamethasone in relapsed/refractory MM; and Study 0007 evaluated IMGN901 in combination with carboplatin and etoposide in patients with SCLC.<sup>22-32</sup>

As of March 2014, safety data is available on 198 patients from studies 001-003 with single agent IMGN901. Study 001 tested weekly dosing for four weeks every 6 weeks at doses ranging from 5 mg/m<sup>2</sup> to 75 mg/m<sup>2</sup>. The MTD was defined as 60 mg/m<sup>2</sup>, with DLTs at 75 mg/m<sup>2</sup> including headache with meningitis-like symptoms. Frequent AEs included headache, peripheral sensory neuropathy, nausea, fatigue, vomiting, rigors, myalgia, diarrhea, pyrexia and anorexia.

Pharmacokinetics demonstrated a  $t_{1/2}$  of approximately 6 hours for doses  $\leq 10$  mg/m<sup>2</sup> and  $t_{1/2}$  of 16 hours at 60 mg/m<sup>2</sup>.

Study 002 tested daily infusion for 3 days every 3 weeks at doses ranging from 4 to 94 mg/m<sup>2</sup>/dose. The RP2D was defined as 60 mg/m<sup>2</sup> with an MTD of 75 mg/m<sup>2</sup>. DLTs at 94 mg/m<sup>2</sup> were headache, fatigue and myalgia. The most frequent AEs were headache, nausea, fatigue, vomiting and peripheral neuropathy. PKs demonstrated that the  $C_{max}$  increased with dose and  $t_{1/2}$  approximated 1 day (20.6-36.6 hours) at doses  $\geq 48$  mg/m<sup>2</sup>/day.

Study 003 tested weekly IV infusions for 2 consecutive weeks every 3 weeks, at doses ranging from 40-140 mg/m<sup>2</sup>. The MTD was defined as 112 mg/m<sup>2</sup>, with DLTs at 140 mg/m<sup>2</sup> including reversible acute renal insufficiency in 1 patient and fatigue in 1 patient. Frequent AEs included fatigue, increased AST, increased uric acid, peripheral neuropathy, paresthesias, headache, constipation and diarrhea. PK findings demonstrated that the  $t_{1/2}$  was 23.7 hours at the highest dose tested.

Study 005 tested weekly infusions of IMGN901 at doses of 75, 90 and 112 mg/m<sup>2</sup> for 3 consecutive weeks, every 4 weeks in combination with lenalidomide and dexamethasone in patients with relapsed/refractory MM. Dose reductions due to late occurring toxicities prompted lowering the expansion dose level of IMGN901 to 75 mg/m<sup>2</sup>. Most frequent AEs included peripheral neuropathy, fatigue, diarrhea, nausea, pyrexia, headache, muscle spasms, and cough. The  $t_{1/2}$  of IMGN901 was 18.2 hours at the highest dose level.

Study 0007 tested weekly infusions of IMGN901 at doses of 60, 75, 90 and 112 mg/m<sup>2</sup> weekly for 2 consecutive weeks every 3 weeks in combination with carboplatin and etoposide with an expansion cohort of SCLC patients. Myelosuppression and infection were more common on this combination therapy trial. As yet unexplained increase in infection on the IMGN901 arm vs control arm without IMGN901 was noted: 16% infection-associated SAEs with 11% being fatal vs 11% infection-associated SAEs with 4% being fatal. On target IMGN901 peripheral neuropathy toxicity from DM1 was dose dependent, dropping from 86% (36% Grade 3) (IMGN901 dose 112 mg/m<sup>2</sup>) to 71% (11% Grade 3) (IMGN901 dose 90 mg/m<sup>2</sup>). PKs of IMGN901 mirrored data achieved in prior trials.

#### **IMGN901 Single Agent Safety Summary:**

Treatment-related AEs in studies 001-003 (single agent studies) occurring in  $> 10\%$  of patients in descending order of frequency include peripheral neuropathy (31%), headache (30%), fatigue (29%), nausea (27%), AST elevations, diarrhea and vomiting (13% each), myalgia (12%), and decreased appetite (11%). While the overall incidence of peripheral neuropathy and paraesthesia, regardless of relationship to study drug, was 33% and 9%, respectively, the Grade 3 incidence was low (3% and  $< 1\%$  respectively), and there were no reports of Grade 4 toxicity.

Fifty-six treatment-related SAEs were observed in 26 patients (13%). The most commonly reported treatment-related SAEs among patients receiving single-agent IMGN901 include headache (3%), constipation (2%), noninfective meningitis (2%, see below), and vomiting (2%). Early in clinical development of IMGN901, there were three cases of serious meningitis-like syndrome (meningitis-like

symptoms associated with headaches) in the single-agent studies. Following implementation of routine steroid prophylaxis and a slowed infusion rate, no additional reports of non-infective meningitis have been documented and Grade 3 and Grade 4 headache have not been reported at the MTD in any of these studies.

Some less frequently reported (less than 2%) but serious toxicities that have been reported with IMG901 and were considered at least possibly related to study drug include fatigue (two patients), renal failure (one patient), posterior reversible encephalopathy syndrome (one patient), and myocardial infarction (one patient). For two patients receiving single-agent IMG901 who died within 30 days after the last study drug dose, the cause of death was considered by the Investigator to be at least possibly related to study drug. One patient treated on the 001 study died 10 days following the last dose of IMG901, due to a retroperitoneal bleed and multi-organ failure that was deemed possibly related to the study treatment regimen. On the 002 study, one patient died 18 days following the last dose of IMG901 due to bronchopneumonia that was assessed by the investigator to be possibly related to study treatment.

DLTs for Studies 001, 002 and 003 were as follows:

- Study 001: DLTs observed in five patients over the course of the study included Grade 4 hyperesthesia; Grade 3 noninfective meningitis (n=3); and single events of Grade 3 fatigue, headache, and peripheral neuropathy.
- Study 002: DLTs observed in six patients over the course of the study included single events of Grade 4 fatigue and headache; and single events of Grade 3 headache, myalgia, pain, paresthesia, and peripheral neuropathy.
- Study 003: DLTs observed in five patients over the course of the study included single events of Grade 3 fatigue, Grade 3 asthenia, Grade 3 lipase, Grade 3 renal failure, Grade 2 fatigue and two events of Grade 3 peripheral neuropathy in one patient,

Studies (001, 002, 003): Laboratory Abnormalities:

Of the 198 patients across the three single-agent studies, 97% reported at least one abnormality. At least one hematologic abnormality of Grade 3 or 4 was reported in 35% and 1% of patients, respectively, with the most common Grade 3 or 4 abnormality being lymphocyte count decreased (29%). All but one patient in the single-agent studies reported at least one serum chemistry abnormality. At least one abnormality of Grade 3 or 4 was reported in 46% and 8% of patients, respectively. Most results were Grade 1 or 2 in intensity. The most common Grade 3 and/or 4 abnormalities were hyperglycemia (18%, all Grade 3) and gamma-glutamyl transferase (GGT) increased (12%, 10% Grade 3 and 2% Grade 4). The institution of corticosteroid-based prophylaxis for the prevention of headache with meningitis-like symptoms, which was reported early in the development of IMG901 may have contributed to the high rate of hyperglycemia. Increases in liver function tests have also been reported, but have been asymptomatic.

### 2.3.2 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

As of 31 March 2014, cycle 1 PK data from closed to accrual and completed clinical studies evaluating various dose regimens are available from Studies 001, 002, 003, 0005 and 0007.

Study 001: The clearance of IMG901 is rapid with a  $t_{1/2}$  of approximately six hours at the lowest doses ( $\leq 10 \text{ mg/m}^2$ ). Clearance decreases at higher dose levels with the terminal elimination  $t_{1/2}$  being about 16 hours in the  $60 \text{ mg/m}^2$  Phase 2 dose expansion cohort. The decreased clearance at higher doses may be due to the saturation of readily accessible CD56-positive expressing cells (e.g., NK cells) and/or soluble CD56 at these dose levels.

Study 002: Decreased plasma clearance with increasing dose of IMG901 was also observed in these patients. The  $C_{\max}$  and  $AUC_{0-\infty}$  for IMG901 from Study 002 generally increased with dose and an observed  $t_{1/2}$  of approximately one day (20.6 to 36.6 hours) at doses  $\geq 48 \text{ mg/m}^2/\text{day}$  is consistent with previous findings.

Study 003 (Table 1): PK findings are similar to those observed previously with the  $t_{1/2}$  of IMG901 approaching one day (23.4 hours) at the highest dose level.  $AUC_{0-\infty}$  and  $C_{\max}$  generally increase linearly with increasing IMG901 dose.

Study 0005: PK findings are similar to those observed previously with the  $t_{1/2}$  of IMG901 approaching one day (18.2 hours) at the highest dose level.

Study 0007, Phase 1: PK findings are similar to those observed previously with the  $t_{1/2}$  of IMG901 approaching one day (23.4 hours) at the highest dose level for cohorts administered carboplatin with dose targeted to an area under the curve of 5 and etoposide at  $100 \text{ mg/m}^2$ .

Study 0007, Phase 2: PK findings are similar to those observed previously, with a  $t_{1/2}$  of IMG901 approaching one day (27.5 and 26.9 hours at Cycle 1, Day 1, and Cycle 4, Day 1, respectively) when IMG901 was dosed at  $112 \text{ mg/m}^2$  along with carboplatin administered at a dose targeted to an area under the curve of 5 and etoposide at  $100 \text{ mg/m}^2$ .

The total antibody component shows similar clearance to that of the intact conjugate in patients. Free maytansinoid levels have been evaluated in plasma samples from patients treated in Study 003. In patients receiving between 40 and  $140 \text{ mg/m}^2$  IMG901, free maytansinoid levels in plasma were detected in 53% of the patients with the average maximal detectable level represented as  $2.0 \pm 0.8\%$  of the maximal conjugated maytansinoid.

Representative PK parameters from Study 003 are shown in Table 1 below:

**Table 1**

Dose g/m <sup>2</sup>	N of patients	C <sub>max</sub> μg/mL	t <sub>1/2</sub> h	AUC <sub>0-inf</sub> μg.h/mL	Cl mL/h/m <sup>2</sup>	V <sub>ss</sub> mL/m <sup>2</sup>
40	3	32.8 (11.3)	14.2 (4.8)	760 (387)	66.1 (40.9)	1242 (627)
60	3	60.0 (15.2)	19.6 (0.46)	1646 (259)	37.1 (6.4)	981 (254)
75	3	42.9 (6.0)	17.1 (5.1)	1012 (49.5)	74.2 (3.7)	2106 (163)
90	3	49.2 (10.9)	16.5 (0.78)	1202 (326)	78.3 (18.7)	1718 (392)
112	18 <sup>a</sup>	55.0 (13.1)	21.3 (7.1)	1503 (700)	88.7 (39.1)	2277 (833)
140	6	81.5 (18.9)	23.7 (2.6)	2289 (656)	66.5 (22.8)	1979 (424)

AUC<sub>0-inf</sub>: area under serum concentration *versus* time curve; V<sub>ss</sub>: apparent volume of distribution;  
C<sub>max</sub>: maximum serum concentration, t<sub>1/2</sub>: half-life, Cl: clearance. Results shown as mean (± standard deviation)  
for patients with evaluable data.

a. Data for Cycle 1 Dose 1 for one patient at 112 mg/m<sup>2</sup> (Patient 218) was excluded from pharmacokinetic calculations due to unexpectedly low IMGN901 plasma levels. IMGN901 levels for later doses in this patient (Cycle 1 Dose 1, Cycle 5 Dose 1) were within the expected range.

## 2.4 Pediatric Studies

There is no prior experience with IMGN901 in children.

## 2.5 Overview of Proposed Pediatric Study

This is a multi-strata Phase 2 study of IMGN901 where each stratum will be analyzed separately. Strata to be evaluated include Wilms tumor (Stratum 1), rhabdomyosarcoma (Stratum 2), neuroblastoma (Stratum 3); and strata for miscellaneous CD56-expressing tumors such as pleuropulmonary blastoma (Stratum 4), malignant peripheral nerve sheath tumor (MPNST) (Stratum 5), and synovial sarcoma (Stratum 6). IMGN901 will be administered weekly for two consecutive weeks every 3 weeks (Day 1 and 8 schedule of each 21-day cycle).

The dose selected for this Phase 2 study is 110 mg/m<sup>2</sup>/dose. This was the RP2D/MTD on two of the adult Phase 1 trials (rounding down from 112 mg/m<sup>2</sup>/dose), and of the schedules studied in adult patients, provided the highest tolerable dose intensity, 73 mg/m<sup>2</sup>/week (as detailed above, the maximum tolerated dose intensity on the adult Phase 1 trials were 40, 56, 64, 75 and 75 mg/m<sup>2</sup>/week). Moreover, the weekly times two schedule every three weeks would be the most favorable schedule to potentially integrate into a standard chemotherapy regimen should sufficient activity be observed to warrant further development.

Careful safety monitoring will include an interim safety analysis following accrual of the first 6 patients as well as ongoing analyses for delayed toxicity (see [Section 9.0](#)). Absent unacceptable toxicity, each stratum will continue to accrue. In the event that 110 mg/m<sup>2</sup> is deemed too toxic, the next six patients will be accrued at 90 mg/m<sup>2</sup> and a second interim safety analysis conducted. Absent unacceptable toxicity, each stratum will continue to accrue at this dose level. In the event that 90 mg/m<sup>2</sup> proves too toxic, the study will cease accrual and amendments considered.

A limited sampling strategy will be employed to assess the pharmacokinetics of IMGN901 from the Cycle 1, Day 1 dose. Peripheral blood will undergo analysis for CD56+ burden

(NK cell, T-cell subpopulations, for example) and considered in PK modeling. Tumor will be assessed for CD56 status via immunohistochemistry and correlated with response.

## 2.6 Development Plan

Considering the targeted nature of drug delivery via the CD56 targeting antibody drug conjugate and different anti-mitotic agent (maytansinoid), it is possible that IMG901 may demonstrate better efficacy than vincristine in the selected tumor types and/or efficacy in vincristine-resistant cancers. If we reach our targeted efficacy endpoints, further development of CD56-Antibody Drug Conjugate based therapy could be advanced via integration into chemotherapy backbones targeting high-risk or recurrent/refractory Wilms tumor, rhabdomyosarcoma, and neuroblastoma, all of which are typically at least partially resistant to vincristine.

## 3.0 ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

### 3.1 Study Enrollment

#### 3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number.

This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens, please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see [Appendix III](#) for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

#### 3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be

located on the CTSU web page (<https://www.ctsu.org>). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206), E-mailed (CTSUSRegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSUS. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at <https://www.ctsu.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

**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.

### 3.1.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing protocol entry with the patient, site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available for the patient. Once a slot-reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

If the study is active, a reservation can be made by following the steps below:

- 1) Log in to <https://open.ctsu.org/open/> using your CTEP IAM user name and password.
- 2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
- 3) Using the OPEN patient number '**RESERVE**' a slot for that patient.

- 4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

Refer to the 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions:

[https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN\\_SlotReservation\\_QuickReference\\_SiteUserGuide\\_102612.pdf&ftype=PDF](https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF)

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps above. Reservations may be obtained 24 hours a day through the OPEN system.

#### 3.1.4 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position 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>.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (<https://open.ctsu.org>). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

#### 3.1.5 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 7 business days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible and will not be able to receive further protocol therapy.**

See [Section 3.2](#) for timing requirements for eligibility studies. See [Section 3.1.7](#) for timing requirements for baseline studies to be obtained prior to start of therapy.

Institutions are advised to plan ahead to ensure adequate and timely delivery of the investigational agent (see [Section 6.1.5](#) for details).

**Note: Repeat laboratory and imaging studies may be required if enrollment and start of therapy do not occur on the same day.**

3.1.6 Institutional Pathology Report

Immediately following enrollment in OPEN, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded as a PDF image within Rave.

3.1.7 Requirements to Initiate Protocol Therapy

3.1.7.1 Laboratory Studies: If more than 7 calendar days elapse between the date laboratory studies to determine eligibility were obtained ([Section 3.2.5](#)) and the start date of treatment, then the following studies must be repeated prior to initiating protocol therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If any of these repeat laboratory studies are outside the parameters required for eligibility (labs may again be repeated within 48-72 hours), then the patient is off protocol therapy.

3.1.7.2 Imaging Studies: Imaging studies must be performed within 14 calendar days of initiating protocol therapy. If more than 14 calendar days have elapsed between the date imaging studies to determine eligibility were obtained ([Section 3.2.3](#)) and the start date of treatment, then repeat imaging studies must be obtained prior to initiating protocol therapy.

3.1.7.3 Bone Marrow Evaluations: For patients with known or clinically suspected bone marrow involvement, BMA and/or biopsy must be performed within 14 calendar days of initiating protocol therapy. If more than 14 calendar days have elapsed between the date bone marrow evaluation to determine eligibility was obtained ([Section 3.2.3](#)) and the start date of treatment, then repeat BMA and/or biopsy must be obtained prior to initiating protocol therapy.

### 3.2 Eligibility: Inclusion Criteria

**Important note: The inclusion criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record. These source documents must be available for verification at the time of audit.**

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment. Imaging studies must be performed within 14 days prior to study enrollment.

#### 3.2.1 Age

- Patients must be  $\geq 12$  months and  $\leq 30$  years of age at the time of study enrollment.

#### 3.2.2 Diagnosis

Patients must have had histologic verification of one of the malignancies listed below at original diagnosis or at relapse

- Primary Strata
  - 1) Wilms tumor
  - 2) Rhabdomyosarcoma
  - 3) Neuroblastoma
- Secondary Strata: Miscellaneous CD56-expressing tumors:
  - 4) Pleuropulmonary blastoma
  - 5) Malignant peripheral nerve sheath tumor (MPNST)
  - 6) Synovial sarcoma

#### 3.2.3 Disease Status

- 3.2.3.1 Patients must have radiographically measurable disease (with the exception of those with neuroblastoma, see [Section 3.2.3.2](#)).

Measurable disease is defined as the presence of at least one lesion on MRI or CT scan that can be accurately measured with the longest diameter a minimum of 10 mm in at least one dimension (CT scan slice thickness no greater than 5 mm).

Note: The following do not qualify as measurable disease:

- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration except that detected by MIBG scan for neuroblastoma, see [Section 3.2.3.2](#)
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans) except as noted in [Section 3.2.3.2](#)
- elevated tumor markers in plasma or CSF
- previously radiated lesions that have not demonstrated clear progression post radiation
- leptomeningeal lesions that do not meet the measurements noted above.

3.2.3.2 Patients with **neuroblastoma** who do not have measurable disease but have MIBG-avid evaluable disease are eligible.

3.2.3.3 Performance Level

Patients must have a Lansky or Karnofsky performance status score of  $\geq 50$ , corresponding to ECOG categories 0, 1 or 2. Use Karnofsky for patients  $> 16$  years of age and Lansky for patients  $\leq 16$  years of age. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. (See [https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp))

3.2.4 Prior Therapy

3.2.4.1 Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

3.2.4.2 Patients must have received standard treatment appropriate for their tumor type.

- a. Myelosuppressive chemotherapy: Patients with solid tumors must not have received myelosuppressive chemotherapy within 3 weeks of enrollment onto this study (6 weeks if prior nitrosourea).
- b. Hematopoietic growth factors: At least 14 days must have elapsed after receiving pegfilgrastim and least 7 days must have elapsed since the completion of therapy with a non-pegylated growth factor.
- c. Biologic (anti-neoplastic agent): At least 7 days must have elapsed since completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period prior to enrollment must be extended beyond the time during which adverse events are known to occur.
- d. Monoclonal antibodies: At least 3 half-lives must have elapsed since prior therapy that included a monoclonal antibody. (See posting of half-lives for commonly used monoclonal antibodies on the DVL homepage; <https://members.childrensoncologygroup.org/Disc/devtherapeutics/default.asp>.)
- e. Radiotherapy:  $\geq 2$  weeks must have elapsed since local palliative XRT (small port);  $\geq 6$  weeks must have elapsed since treatment with therapeutic doses of MIBG;  $\geq 3$  months must have elapsed if prior craniospinal XRT was received, if  $\geq 50\%$  of the pelvis was irradiated, or if TBI was received;  $\geq 6$  weeks must have elapsed if other substantial bone marrow irradiation was given.
- f. Stem Cell Transplant or Rescue without TBI: No evidence of active graft vs. host disease and  $\geq 2$  months must have elapsed since

transplant.

### 3.2.5 Organ Function Requirements

#### 3.2.5.1 Adequate Bone Marrow Function Defined As:

- a. For patients with solid tumors without bone marrow involvement:
  - Peripheral absolute neutrophil count (ANC)  $\geq 1000/\mu\text{L}$
  - Platelet count  $\geq 100,000/\mu\text{L}$  (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to enrollment)
- b. For patients with solid tumors and known bone marrow metastatic disease:
  - Peripheral absolute neutrophil count (ANC)  $\geq 750/\mu\text{L}$
  - Platelet count  $\geq 75,000/\mu\text{L}$  (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment).

#### 3.2.5.2 Adequate Renal Function Defined As:

- Creatinine clearance or radioisotope GFR  $\geq 70 \text{ mL/min/1.73 m}^2$  **or** a serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
$\geq 16$ years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

#### 3.2.5.3 Adequate Liver Function Defined As:

- Total bilirubin  $\leq 1.5$  x upper limit of normal (ULN) for age
- SGPT (ALT)  $\leq 110 \text{ U/L}$  (for the purpose of this study, the ULN for SGPT is 45 U/L)
- Serum albumin  $\geq 2 \text{ g/dL}$ .

#### 3.2.5.4 Adequate Cardiac Function Defined As:

- Shortening fraction of  $\geq 27\%$  by echocardiogram, or
- Ejection fraction of  $\geq 50\%$  by gated radionuclide study.

#### 3.2.5.5 Central Nervous System Function

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.

### 3.3 Eligibility: Exclusion Criteria

**Important note: The exclusion criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record. These source documents must be available for verification at the time of audit.**

3.3.1 Pregnancy or Breastfeeding

Patients who are pregnant or breastfeeding are not eligible for this study as there is yet no available information regarding human fetal or teratogenic toxicities. Negative pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study therapy and for 4 weeks after the last dose of study therapy. Study drug may also potentially be secreted in milk and therefore breastfeeding women are excluded.

3.3.2 Concomitant Medications

3.3.2.1 Corticosteroids: Patients requiring corticosteroids who have not been on a stable or decreasing dose of corticosteroid for the 7 days prior to enrollment are not eligible.

3.3.2.2 Patients who have received previous treatment with IMGN901 are not eligible.

3.3.2.3 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

3.3.2.4 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

3.3.2.5 Anti-GVHD or agents to prevent organ rejection post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent either graft-versus-host disease post bone marrow transplant or organ rejection post-transplant are not eligible for this trial.

3.3.3 Central Nervous System Function

Patients who have a CNS toxicity > Grade 2 are not eligible.

3.3.4 CNS Metastases

Patients must not have known active CNS metastases. Patients with known central nervous system metastases are excluded unless treated surgically or with radiotherapy, and stable with no recurrent lesions for at least 6 months.

3.3.5 Peripheral Neuropathy

Patients who have baseline peripheral neuropathy  $\geq$  Grade 2 are not eligible.

3.3.6 Infection

Patients who have an uncontrolled infection are not eligible.

3.3.7 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

3.4 **Regulatory**

- 3.4.1 All patients and/or their parents or legal guardians must sign a written informed consent.
- 3.4.2 All institutional, FDA, and NCI requirements for human studies must be met.

## 4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

### 4.1 Overview of Treatment Plan

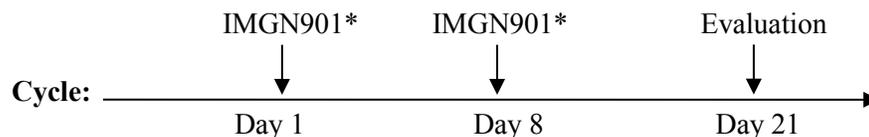
#### 4.1.1 Treatment Overview:

**NOTE:** Accrual of the first 6 patients is limited to Phase 1 Consortium institutions. Subsequent enrollments are open to COG institutions within the United States.

This will be a single-arm open label trial with three primary disease strata as outlined in the statistical section ([Section 9.0](#)) and three additional secondary strata for rarer cancers known to frequently express CD56.

All patients will receive IMG901 intravenously on Days 1 and 8 every 21 days. See [Section 4.1.4](#) for dose information. A cycle of therapy is 21 days. Treatment may consist of up to 17 cycles, for an approximate total therapy duration of 12 months, absent disease progression or unacceptable toxicity.

#### 4.1.2 Treatment Schema:



\* IMG901 is administered via intravenous infusion. Cycle 1 Day 1 infusion will start at 0.02 mg/kg/min (maximum 1 mg/min) x 15 minutes and if tolerated, the rate may then increase to 0.06 mg/kg/min (maximum 3 mg/min) to complete the infusion. If the patient tolerates the Cycle 1, Day 1 infusion, all subsequent infusions may be delivered at the 0.06 mg/kg/min (maximum 3 mg/min) rate.

All patients should receive pre-medication with dexamethasone. See [Sections 4.2.3](#) and [4.3.3](#) for details.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

#### 4.1.3 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 21 days if the patient has at least stable disease, has again met laboratory parameters as defined in the eligibility section ([Section 3.2.5](#)) and has not met one of the Off Protocol Therapy or Off Study Criteria ([Section 8.0](#)). Patients who have experienced dose-limiting toxicity (DLT) (see

[Section 5.0](#)) in the previous cycle should have the dose modified (see [Section 4.1.4](#)). Treatment may consist of up to 17 cycles, for a total duration of therapy approximating 12 months, absent disease progression or unacceptable toxicity. To continue on therapy the patient must have at least clinically and radiographically stable disease. Radiographic disease evaluations will be done after the 2<sup>nd</sup> cycle of therapy, after every other cycle until 6 months, and then every 3 months.

4.1.4 Dose Schema:

The starting dose will be 110 mg/m<sup>2</sup> (dose level 1). For patients with toxicities as outlined in [Section 5.0](#) and who recover to starting criteria within 7 days as outlined in [Section 4.1.3](#), a single dose reduction to the next lowest dose level will be allowed.

Dose Level	IMGN901 (mg/m <sup>2</sup> )	Day(s) of Administration
-2	75	1 and 8
-1	90	1 and 8
<b>1*</b>	<b>110</b>	<b>1 and 8</b>

\*Starting dose level

Further dose reduction for toxicity will be considered if dose level -1 is not tolerated. No dose escalations will occur.

4.1.5 Concomitant Therapy

1. No other anti-cancer agents may be used while on protocol therapy.
2. No other investigational agents may be used while on protocol therapy.

For COG Supportive Care Guidelines see:

[https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp) under Standard Sections for Protocols.

**4.2 Cycle 1**

**4.2.1 Therapy Delivery Map – Cycle 1**

This therapy delivery map (TDM) relates to Cycle 1, which lasts 21 days.

_____
Patient COG ID number
_____
DOB

Criteria to start Cycle 1 are listed in [Section 3.1.7](#) and [3.2.5](#). Extensive treatment details are in [Section 4.2.3](#). This TDM is on 1 page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
IMGN901 IND # 126953	IV	110 mg/m <sup>2</sup> (dose level 1). See Dose Schema in <a href="#">Section 4.1.4</a>	1 and 8	<p><u>Day 1</u>: Start at 0.02 mg/kg/min (maximum 1 mg/min) x 15 minutes and may then increase to 0.06 mg/kg/min (maximum 3 mg/min) to complete the infusion.</p> <p><u>Day 8</u>: If the patient tolerates Cycle 1 Day 1 infusion, all subsequent infusions may be delivered at the 0.06 mg/kg/min (maximum 3 mg/min) rate.</p> <p>The administration of the study drug is approximately 1-1.5 hours in duration and will vary slightly depending on the dose.</p>
Dexamethasone	PO/IV	4 mg/m <sup>2</sup> /dose (max 10 mg) BID	0 and 7	Total daily dose: 8 mg/m <sup>2</sup> /day
Dexamethasone	IV	4 mg/m <sup>2</sup> /dose (max dose 10 mg)	1 and 8	Administer approximately one hour prior to the first chemotherapy infusion.

Ht \_\_\_\_\_ cm      Wt \_\_\_\_\_ kg      BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Day	DEX (PO/IV) mg	DEX (IV) mg	IMGN901 mg	Studies
Enter calculated dose above and actual dose administered below						
		0	_____ mg			
		1		_____ mg	_____ mg	a-m
		7	_____ mg			
		8		_____ mg	_____ mg	c-f, k, l
		15				c-f
		21				c-f, h
Following completion of Cycle 1, the next cycle starts on Day 22 or when patient has again met laboratory parameters as defined in eligibility <a href="#">Section 3.2.5</a> (whichever occurs later).						

See [Section 5.0](#) for Dose Modifications for Toxicities (including specific criteria for Day 8 IMGN901 infusions) and the COG Member website for Supportive Care Guidelines.



4.2.3 Treatment Details: Cycle 1

**IMGN901: IV**

Days: 1 and 8

Dose: 110 mg/m<sup>2</sup>/dose

Administer IMGN901 IV infusion within 8 hours of preparation using a low protein binding 0.22-micron filter.

Administer at a rate of 0.02 mg/kg/min (maximum 1 mg/min) for the first 15 minutes. Provided the patient tolerates this rate, the rate can be increased to 0.06 mg/kg/min (maximum 3 mg/min). If the patient tolerates Cycle 1 Day 1 infusion, all subsequent infusions may be delivered at the 0.06 mg/kg/min (maximum 3 mg/min) rate. The administration of the study drug is approximately 1-1.5 hours in duration and will vary slightly depending on the dose. The table below provides examples of infusion rate calculations.

If an infusional reaction occurs, the infusion should be stopped and supportive care given as per institutional guidelines. Anaphylactic precautions should be observed during IMGN901 administration. Patients should be monitored for at least 1 hour after completion of the infusion. See [Section 5.4.4](#) for management and dose modification guidelines for infusional reactions.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

Note: Pretreatment use of acetaminophen and/or diphenhydramine may be considered as per Investigator's routine practice. If provided, it is recommended that these agents be administered 30 to 60 minutes prior to the start of the IMGN901 infusion.

**IMGN901 Infusion Rate Calculation Examples Cycle 1 (Dose Level 1 (110 mg/m<sup>2</sup>/dose))**

Example #	Patient demographics	Initial fusion rate (0.02 mg/kg/min)	Subsequent infusion rate (0.06 mg/kg/min)	Total Infusion Duration
1	Weight – 12 kg BSA – 0.52 m <sup>2</sup> IMGN901 dose = 57 mg	0.02 mg/kg/min x 12 kg = 0.24 mg/min x 15 min = 3.6 mg  (3.6 mg of IMGN901 delivered over initial 15 min, with 53.4 mg remaining)	0.06 mg/kg/min x 12 kg = 0.72 mg/min  53.4 mg : 0.72 mg/min = 74.2 min  (remaining 53.4 mg of IMGN901 delivered over 74.2 min)	15 min + 74.2 min = <b>89.2 min</b>
2	Weight – 30 kg BSA – 1.1 m <sup>2</sup> IMGN901 dose = 121 mg	0.02 mg/kg/min x 30 kg = 0.6 mg/min x 15 min = 9 mg  (9 mg of IMGN901 delivered over initial 15 min, with 112 mg remaining)	0.06 mg/kg/min x 30 kg = 1.8 mg/min  112 mg : 1.8 mg/min = 62.2 min  (remaining 112 mg of IMGN901 delivered over 62.2 min)	15 min + 62.2 min = <b>77.2 min</b>

<b>3</b>	Weight – 77 kg BSA – 1.92 m <sup>2</sup> IMGN901 dose = 211 mg	0.02 mg/kg/min x 77 kg = 1 mg/min (max rate) x 15 min = 15 mg  (15 mg of IMGN901 delivered over initial 15 min, with 196 mg remaining)	0.06 mg/kg/min x 77 kg = 3 mg/min (max rate)  196 mg : 3 mg/min = 65.3 min  (remaining 196 mg of IMGN901 delivered over 65.3 min)	15 min + 65.3 min = <b>80.3 min</b>
----------	--	--	---	--

**Dexamethasone: PO or IV**

Days: 0 and 7

Dose: 4 mg/m<sup>2</sup>/dose (max dose 10 mg) BID (i.e., total daily dose = 8 mg/m<sup>2</sup>/day)

On the day prior to administration of IMGN901, patients should receive dexamethasone twice a day (BID). The administration of dexamethasone BID 1 day prior to IMGN901 in patients with diabetes may be omitted at the discretion of the Investigator. Additionally, modifications in dexamethasone dosing such as the elimination or reduction of doses may be taken if a patient is shown to be intolerant of full dosing.

**Dexamethasone: IV**

Days: 1 and 8

Dose: 4 mg/m<sup>2</sup>/dose (max dose 10 mg)

On the day of infusion, patients should receive dexamethasone approximately one hour prior to the first chemotherapy infusion.

See [Section 5.0](#) for Dose Modifications based on Toxicities, including specific criteria for Day 8 IMGN901 infusions.

Following completion of Cycle 1, the next cycle starts on Day 22 or when patient has again met laboratory parameters as defined in eligibility [Section 3.2.5](#) (whichever occurs later).

**4.3 Therapy Subsequent to Cycle 1 (Cycles 2-17)**

<p>4.3.1 <b>Therapy Delivery Map – Cycles 2-17</b>                  This therapy delivery map (TDM) relates to all cycles given <u>after</u> Cycle 1. Each cycle lasts 21 days. Patient may receive additional cycles if they meet the requirements described in <a href="#">Section 4.1.3</a>. Cycles may be repeated for up to 17 cycles of therapy in total, up to a total duration of therapy of 12 months, absent disease progression or unacceptable toxicity.</p>	_____ Patient COG ID number
	_____ DOB

See [Section 4.1.3](#) for guidelines for starting next cycle. Extensive details are [Section 4.3.3](#). This TDM is on 1 page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
IMGN901 IND # 126953	IV 0.06 mg/kg/min (maximum 3 mg/min)*	110 mg/m <sup>2</sup> (dose level 1). See Dose Schema in <a href="#">Section 4.1.4</a>	1 and 8	*unless patient did not tolerate Cycle 1 Day 1 infusion (see <a href="#">Section 4.2.3</a> ). The administration of the study drug is approximately 1-1.5 hours in duration and will vary slightly depending on the dose.
Dexamethasone	PO/IV	4 mg/m <sup>2</sup> /dose (max 10 mg) BID	0 and 7	Total daily dose: 8 mg/m <sup>2</sup> /day
Dexamethasone	IV	4 mg/m <sup>2</sup> /dose (max dose 10 mg)	1 and 8	Administer approximately one hour prior to the first chemotherapy infusion.

Enter Cycle #: \_\_\_\_\_ Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Day	DEX (PO/IV) mg	DEX (IV) mg	IMGN901 mg	Studies	
Enter calculated dose above and actual dose administered below							
		0	_____ mg				
		1		_____ mg	_____ mg	a-e, g, h	
		7	_____ mg				
		8		_____ mg	_____ mg		
		15					
		21					
		Following completion of this cycle, the next cycle starts on Day 22 or when patient has again met laboratory parameters as defined in eligibility <a href="#">Section 3.2.5</a> (whichever occurs later).					f

See [Section 5.0](#) for Dose Modifications for Toxicities (including specific criteria for Day 8 IMGN901 infusions) and the COG Member website for Supportive Care Guidelines.



4.3.3 Treatment Details: Cycles 2-17

**IMGN901: IV**

Days: 1 and 8

Dose: 110 mg/m<sup>2</sup>/dose

Administer IMGN901 IV infusion within 8 hours of preparation using a low protein binding 0.22-micron filter.

Administer at a rate of 0.06 mg/kg/min (maximum 3 mg/min) unless patient did not tolerate Cycle 1 Day 1 infusion (see Section 4.2.3). The administration of the study drug is approximately 1-1.5 hours in duration and will vary slightly depending on the dose. The table below provides examples of infusion rate calculations.

If an infusional reaction occurs, the infusion should be stopped and supportive care given as per institutional guidelines. Anaphylactic precautions should be observed during IMGN901 administration. Patients should be monitored for at least 1 hour after completion of the infusion. See Section 5.4.4 for management and dose modification guidelines for infusional reactions.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

Note: Pretreatment use of acetaminophen and/or diphenhydramine may be considered as per Investigator's routine practice. If provided, it is recommended that these agents be administered 30 to 60 minutes prior to the start of the IMGN901 infusion.

**IMGN901 Infusion Rate Calculation Examples Cycles 2-17 (Dose Level 1 (110 mg/m<sup>2</sup>/dose))**

<b>Example #</b>	<b>Patient demographics</b>	<b>Infusion rate calculations (0.06 mg/kg/min)</b>	<b>Total Infusion Duration</b>
<b>1</b>	Weight – 12 kg BSA – 0.52 m <sup>2</sup> IMGN901 dose = 57 mg	0.06 mg/kg/min x 12 kg = 0.72 mg/min  57 mg : 0.72 mg/min = 79.2 min	<b>79.2 min</b>
<b>2</b>	Weight – 30 kg BSA – 1.1 m <sup>2</sup> IMGN901 dose = 121 mg	0.06 mg/kg/min x 30 kg = 1.8 mg/min  121 mg : 1.8 mg/min = 67.2 min	<b>67.2 min</b>
<b>3</b>	Weight – 77 kg BSA – 1.92 m <sup>2</sup> IMGN901 dose = 211 mg	0.06 mg/kg/min x 77 kg = 3 mg/min (max rate)  211 mg : 3 mg/min = 70.3 min	<b>70.3 min</b>

**Dexamethasone: PO or IV**

Days: 0 and 7

Dose: 4 mg/m<sup>2</sup>/dose (max dose 10 mg) BID (i.e., total daily dose = 8 mg/m<sup>2</sup>/day)

On the day prior to administration of IMGN901, patients should receive dexamethasone twice a day (BID). The administration of dexamethasone BID 1 day prior to IMGN901 in patients with diabetes may be omitted at the discretion of the Investigator. Additionally, modifications in

dexamethasone dosing such as the elimination or reduction of doses may be taken if a patient is shown to be intolerant of full dosing.

**Dexamethasone: IV**

Days: 1 and 8

Dose: 4 mg/m<sup>2</sup>/dose (max dose 10 mg)

On the day of infusion, patients should receive dexamethasone approximately one hour prior to the first chemotherapy infusion. Additionally, modifications in dexamethasone dosing such as the elimination or reduction of doses may be taken if a patient is shown to be intolerant of full dosing.

See [Section 5.0](#) for Dose Modifications based on Toxicities, including specific criteria for Day 8 IMG901 infusions.

Following completion of this cycle, the next cycle starts on Day 22 or when patient has again met laboratory parameters as defined in eligibility [Section 3.2.5](#) (whichever occurs later).

## 5.0 DEFINITIONS AND DOSE MODIFICATIONS FOR TOXICITY

### 5.1 Dose Modifications for Day 8 Dosing due to Toxicity on Day 8

#### 5.1.1 Hematological Toxicity (All Age Cohorts)

Patients who have Grade 4 neutropenia or platelets  $< 75,000/\mu\text{L}$  on Day 8 will have their IMG901 dose (and Day 7 and 8 dexamethasone doses if not yet given) withheld. If the toxicity resolves to  $\text{ANC} \geq 750/\mu\text{L}$  and platelets  $\geq 75,000/\mu\text{L}$  (transfusion independent) by Day 11, the dose may be given with appropriately timed dexamethasone support as is feasible and future doses should not be reduced. If the toxicity does not resolve to  $\text{ANC} \geq 750/\mu\text{L}$  and platelets  $\geq 75,000/\mu\text{L}$  by Day 11, the dose will be omitted and this will be considered a DLT. Patients should receive subsequent cycles of drug but at the next lower dose level. Patients who require that their Day 8 dose be omitted for Grade 4 neutropenia or platelets  $< 75,000/\mu\text{L}$  after an initial dose reduction should have all future Day 8 doses omitted.

Patients who meet hematological DLT criteria as defined in [Section 5.2.2](#) on Day 8 will have their Day 8 dose (and Day 7 and 8 dexamethasone doses if not yet given) omitted. Patients should receive subsequent cycles of drug but at the next lower dose level. Patients who require that their Day 8 dose be omitted for hematologic DLT as defined in [Section 5.2.2](#) after an initial dose reduction should have all future Day 8 doses omitted.

Patients who require more than 2 dose reductions must be removed from protocol therapy.

#### 5.1.2 Non-Hematological Toxicity

Patients who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug prior to the Day 8 dose (with the exception of the DLT exclusions in [Section 5.2.1.1](#)) will be considered to have had a DLT. If the toxicity resolves to meet eligibility or  $\leq$  Grade 2 (if not part of eligibility criteria) by Day 8, the dose (along with dexamethasone support) may be given but at the next lower dose level. If the toxicity does not resolve by Day 11, the dose (along with dexamethasone support) will be omitted. Patients should receive subsequent cycles of drug but with dose modifications according to [Section 5.4](#).

Patients who require more than 2 dose reductions must be removed from protocol therapy.

All dose modifications should be based on the worst preceding toxicity.

### 5.2 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are at least possibly, probably or definitely attributable to IMG901. Dose-limiting hematological and non-hematological toxicities are defined differently.

### 5.2.1 Non-Hematological Dose-Limiting Toxicity

5.2.1.1 Any Grade 3 or higher non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea and vomiting
- Grade 3 ALT/AST elevation that returns to Grade  $\leq 1$  or baseline prior to the time for the next treatment cycle. Note: For the purposes of this trial the ULN for ALT is defined as 45 U/L.
- Grade 3 fever or infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia and/or hypomagnesemia responsive to oral supplementation.
- Peripheral neuropathy Grade 3 for  $\leq 7$  days

5.2.1.2 Non-hematological toxicity that causes a delay of  $\geq 14$  days between treatment cycles.

5.2.1.3 Grade 2 allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

### 5.2.2 Hematological Dose-Limiting Toxicity

5.2.2.1 Definition of a Hematological Dose-Limiting Toxicity for Patients without Bone Marrow Involvement at Enrollment

- Grade 3 thrombocytopenia occurring in conjunction with Grade 3 bleeding (CTCAE terms hemorrhage or epistaxis)
- Grade 4 neutropenia for  $> 7$  days
- Platelet count  $< 20,000/\mu\text{L}$  on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7 day period
- Myelosuppression that causes a delay of  $\geq 14$  days between treatment cycles
- Any Grade 5 hematological toxicity.

## 5.3 **Dose Modifications for Hematological Toxicity**

5.3.1 Patients who have dose-limiting thrombocytopenia should receive subsequent cycles at the next lower dose level. Patients who require that their Day 8 dose be omitted for platelets  $< 75,000 \mu\text{L}$  after an initial dose reduction should have all future Day 8 doses omitted.

5.3.2 Patients who have dose-limiting neutropenia (Grade 4 neutropenia of  $> 7$  days duration or delay in the start of the next cycle for  $> 14$  days due to neutropenia) with no other dose-limiting toxicity should receive the same dose in the next cycle with myeloid growth factor support administered the next day after the Day 8 dose of IMGN901 is given. [Note: Patients MUST NOT receive prophylactic myeloid growth factor in the first cycle of therapy.] If dose-limiting neutropenia recurs after myeloid growth factor is added, then the patient should be given the next lower dose level followed by myeloid growth factor support beginning the next day after

the Day 8 dose of IMG901 is given for subsequent cycles. Patients who experience dose-limiting neutropenia after the addition of myeloid growth factor and one dose reduction must have all future Day 8 doses omitted.

- 5.3.3 Patients who experience dose-limiting hematological toxicity after a single dose reduction (and the addition of myeloid growth factor if the DLT is neutropenia) must have all future Day 8 doses omitted.
- 5.3.4 Patients who experience dose-limiting hematological toxicity in cycles after Day 8 doses were required to be omitted as above must be removed from protocol therapy.

#### 5.4 **Dose Modifications for Non-Hematological Toxicity**

- 5.4.1 Patients who have any dose-limiting non hematological toxicity (as defined in [Section 5.2.1](#)) that returns to eligibility lab requirements within 14 days after the planned start of the next treatment cycle may continue on study but should receive subsequent doses at the next lower dose level. Peripheral neuropathy must resolve to Grade 2 or lower following Grade 3 or 4 peripheral neuropathy prior to resumption of therapy, but it does not need to resolve to eligibility criteria.
- 5.4.2 If non-hematological dose-limiting toxicity recurs at the reduced dose, the patient must have all future Day 8 doses omitted.
- 5.4.3 Patients who experience dose-limiting non-hematological toxicity in cycles after Day 8 doses were required to be omitted as above must be removed from protocol therapy.

5.4.4 For patients who have allergic or acute infusional reactions to IMG901 therapy modifications based on grade should be as follows:

<b>Infusion reactions and delayed infusion-related reactions</b>	Any potential infusion reaction should be classified based upon severity and time of onset relative to the infusion and reported as an infusion reaction and the underlying symptoms on the AE CRF.	
	Mild or moderate (Grade 1-2)	<ul style="list-style-type: none"> <li>• Grade 1: Slow infusion rate by 50% and monitor patient for worsening of condition. Future infusions should be given at the 50% rate.</li> <li>• Grade 2: Stop infusion; symptom control as per institutional guidelines (e.g., narcotics, IV fluids). Give diphenhydramine 0.5-1 mg/kg (max 50 mg IV) and may consider additional hydrocortisone 1-2 mg/kg (max 250 mg IV) or dexamethasone 4 mg/m<sup>2</sup> (max 10 mg IV or PO). Resume infusion at 50% of the prior rate once the reaction has decreased to ≤ Grade 1. Monitor patient for worsening condition. Discontinue IMG901 treatment if condition worsens. For subsequent doses, add diphenhydramine 0.5-1 mg/kg (max 50 mg IV) to the premedication regimen and infuse at 50% rate.</li> </ul>
	Severe or life-threatening: (Grade 3-4)	<ul style="list-style-type: none"> <li>• Grade 3: Stop infusion immediately and disconnect the infusion tubing. Administer bronchodilators for bronchospasms, and other medications (e.g., epinephrine, Normal Saline) as medically indicated. Hospital admission should be considered. For subsequent doses, add diphenhydramine 0.5-1 mg/kg (max 50 mg IV) to the premedication regimen and infuse at 50% rate.</li> <li>• Grade 4: Discontinue IMG901. Treat per institutional guidelines.</li> </ul>
	*NOTE: Infusional reactions usually occur during or within 24 hours of the drug administration. If infusional reactions are suspected more than 24 hours after the dosing of IMG901, the patients should be treated as per institutional guidelines and the study chair should be notified.	





[REDACTED]

6.1.6

[REDACTED]

[REDACTED]

6.2

[REDACTED]



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol). This policy does NOT apply to eligibility requirements; but to therapy and evaluations post consent and post the start of protocol directed care.

### 7.1 End of Therapy & Follow-up

STUDIES TO BE OBTAINED	End of Therapy
History	X
Physical exam with VS	X
Ht, Wt, BSA	X
Performance status	X
Pregnancy test	X
CBC, differential, platelets	X
Electrolytes including Ca <sup>++</sup> , PO <sub>4</sub> , Mg <sup>++</sup>	X
Creatinine, SGPT, total bilirubin	X
Tumor disease evaluation	X

See COG Late Effects Guidelines for recommended post treatment follow-up:

<http://www.survivorshipguidelines.org/>

**Note:** Follow-up data must be submitted in accordance with the Case Report Forms (CRFs) schedule.

### 7.2 Correlative Biology Studies

#### 7.2.1 Pharmacokinetics

**Currently PK is optional for all patients.**

Pharmacokinetics was required for the first 6 patients enrolled at COG Consortium (Phase 1) sites.

#### 7.2.1.1 **Description of Studies and Assay**

Peripheral blood samples will be collected for the purpose of determining 1) IMGN901 conjugate, 2) total antibody which measures the concentration of both free huN901 antibody and conjugated antibody, 3) free DM1 maytansinoid, and 4) immunogenicity (ADA). Concentrations of IMGN901 conjugate, total antibody, and ADA will be measured using validated ELISA assays. Free DM1 maytansinoid will be measured using a validated LC/MS/MS assay.

#### 7.2.1.2 **Sample Collection and Schedule**

Peripheral blood samples for IMG901 conjugate, total antibody, and ADA measurements will be collected in red top vacutainer tubes. Blood samples for free DM1 maytansinoid will be collected in vacutainer tubes containing heparin (green top) or EDTA (lavender top) and chemical additives to maintain DM1 maytansinoid stability. All samples should be drawn from a site distant from the infusion. The exact time that the sample is drawn along with the exact time that the drug is administered is to be recorded on the Pharmacokinetic Transmittal form in Rave.

Peripheral blood samples will be collected at the following time points during Cycle 1:

- **Day 1:** Pretreatment, end of infusion, and 2 hrs, 6 hrs, 24 hrs, and 72-120 hrs after the end of the infusion.
- **Day 8:** Pretreatment, end of infusion, and 2 hrs and 6 hrs after the end of the infusion.

#### 7.2.1.3 Sample Processing

IMG901 conjugate, total antibody, and ADA:

- a. Draw 3 mL of blood in red top or tiger top vacuum tube (no anticoagulant) at each indicated time point.
- b. Allow the tubes to remain at room temperature for 30 to 60 minutes to clot.
- c. Centrifuge tubes at 1500 RPM for 15 minutes at room temperature.
- d. Transfer serum to a separate tube and store in a -70°C freezer.

Free DM1 maytansinoid:

- a. Draw 3 mL of blood in chilled vacutainer tubes containing heparin (green top) or EDTA (lavender top) and chemical additives at each indicated time point.
- b. Invert tube 8-12 times and place in an ice water bath.
- c. Centrifuge at 2,000 rpm for 10 min in a refrigerated centrifuge set at 4°C.
- d. Following centrifugation, transfer plasma to a separate tube and store in a -70°C freezer (within 30 minutes of collection).

#### 7.2.1.4 Sample Shipping:

1. Day 1 and Day 8 PK samples should be batched, maintained at -70°C until shipment, and shipped together for each patient at the end of Cycle 1. Include a printed copy of the completed Pharmacokinetic Transmittal form (in Rave).
2. Place samples in a cryobox. Ensure the cryobox is closed and remains so in transit using shipping tape. Place the cryobox in a shipping container with sufficient dry ice to maintain samples at -20°C for at least 72 hours.
3. Each shipment should be prepared in accordance with IATA regulations.

4. Frozen samples should be shipped via **overnight FedEx, Monday through Wednesday. No shipments should be made later than Wednesday of any given week.**
5. **On the day of shipment:** Email a copy of the completed Pharmacokinetic Transmittal form (in Rave) and the tracking number to **Dr. Joel Reid** (reid.joel@mayo.edu) and copy the **ADV1522 COG Study Assigned Research Coordinator** on the email.
6. Ship the PK samples to the following address

Attention: **Dr. Joel M. Reid**  
Department of Oncology  
Mayo Clinic  
Room 19-151, Gonda Building  
200 First Street SW  
Rochester, MN 55905.  
Phone (507) 284-0822  
Fax (507) 284-3906  
Email: reid.joel@mayo.edu

#### 7.2.2 Peripheral Blood Cells CD56

**Peripheral blood cells CD56 count analyses will be performed for all patients participating in the optional pharmacokinetic studies.**

##### 7.2.2.1 **Summary of CD56 absolute count in whole blood:**

CD56-positive cells in peripheral blood will be measured using a MiltenyiMACSQuant 10 flow cytometer (MiltenyiBiotec) and a lyse-no-wash staining technique. The MACSQuant Instrument employs a volumetric sample uptake system, which allows for direct determination of an absolute cell count of the sample. Fifty microliters ( $\mu\text{L}$ ) of EDTA blood will be labeled with 10  $\mu\text{L}$  of anti-CD56 APC and 15  $\mu\text{L}$  of anti-CD45 FITC antibodies (BD Biosciences). The addition of CD45, a pan-leukocyte marker, allows for separation of debris and red blood cells from the leukocytes, and makes gating on the lymphocyte population more accurate. The blood is incubated with the antibodies and lysed with 925  $\mu\text{L}$  of FACSLyse red blood cell lysis solution. The sample is then analyzed on the MACSQuant flow cytometer using a program that yields both the percent of CD56-positive cells and the absolute number of positive cells per milliliter and per microliter.

##### 7.2.2.2 **Sample collection and Schedule:**

Peripheral blood samples are collected in an EDTA tube on Day 1 and Day 8 of Cycle 1 prior to (within 12 hours of starting) IMG901 administration. Minimum volume 1 mL. All samples should be drawn from a site distant from the infusion.

### 7.2.2.3 Sample Shipping

- a. Ship whole blood at room temperature along with a printed copy of completed Study Specimen Transmittal-Peripheral Blood CD56 form (in Rave). Note that extreme temperatures (hot or cold) can adversely affect shipped blood specimens. In winter when shipping temperatures can be far below freezing, it is best to ship with a warm pack or room-temperature cold packs in a well-insulated, double box (Styrofoam interior box/cardboard exterior box).
- b. Specimens may be shipped **Monday through Thursday** to be received Tuesday through Friday.  
Ship using FedEx First Overnight delivery. Specimen must be received in the laboratory within 24 hours of collection. We cannot accept deliveries on Saturdays or Sundays.
- c. **Shipping address**  
**Ship FedEx First Overnight to:**  
Attn: Sue Vergamini  
CCHMC-Julie Beach  
DIL- Room R2328  
3333 Burnet Ave.  
Cincinnati, Ohio, 45229-3039
- d. **Contact person:**  
Sue Vergamini  
Phone: 513) 636-6903  
Email: sue.vergamini@cchmc.org

### 7.2.3 Tumor CD56 Expression (required)

CD56 expression will be assessed using standard immunohistochemistry. CD56 antibody, clone 123C3 from Ventana will be used. The procedure will be a fully automated immunohistochemical staining, performed at a Ventana Benchmark Ultra staining system and following a protocol clinically validated at Lurie Children's Hospital (Chicago).

Tumor cells will be recorded as either negative or positive. Only membranous expression will be considered. Positive staining will be interpreted qualitatively as the presence of coarse granular staining of the cell membrane in a circumferential pattern.

Scoring: 0-3+ according to percentage of positive cells (as defined above)

0-10% positive cells: 0

10-25% positive cells: 1+

25-50% positive cells: 2+

> 50% positive cells: 3+

Controls:

- 3+ blastemal Wilms tumor as positive control
- Patient's tumor sample not treated with CD56 antibody as negative control.

- 7.2.3.1 **Sample Collection**  
5 unstained slides of pre-treated tumor should be prepared on positively charged (“plus”) slides for immunohistochemistry.
- 7.2.3.2 **Sample Shipping**  
Slides should be shipped by regular mail in protective slide mailers along with a printed copy of the completed Specimen Transmittal-Unstained Tumor CD56 form (in Rave).
- 7.2.3.3 **Shipping address**  
See the Correlative Studies Shipment sheet on the ADVL1522 protocol web page for shipping account numbers.
- Ship Slides to:**  
Mariana Cajaiba, MD  
Department of Pathology  
Ann and Robert H Lurie Children’s Hospital of Chicago  
225 East Chicago Avenue – Room 08-413  
Chicago, IL 60611
- 7.2.3.4 **Contact**  
Please contact Dr. Mariana Cajaiba at (312) 227-3963 or email [mcajaiba@luriechildrens.org](mailto:mcajaiba@luriechildrens.org) for questions.

### 7.3 **Central Review**

The pertinent imaging studies (CT, MRI—and MIBG for neuroblastoma patients with <sup>123</sup>I-MIBG positive lesions at start of therapy) of those patients who respond to therapy or have long term stable disease on protocol therapy will be centrally reviewed. COG Operations Center will notify the Imaging Research Center of any patient requiring central review. The Imaging Research Center will then request that the treating institution forward the requested images for central review. The central image evaluation results will be entered into Rave for review by the COG Operations Center and for data analysis.

The images are to be forwarded electronically to the Imaging Research Center at Children’s Hospital Los Angeles via the ImageInBox.

COG institutions that are not connected to the Imaging Research Center via the ImageInBox can send the images on CD ROM, DVD or USB flash drive for central review. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADV L1522) and date, and shipped to Syed Aamer at the address below:

Syed Aamer, MBBS, CCRP  
Administrator, Imaging Research Center  
Children’s Hospital Los Angeles  
4650 Sunset Boulevard, MS # 81  
Los Angeles, CA 90027  
Phone: (323) 361-3898  
Fax: (323) 361-3054  
Email: [saamer@chla.usc.edu](mailto:saamer@chla.usc.edu)

## 8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

### 8.1 Criteria for Removal from Protocol Therapy

- a) Relapse/progressive disease.
- b) Adverse Events requiring removal from protocol therapy, as stated in [Section 5.0](#).
- c) Patients who receive concurrent anticancer or investigational therapy, as stated in [Section 4.1.5](#).
- d) Refusal of further protocol therapy by patient/parent/guardian.
- e) Completion of planned protocol therapy.
- f) Physician determines it is in patient's best interest.
- g) Repeat eligibility studies (if required) are outside the parameters required for eligibility.
- h) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
- i) Patients who develop a second malignant neoplasm.
- j) Pregnancy.
- k) Breastfeeding.

Patients who are removed from protocol therapy (except for 8.1.g) are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

### 8.2 Off Study Criteria

- a) Death.
- b) Lost to follow-up.
- c) Entry into another COG study with tumor therapeutic intent (e.g., at recurrence).
- d) Patient did not receive protocol treatment after study enrollment.
- e) Withdrawal of consent for any further data submission.
- f) The fifth anniversary of study entry.

## 9.0 STATISTICAL CONSIDERATIONS

### 9.1 Sample Size and Study Duration

#### 9.1.1 Patient Accrual and Expected Duration of the Study:

Three disease strata have been identified for reporting upon completion of evaluation of the particular disease stratum ('primary disease groups'). These disease strata are: (1) Wilms; (2) rhabdomyosarcoma; and (3) neuroblastoma. The evaluation rule is described in [Section 9.2](#) below.

In addition to the three main strata, enrollment into each of the following tumor groups ('secondary strata'): (4) pleuropulmonary blastoma, (5) malignant peripheral nerve sheath tumor, and (6) synovial sarcoma; will be open to accrual.

When the evaluation of the three primary disease groups is complete, enrollment to the study will be terminated unless the DVL committee leadership indicates further enrollment on the secondary strata is warranted.

If two of the three primary disease strata (Wilms, rhabdomyosarcoma, and neuroblastoma) have met their accrual and one remains open, the Cancer Therapy Evaluation Program (CTEP) and the ADVL1522 Investigators will discuss the study timeline.

Based on the enrollment rates prior to activation of Amendment #1, the following entry rates for the various tumors under study can be expected:

<u>Disease Group/Strata</u>	<u>Patients/Year</u>
1) Wilms tumor	18
2) Rhabdomyosarcoma	14
3) Neuroblastoma	9

For Wilms: 10 patients enrolled prior to activation of Amendment #1. Accrual of an additional 6 patients is expected to take approximately 4 months.

For rhabdomyosarcoma: 8 patients enrolled prior to activation of Amendment #1. Accrual of an additional 8 patients is expected to take approximately 7 months.

For neuroblastoma: 5 patients enrolled prior to activation of Amendment #1. Accrual of an additional 11 patients is expected to take approximately 14.5 months.

Allowing for roughly a 15% rate of ineligible/inevaluable patients, each stratum could need to enroll up to 19 patients to allow for 16 evaluable patients.

The study will likely require 2 to 3 years for sufficient patient enrollments to evaluate IMG901 in the three primary disease groups. If activity is detected in any category, further trials in subcategories of that category may be conducted at the discretion of the Developmental Therapeutics Steering and study committees. A maximum of 114 patients is anticipated.

### 9.2 Definition of Recommended Phase 2 Dose (RP2D)/ Tolerable Dose

The initial MTD defined in the adult trial is 112 mg/m<sup>2</sup>/dose, approximated herein as dose

level 1 at 110 mg/m<sup>2</sup>/dose. If there are < 2 DLTs in the first 6 patients treated at dose level 1 during the first cycle of therapy, this will be considered the RP2D and all subsequent patients will be enrolled at this dose level. If the MTD has been exceeded at Dose Level 1 as noted from the first six patients enrolled ( $\geq 2$  DLTs at least possibly attributed to IMG901), then the subsequent patients will be treated at Dose Level -1. If there are < 2 DLTs in the first 6 patients treated at dose level -1, this will be considered the RP2D and all subsequent patients will be enrolled at this dose level. A dose level -2 has been included in the proposal for purposes of providing a dose for those patients potentially accrued at dose level -1 (in the event it becomes the RP2D) and then subsequently requiring a dose reduction due to toxicity.

**Delayed Toxicity Monitoring:** We will monitor all serious adverse events on an ongoing basis. Analyses will be incorporated to screen for excess delayed peripheral neuropathy specifically.

A patient will be considered for toxicity monitoring if the patient is eligible and one of the following occurs: (1) completes one cycle of protocol therapy; (2) dies on protocol therapy for a reason considered possibly, probably, or likely related to protocol therapy; or (3) is removed from protocol therapy because of an adverse experience possibly, probably, or likely related to one of the agents. A toxicity-evaluable patient will be considered in the analysis during the interval from study enrollment until protocol therapy is terminated or, a toxicity-event is observed, whichever occurs first. A toxicity-evaluable patient will be considered to have experienced an excessive toxicity event if: (1) the patient dies on protocol therapy for a reason considered possibly, probably, or likely related to protocol therapy; or (2) experiences a dose-limiting toxicity.

The analytic unit for monitoring for excessive toxicity will be the patient-cycle: Each cycle where an excessive toxicity event is observed or where the patient receives the agent and completes the full cycle of treatment will be considered in the analysis. If there is overwhelming evidence that the dose selected for this trial has a per-cycle-excessive peripheral neuropathy (Grade 3 or higher) probability of more than 1/3, such information will be presented to the DSMB and consideration will be given to modifying any defined RP2D to one dose level lower.

We will use a Bayesian rule to monitor for excessive peripheral neuropathy.<sup>32,33</sup> We will assume a beta prior distribution with  $\alpha = 0.6$  and  $\beta = 1.2$ . At least once per month, we will calculate the posterior probability (given the data) that the probability of Grade 3 or higher peripheral neuropathy (“Excessive PN”) exceeds the 1/3 threshold:

$$P(p_{\text{Excessive PN}} > 1/3 | \text{Data}) = \int_{1/3}^1 \frac{\binom{n}{x} p^x (1-p)^{n-x} \frac{\Gamma(1.8)}{\Gamma(0.6)\Gamma(1.2)} p^{-0.4} (1-p)^{0.2}}{\int_0^1 \binom{n}{x} q^x (1-q)^{n-x} \frac{\Gamma(1.8)}{\Gamma(0.6)\Gamma(1.2)} q^{-0.4} (1-q)^{0.2} dq} dp$$

where n is the number of excessive-PN-evaluable cycles and x is the number of such cycles on which an excessive PN event is observed. If this posterior probability exceeds 80%, such information will be presented to the DSMB and consideration will be given to modifying any defined RP2D to one dose level lower. Examples of situations in which this rule will indicate excessive toxicity have been noted and are presented below:

Number of Excessive PN-Evaluable Cycles	Number of Cycles with Excessive PN Observed	$P(p_{\text{Excessive PN}} > 1/3 \mid \text{Data})$
5	3	0.848
10	5	0.834
15	7	0.837
20	9	0.843
25	11	0.852
30	13	0.860
35	15	0.869
40	17	0.876

### 9.3 Study Design

This trial is a multi-strata Phase 2 study of IMG901. The primary endpoint will be objective response by RECIST criteria. As of Amendment #1, each stratum will accrue a maximum of 16 evaluable patients. IMG901 will be identified as having sufficient activity for further study in a particular stratum if there are at least 4 responses (PR or CR) confirmed by central review. This design will be used for all strata which have not been closed prior to the activation of Amendment #1.

We will consider the agent not of sufficient interest for further evaluation in a disease category if the true response rate is 15%. ( $H_0$  is a true response rate of 15%.)  $H_a$  is a true response rate of 40%. Each stratum will accrue 16 evaluable patients. Thus, there will be a maximum of 96 evaluable patients. If the agent has a true response rate of 15%, the rule described herein will identify the agent of sufficient activity for further study with probability 0.079 (Type I error). If the agent has a true response rate of 40%, the rule described herein will identify the agent of sufficient activity for further study with probability 0.833 (power against the alternative hypothesis  $p = 0.40$ ). In addition to making the decision to accept or reject the drug, the final results will be reported after all patients have been identified as having a CR, PR, or PD as their response according to protocol-specified criteria.

Prior to Amendment #1, the trial used a Simon two-stage optimal design in each stratum. The best response of disease was examined separately in each stratum. Within each stratum, the following two-stage design for 15% response rate vs. 40% response rate with  $\alpha = \beta = 0.10$  was employed:

	Cumulative Number of Responses at the End of the Stage	Decision
Stage 1: Enter 10 evaluable patients	0 or 1 2 or more	Terminate the trial for this stratum because the agent is ineffective. Proceed to Stage 2.
Stage 2: Enter 12 additional evaluable patients	5 or fewer 6 or more	Terminate the trial for this stratum because the agent is ineffective. Terminate the trial for this stratum because the agent is effective.

A comparison of the operating characteristics of the single stage and two-stage designs

appears below.

True response rate	Simon's optimal design (10 + 12 [2,6])			Single- stage design (16[4])
	Probability of stopping early for lack of activity	Probability of identifying agent as effective	Expected number of patients accrued	Probability of identifying agent as effective
5%	0.914	0.001	11.03	0.001
10%	0.736	0.016	13.17	0.017
15%	0.544	0.091	15.47	0.079
20%	0.376	0.246	17.49	0.202
25%	0.244	0.451	19.07	0.370
30%	0.149	0.650	20.21	0.550
35%	0.086	0.804	20.97	0.711
40%	0.046	0.903	21.44	0.833
45%	0.023	0.957	21.72	0.915
50%	0.011	0.983	21.87	0.962

#### 9.4 Methods of Analysis

Response criteria are described in [Section 10.0](#). A responder is defined as a patient who achieves a best response (as defined in [Section 10.6](#)) of PR or CR on the study. Response rates will be calculated as the percent of evaluable patients who are responders, and Clopper-Pearson confidence intervals will be constructed.

Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. A patient will be counted only once per cycle for a given toxicity for the worst grade of that toxicity reported for that patient. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen.

#### 9.5 Evaluability for Response

Any eligible patient who receives at least one dose of IMG901 will be considered evaluable for response with the following exception: if a patient receives non-protocol anti-cancer therapy (including surgery) during the response evaluation period after the patient is considered as having a partial or complete response but prior to confirmation of this status by tumor imaging and before progressive disease is noted, the individual will be considered inevaluable for the response endpoint. Further, patients who stop IMG901 after the first evaluation because of toxicities or death will be considered evaluable for the response evaluation and will be counted as non-responders for the response endpoint. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule given in [Section 9.2](#). The evaluation period for determination of the best response will be 6 treatment cycles. All other patients will be considered non-responders. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. See [Section 7.3](#) regarding shipping instructions. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

### 9.6 Evaluability for Toxicity

All patients who receive at least one dose of IMG901 according to protocol guidelines and either 1) experience a toxicity, or 2) complete the first cycle with no toxicity, will be considered in the evaluation of toxicity.

### 9.7 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Racial category	Ethnicity				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	1	4	0	0	5
Black or African American	14	6	0	0	20
White	38	27	8	16	89
More than one race	0	0	0	0	0
<b>Total</b>	53	37	8	16	114

This distribution was derived from the demographic data for patients enrolled on recent COG Phase 2 trials ADVL0821 and ADVL0921 with diagnoses among the primary disease groups.

### 9.8 Analysis of the Pharmacokinetic Parameters

A descriptive analysis of pharmacokinetic (PK) parameters of IMG901 will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

### 9.9 Analysis of Biological and Correlative Endpoints

#### CD56 Expression

The association between CD56+ expression and response will be evaluated using the exact conditional test of proportions (Fisher's Exact Test).

#### Pharmacokinetics

A descriptive analysis of pharmacokinetic (PK) parameters of IMG901 will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

All these analyses will be descriptive and exploratory and hypotheses generating in nature.

## 10.0 EVALUATION CRITERIA

### 10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. The descriptions and grading scales found in the revised CTCAE version 4.0 will be utilized for reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0, which can be downloaded from the CTEP web site ([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)). Additionally, toxicities are to be reported on the appropriate case report forms.

### 10.2 Response Criteria

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor and measurable disease ([Section 10.3](#)); b) neuroblastoma with MIBG positive lesions ([Section 10.4](#)); c) neuroblastoma with bone marrow involvement ([Section 10.5](#)); Note: Neuroblastoma patients who do not have MIBG positive lesions or bone marrow involvement should be assessed for response as solid tumor patients with measurable or evaluable disease.

### 10.3 Response Criteria for Patients with Solid Tumors (non-CNS)

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1.)<sup>34</sup> Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v 1.1 criteria.

#### 10.3.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm (CT scan slice thickness no greater than 5 mm). The investigator will identify up to 5 measurable lesions to be followed for response. Previously irradiated lesions must demonstrate clear evidence of progression to be considered measurable.

Serial measurements of lesions are to be done with appropriate imaging modalities, e.g., CT or MRI. Bone scans cannot be used to measure lesions. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

#### 10.3.2 Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

#### 10.3.3 End-of-Cycle Response

Note: Please also see Table 1 in [Section 10.6](#).

##### a) Complete Response (CR)

Disappearance of all target and non-target lesions. Normalization of urinary catecholamines (for patients with neuroblastoma), immunocytologic findings, or other tumor markers if abnormal or elevated at study enrollment.

b) Partial Response (PR)

At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment. No new lesions or progression of any non-target measurable lesion.

c) Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

d) Progressive Disease (PD)

At least a 20% increase in the sum of the disease measurements for measurable lesions, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions.

10.3.4 Overall Best Response Assessment

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described in [Section 10.6 \(Tables 1-3\)](#).

10.4 **Response Criteria for Neuroblastoma Patients with <sup>123</sup>I-MIBG Positive Lesions**10.4.1 MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of <sup>123</sup>I for MIBG imaging is recommended for all scans. If this isotope is unavailable at the treating institution, the use of the same radioisotope for all MIBG scans for an individual patient is strongly encouraged.

10.4.2 The following criteria will be used to report MIBG response by the treating institution:

- **Complete Response:** Complete resolution of all MIBG positive lesions
- **Partial Response:** Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions.
- **Stable Disease:** No change in MIBG scan in number of positive lesions (includes patients who have same number of positive lesions but decreased density).
- **Progressive Disease:** Development of new MIBG positive lesions.

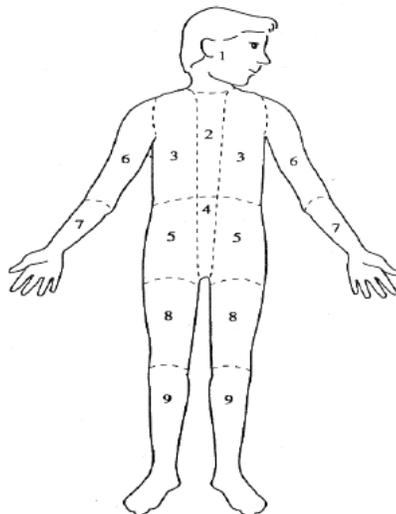
10.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale as outlined below. Central review responses will be used to assess efficacy for study endpoint. See [Section 7.3](#) for details on transferring images to the Imaging Research Center.

NOTE: This scoring is NOT required to be done by the treating institution for end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10<sup>th</sup> general sector allocated for any extra-osseous lesion visible on MIBG scan. In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

- 0 = no site per segment,
- 1 = 1 site per segment,
- 2 = more than one site per segment,
- 3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 3 weeks apart to be considered a **Complete Response**.
2. **Partial response:** Relative score  $\leq 0.2$  (lesions almost disappeared) to  $\leq 0.5$  (lesions strongly reduced).
3. **Stable disease:** Relative score  $> 0.5$  (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease:** New lesions on MIBG scan

#### 10.4.4 Overall Best Response Assessment

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes described in Table 3 in [Section 10.6](#).

#### 10.4.5 Response Criteria for Patients Enrolled with Evaluable Disease on Bone Scan

Patients who have a positive bone scan at the start of therapy will be evaluable for bone scan response. NOTE: Bone Scans are not required imaging tests on this study. However, if a bone scan is performed at baseline and on subsequent evaluations, the following criteria will be used for assessment of response.

Bone scan response is defined as:

- Complete Response (CR): all areas of uptake on bone scan are completely resolved and no new lesions have occurred.
- Progressive Disease (PD): new lesions on bone scan.
- Non-CR, Non-PD: neither complete response, nor progressive disease.

## 10.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

### 10.5.1 Bone Marrow Involvement

**Note:** patients with bone marrow as the ONLY site of disease are not eligible for this study. Response criteria in this section are intended to be used when assessing marrow involvement as a component of overall response.

Histologic analysis at the local institution of marrow tumor cell involvement is **required** for patients with a history of marrow involvement. Marrow aspirate and biopsy should be evaluated at baseline and every 2 cycles thereafter. Note: If progressive disease is documented by RECIST criteria using tumor measurements or by MIBG scan, then a repeat BM is not needed to confirm PD.

- Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 3 weeks apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.
- Progressive Disease:
  - Patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to  $\geq 25\%$  tumor to have progressive disease; a patient entering with 30% tumor must increase to  $> 60\%$ ).
  - Patients who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 3 weeks apart or the treating physician determines that a single positive bone marrow indicates clinical progression of disease.
- Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

### 10.5.2 Overall Best Response Assessment

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described in [Section 10.6](#).

## 10.6 Best Response (Solid Tumors)

Two objective status determinations of disease status, by CT or MRI, obtained on two consecutive determinations, separated by at least a 3 week time period, are required to determine the patient’s overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify

for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

Table 1: Sequences of objective statuses with corresponding best response.

<b>1<sup>st</sup> Status</b>	<b>2<sup>nd</sup> Status</b>	<b>3<sup>rd</sup> Status</b>	<b>Best Response</b>
Progression			Progressive disease
Stable, PR, CR	Progression		Progressive disease
Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable
Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

Table 2: Overall Response for Patients with Neuroblastoma and Measurable Disease

<b>CT or MRI</b>	<b>MIBG</b>	<b>Bone Scan</b>	<b>Bone Marrow</b>	<b>Catechol</b>	<b>Overall</b>
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

Table 3: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only

Since patients in Stratum 3 may be enrolled without disease measurable by CT or MRI, any new or newly identified lesion by CT or MRI that occurs during therapy would be considered progressive disease.

<b>MIBG</b>	<b>CT or MRI</b>	<b>Bone Scan</b>	<b>Bone Marrow</b>	<b>Catechol</b>	<b>Overall</b>
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-CR, Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-CR, Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-CR, Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

## 11.0 ADVERSE EVENT REPORTING REQUIREMENTS

### 11.1 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. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

### 11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (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 is used in combination with a commercial agent, 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 and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events that occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

### 11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERSCTEP-AERS).

***Any AE that is serious qualifies for expedited reporting.*** An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

- 1) Death.
- 2) A life-threatening adverse drug experience.
- 3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for  $\geq 24$  hours). This does not include hospitalizations that are part of routine medical practice.
- 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 a serious adverse drug experience 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.

#### 11.4 Specific Examples for Expedited Reporting

##### 11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

##### 11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI, COG, or industry sponsor IND/IDE since these are considered to be serious AEs.

##### 11.4.3 Death

###### **Reportable Categories of Death**

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with grade 5.
- Death due to progressive disease should be reported as **Grade 5 “Disease progression”** under the system organ class (SOC) of “General disorder and administration site conditions”. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring **within 30 days** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring **greater than 30 days** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

#### 11.4.4 Secondary Malignancy

A **secondary malignancy** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

#### 11.4.5 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 **ONLY** routine reporting via CDUS unless otherwise specified.

#### 11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for “Pregnancy”, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form, available at [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/PregnancyReportForm.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf), needs to be completed and faxed along 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.

##### 11.4.6.1 Pregnancy

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy 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.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

##### 11.4.6.2 Pregnancy Loss (Fetal Death)

Pregnancy loss is defined in CTCAE as “Death in utero.”

Any pregnancy loss should be reported expeditiously as **Grade 4 “Pregnancy loss”** under the **“Pregnancy, puerperium and perinatal condition” SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

#### 11.4.6.3 Death Neonatal

Neonatal death, defined in CTCAE as **“Newborn deaths occurring during the first 28 after birth”** 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 “Death neonatal” under the **“General disorders and administration” SOC when the death is the result of a patient pregnancy or pregnancy in partners of men on study.**

Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

### 11.5 Reporting Requirements for Specialized AEs

#### 11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as “Course Zero” using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

- a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
- b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
- c. No modification in grading is to be made to account for abnormalities existing at baseline.

#### 11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

#### 11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

- 1) The grade increases OR
- 2) Hospitalization is associated with the recurring AE.

## 11.6 Exceptions to Expedited Reporting

### 11.6.1 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

## 11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

## 11.8 General Instructions for Expedited Reporting via CTEP-AERS

**The reporting methods described below are specific for clinical trials evaluating agents for which the IND is held by COG, an investigator, or a pharmaceutical company. It is important to note that these procedures differ slightly from those used for reporting AEs for clinical trials for which CTEP holds the IND.**

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting and are located on the CTEP website at:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTCAE.

An expedited AE report must be submitted electronically via CTEP-AERS at:

<https://eapps-ctep.nci.nih.gov/ctepaers>

- 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 event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days** - A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention requires expedited reporting **within 24 hours** via e-mail to the COG CTEP-AERS Coordinator and Study Chair.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention requires expedited reporting **within 24 hours** via e-mail to the COG CTEP-AERS Coordinator and Study Chair.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Fax or email supporting documentation **for AEs related to investigational agents** to COG: Fax #310-640-9193; email: [COGAERS@childrensoncologygroup.org](mailto:COGAERS@childrensoncologygroup.org); Attention: COG AERS Coordinator.

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

Copies of all Adverse Event reports submitted to the FDA should be forwarded electronically to [CTEPSupportAE@tech-res.com](mailto:CTEPSupportAE@tech-res.com).

**11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A**

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention <sup>1</sup>

<p><b>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)</b>  <b>NOTE:</b> Investigators <b>MUST</b> immediately report to the sponsor (COG) <b>ANY</b> 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 <b>ANY</b> of the following outcomes:  1) Death.  2) A life-threatening adverse event.  3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for <math>\geq 24</math> hours. This does not include hospitalizations that are part of routine medical practice.  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.)</p>				
<p><b>ALL SERIOUS</b> adverse events that meet the above criteria <b>MUST</b> be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.</p>				
<b>Hospitalization</b>	<b>Grade 1 Timeframes</b>	<b>Grade 2 Timeframes</b>	<b>Grade 3 Timeframes</b>	<b>Grade 4 &amp; 5 Timeframes</b>
<b>Resulting in Hospitalization <math>\geq 24</math> hrs</b>	<b>7 Calendar Days</b>			<b>24-Hour Notification 5 Calendar Days</b>
<b>Not resulting in Hospitalization <math>\geq 24</math> hrs</b>	<b>Not Required</b>		<b>7 Calendar Days</b>	
<p><b>NOTE:</b> Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.  <b>Expedited AE reporting timelines are defined as:</b>  “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 notification.  “7 Calendar Days” – A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.</p>				
<p><sup>1</sup>SAEs 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:  <b>Expedited 24-hour notification followed by complete report within 5 calendar days for:</b></p> <ul style="list-style-type: none"> <li>• All Grade 4, and Grade 5 AEs</li> </ul> <p><b>Expedited 7 calendar day reports for:</b></p> <ul style="list-style-type: none"> <li>• Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization</li> <li>• Grade 3 adverse events</li> </ul>				

**11.10 Protocol Specific Additional Instructions and Reporting Exceptions**

- **Grades 1-4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not require expedited reporting.**
- **Grades 1-2 AST/ALT elevations do not require expedited reporting.**

**11.11 Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway**

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study. Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

**Table B**

**Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.**

**CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days<sup>1</sup>**

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

<sup>1</sup>This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

**11.12 Routine Reporting of Adverse Events**

**Note:** The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and Grade 3 and higher Adverse Events.

## 12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG website with each protocol under “Data Collection/Specimens”. A submission schedule is included.

### 12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

### 12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children’s Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair’s report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

### 12.3 CRADA/CTA

***NCI/DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA), a Cooperative Research and Development Agreement (CRADA) or a Clinical Supply Agreement, hereinafter referred to as Collaborative Agreement:***

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” ([http://ctep.cancer.gov/industryCollaborations2/intellectual\\_property.htm](http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm)) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the

permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
  - a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
  - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
  - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator ([http://ctep.cancer.gov/industryCollaborations2/intellectual\\_property.htm](http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm)). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for

publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: [ncicteppubs@mail.nih.gov](mailto:ncicteppubs@mail.nih.gov)

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

**APPENDIX I: YOUTH INFORMATION SHEETS****INFORMATION SHEET REGARDING RESEARCH STUDY ADV1522  
(for children from 7 through 12 years of age)**

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**A study of the drug IMG901 in children  
with a cancer that has come back after treatment or is difficult to treat**

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.
2. We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have. We will do this by trying a new medicine to treat your cancer.
3. Children who are part of this study will be treated with a cancer-fighting medicine called IMG901. You will also have regular tests and exams done more often while you are in this study. The doctors want to see if IMG901 will make children with your type of cancer get better. We don't know if IMG901 will work well to get rid of your cancer. That is why we are doing this study.
4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that IMG901 may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.
5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from IMG901 than other treatments. Other things may happen to you that we don't yet know about.
6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.
7. As part of your regular care, your doctor may have removed some tissue to see if you have cancer. If you take part in this study, we will keep some of the tissue that is left over to do special tests. These tests may help us learn more about how IMG901 works.

**INFORMATION SHEET REGARDING RESEARCH STUDY ADV L1522  
(for teens from 13 through 17 years of age)**

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**A study of the drug IMG N901 in children  
with a cancer that has come back after treatment or is difficult to treat**

1. We have been talking with you about your cancer. You have been diagnosed with one of the following types of cancer: Wilms tumor, Rhabdomyosarcoma, Neuroblastoma, Pleuropulmonary blastoma, Malignant peripheral nerve sheath tumor, or Synovial sarcoma. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.
2. We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have.
3. Children and teens who are part of this study will be given a cancer-fighting medicine called IMG N901. IMG N901 is a drug made of an antibody attached to an anti-cancer drug. An antibody is a protein used by the body's immune system to fight foreign or diseased cells. The antibody used in IMG N901 attaches to cancer cells that have a protein called CD56. Then the anti-cancer drug causes these cancer cells to die. We are using IMG N901 in this study because it seems to work against certain types of cancer cells in test tubes and animals. IMG N901 is considered experimental because the Food and Drug Administration (FDA) has not approved this drug. The dose of IMG N901 used in this study was found to be well-tolerated in adults.
4. You will get IMG N901 by vein on Days 1 and 8 of a 21-day period. This entire 21-day period is called a cycle. You may continue to receive IMG N901 for up to about 12 months (up to 17 cycles) as long as you do not have bad effects from it and your cancer does not get any worse. You will also have exams and tests done that are part of normal cancer care. But, the exams and tests will be done more often while you are being treated with IMG N901. The doctors want to see if IMG N901 will make children with your type of cancer get better. We don't know if IMG N901 is better than other medicines. That is why we are doing this study.
5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that IMG N901 may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.
6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from IMG N901 than other treatments. Other things may happen to you that we don't yet know about.
7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.
8. As part of your regular care, your doctor may have removed some tissue to see if you have cancer. If you take part in this study, we will keep some of the tissue that is left over to do special research tests. These tests may help us learn more about how IMG N901 works. The samples will come from leftover tissue so there would be no extra procedures.

**APPENDIX II: Possible Drug Interactions**

*The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.*

**Dexamethasone**

<b>Drugs that may interact with dexamethasone</b>
<ul style="list-style-type: none"> <li>• Antibiotics               <ul style="list-style-type: none"> <li>○ Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin</li> </ul> </li> <li>• Antidepressants and antipsychotics               <ul style="list-style-type: none"> <li>○ Aripiprazole, bupropion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine</li> </ul> </li> <li>• Antifungals               <ul style="list-style-type: none"> <li>○ Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole</li> </ul> </li> <li>• Arthritis medications               <ul style="list-style-type: none"> <li>○ Leflunomide, tofacitinib</li> </ul> </li> <li>• Anti-rejection medications               <ul style="list-style-type: none"> <li>○ Cyclosporine, sirolimus, tacrolimus</li> </ul> </li> <li>• Antiretrovirals and antivirals               <ul style="list-style-type: none"> <li>○ Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir</li> </ul> </li> <li>• Anti-seizure medications               <ul style="list-style-type: none"> <li>○ Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone</li> </ul> </li> <li>• Heart medications               <ul style="list-style-type: none"> <li>○ Amiodarone, amlodipine, dronedenarone, verapamil</li> </ul> </li> <li>• Some chemotherapy (be sure to talk to your doctor about this)</li> <li>• Some oral contraceptives or birth control medications</li> <li>• Many other drugs, including the following:               <ul style="list-style-type: none"> <li>○ Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin</li> </ul> </li> </ul>

<b>Food and supplements that may interact with dexamethasone*</b>
<ul style="list-style-type: none"> <li>• Echinacea</li> <li>• St. John's Wort</li> <li>• Grapefruit, grapefruit juice, Seville oranges, star fruit</li> </ul>

*\*Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

## APPENDIX III: CTEP AND CTSU REGISTRATION PROCEDURES

### CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed *Statement of Investigator Form* (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed *Supplemental Investigator Data Form* (IDF)
- a completed *Financial Disclosure Form* (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at [http://ctep.cancer.gov/investigatorResources/investigator\\_registration.htm](http://ctep.cancer.gov/investigatorResources/investigator_registration.htm). For questions, please contact the *CTEP Investigator Registration Help Desk* by email at [pmbregpend@ctep.nci.nih.gov](mailto:pmbregpend@ctep.nci.nih.gov).

### CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at [http://ctep.cancer.gov/branches/pmb/associate\\_registration.htm](http://ctep.cancer.gov/branches/pmb/associate_registration.htm). For questions, please contact the *CTEP Associate Registration Help Desk* by email at [ctepreghelp@ctep.nci.nih.gov](mailto:ctepreghelp@ctep.nci.nih.gov).

### CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

#### **Requirements for ADVL1522 Site Registration:**

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

**Submitting Regulatory Documents:**

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office

1818 Market Street, Suite 1100

Philadelphia, PA 19103

Phone: 1-866-651-2878

Fax: 215-569-0206

E-mail: [CTSURegulatory@ctsu.coccg.org](mailto:CTSURegulatory@ctsu.coccg.org) (for regulatory document submission only)

**Checking Your Site's Registration Status:**

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

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