Activated: January 16, 2018
Closed: April 24, 2020

Version Date: 01/31/2019
Amendment #: 3

CHILDREN'S ONCOLOGY GROUP
ADVL1614

A PHASE 1/2 STUDY OF VX15/2503 [redacted] in Children, Adolescents, or Young Adults with Recurrent or Relapsed Solid Tumors

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

STUDY CHAIR

[redacted]

For PEP-CTN Operations and Data/Statistics Contacts see: http://members.childrensoncologygroup.org

TABLE OF CONTENTS

STUDY COMMITTEE, CONT.

[redacted]

[redacted]

[redacted]

[redacted]

IND Sponsor: COG

For PEP-CTN Operations and Data/Statistics Contacts see: http:members.childrensoncologygroup.org

SEE SECTION 8.3.6, 8.4.6, 8.5.6, 8.6.6, and 8.7.3 FOR SPECIMEN SHIPPING ADDRESSES

This trial is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

ABSTRACT

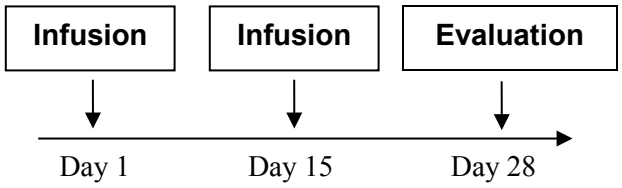
Semaphorins consist of a family of soluble and transmembrane proteins, originally defined as axonal-guidance factors[1]. Binding of Semaphorin 4D (SEMA4D, CD100) to cells expressing the cognate plexin B1/2 receptors can induce cytoskeletal changes in immune, endothelial, and tumors cells and regulate their migration and differentiation within the tumor microenvironment (TME).[2-4] SEMA4D has been shown to regulate leukocyte infiltration into tumors and promote tumor growth. Immunohistochemical analysis of SEMA4D expression on tissues from several human tumor types has shown that SEMA4D is overexpressed in multiple malignancies, including urogenital, ovarian, pancreatic, head and neck, prostate, colon, breast, and lung cancer and correlates with invasive disease and poor prognosis.[5,6,7] Expression of SEMA4D by tumor and cells of the tumor microenvironment, including inflammatory cells and tumor-associated macrophages, may be regulated by hypoxia. Additionally, strong expression of SEMA4D at the invasive margins of actively growing tumors influences distribution of leukocytes in the tumor microenvironment.[8] Investigators have studied the expression of SEMA4D in a variety of soft tissue sarcomas; two separate analyses have shown high level expression to correlate with poor prognosis and overall disease free survival.[6,7] Recently, through a *Sleeping Beauty* forward genetic screen that induced osteosarcoma in mice, analysis of common insertion site-associated genes found SEMA4D to be a strong candidate proto-oncogene. Human osteosarcoma tumors demonstrated up-regulation of SEMA4D compared to normal human osteoblasts. Expression was confirmed in nearly all human osteosarcomas, with high level expression in over half of the tumors.[9] Over-expression of SEMA4D in osteosarcoma cell lines led to activation of MET or ERBB2 and subsequent increased phosphorylation of AKT and/or ERK. In addition, overexpression of SEMA4D resulted in increased colony formation in soft agar and proliferation and xenograft tumor formation in immunodeficient mice. The oncogenic role of SEMA4D in osteosarcoma was further confirmed by shRNA knockdown which resulted in significantly decreased colony formation.[9] VX15/2503 is a humanized IgG4 monoclonal antibody that binds specifically to the SEMA4D (CD100) antigen, blocking the binding of SEMA4D to its high affinity receptor, plexin B1 (PLXNB1), plexin B2 (PLXNB2), and a low-affinity receptor, CD72. It has strong affinity for SEMA4D with an antibody-antigen dissociation constant (K_d) ranging from 1-5 nM.[10] Treatment of osteosarcoma cell lines with VX15/2503 resulted in decreased cell migration and colony formation as compared to controls. Additionally, a syngeneic mouse model of osteosarcoma treated with MAb67-2, a mouse analog of VX15/2503, had

significantly reduced tumor growth compared to controls.[10]

This is a parallel phase 1/2 study of VX15/2503 in children and adolescent/young adults with relapsed or refractory solid tumors and osteosarcoma, respectively. The phase 1 study will employ a rolling six design, whereas the phase 2 study will employ a two-stage design. The aims of the phase 1 study include to determine the maximum tolerated dose or recommended phase 2 dose of VX15/2503 in children, as well as defining the pharmacokinetic and pharmacodynamic activity of VX15/2503 in pediatric malignancies. The aim of the phase 2 study will be to determine the activity of VX15/2503 in treating relapsed or refractory osteosarcoma.

EXPERIMENTAL DESIGN SCHEMA

Part A & B Treatment Schedule Table

Cycles- 28 day duration	Agent
	**VX15/2503 intravenous infusion over 60 minutes**

Treatment will be discontinued if there is evidence of progressive disease or drug-related dose-limiting toxicity that requires removal from therapy. Patients with stable disease or greater response may continue receiving protocol therapy provided that the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy or off study criteria (Section 10.0).

1. GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose of VX15/2503 administered as an intravenous infusion every 14 days to children with recurrent or refractory solid tumors (Part A)

1.1.2 To define and describe the toxicities of VX15/2503 administered on this schedule (Parts A-B)

1.1.3 To characterize the pharmacokinetics of VX15/2503 in children with recurrent or refractory cancer (Parts A-B)

1.1.4 To preliminarily define the antitumor activity of VX15/2503 for the treatment of relapsed or refractory osteosarcoma (Part B)

1.1.5 To determine if VX15/2503 either improves the disease control rate at 4 months in patients with recurrent measurable osteosarcoma or produces an objective response rate in patients with relapsed or refractory osteosarcoma (Part B)

1.2 Secondary Aims

1.2.1 To assess the pharmacodynamics of VX15/2503 through VX15/2503 saturation of T-lymphocytes

1.2.2 To assess the immunogenicity of VX15/2503 in pediatric patients with recurrent or refractory cancer.

1.3 Exploratory Aim

1.3.1 To evaluate potential biomarkers of VX15/2503 sensitivity including SEMA4D, PlexinB1, and other markers of immune cell infiltration in archival tumor tissues.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Semaphorins consist of a family of soluble and transmembrane proteins, originally defined as axonal-guidance factors.[1] Binding of Semaphorin 4D (SEMA4D, CD100) to cells expressing the cognate plexin B1/2 receptors can induce cytoskeletal changes in immune, endothelial, and tumors cells and regulate their migration and differentiation within the tumor microenvironment (TME).[2-4] SEMA4D has been shown to regulate leukocyte infiltration into tumors and promote tumor growth.

Immunohistochemical analysis of SEMA4D expression on tissues from several human tumor types has shown that SEMA4D is overexpressed in multiple malignancies, including urogenital, ovarian, pancreatic, head and neck, prostate, colon, breast, and lung cancer and correlates with invasive disease and poor prognosis.[5,6,7] Expression of SEMA4D by tumor

and cells of the tumor microenvironment, including inflammatory cells and tumor-associated macrophages, may be regulated by hypoxia. Additionally, strong expression of SEMA4D at the invasive margins of actively growing tumors influences distribution of leukocytes in the tumor microenvironment.[8] Investigators have studied the expression of SEMA4D in a variety of soft tissues sarcomas; two separate analyses have shown high level expression to correlate with poor prognosis and overall disease free survival.[6,7]

Recently, through a *Sleeping Beauty* forward genetic screen that induced osteosarcoma in mice, analysis of common insertion site-associated genes found SEMA4D to be a strong candidate proto-oncogene. Human osteosarcoma tumors demonstrated up-regulation of SEMA4D compared to normal human osteoblasts. Expression was confirmed in nearly all human osteosarcomas, with high level expression in over half of the tumors.[9] Over-expression of SEMA4D in osteosarcoma cell lines led to activation of MET or ERBB2 and subsequent increased phosphorylation of AKT and/or ERK. In addition, overexpression of SEMA4D resulted in increased colony formation in soft agar and proliferation and xenograft tumor formation in immunodeficient mice. The oncogenic role of SEMA4D in osteosarcoma was further confirmed by shRNA knockdown which resulted in significantly decreased colony formation.[9]

The role of SEMA4D and potential application of an anti-SEMA4D antibody is likely much broader than osteosarcoma. SEMA4D is expressed on cells within the tumor stroma and modulates the activity of the immune system. Expression of SEMA4D by tumor associated macrophages (TAMs) can be regulated by hypoxia and contribute to aggressive tumor growth. High levels of SEMA4D positively correlate with the presence of immunosuppressive TAMs and myeloid-derived suppressor cells (MDSCs) with concomitant exclusion of activated antigen presenting cells (APCs) and CD8+ cytotoxic T lymphocytes (CTLs) from the tumor. Antibody neutralization of SEMA4D results in a marked redistribution of immune cells at the tumor invasive margins in multiple tumor models. This includes an increased frequency of activated tumor-infiltrating macrophages, a significant increase in intratumoral CD8+ T cells and dispersion of M2 TAMs and MDSCs. Increased levels of interferon γ (IFNγ) and tumor necrosis factor α (TNFα) are also seen, indicating a shift to a pro-inflammatory environment. Treatment with anti-SEMA4D antibody also increases Teffector:Tregulatory (Teff:Treg) cell ratios within the tumor and tumor-specific cytotoxic T-cell activity. This immunologic response is localized to the tumor, with minimal T-cell and cytokine activity in the peripheral lymphoid organs. This is important because it has been reported that efficient entry of functional tumor-specific T-cells into the tumor correlated with improved survival and response to immunotherapy.[12,15]

The combined role of SEMA4D in tumorigenesis from both the tumor cells and tumor microenvironment and the fact that it is a cell surface and soluble ligand makes it an attractive therapeutic target. Similar to checkpoint inhibitors, its role in controlling the tumor microenvironment by modulating interactions with key players in the immune system make it an attractive target for many pediatric malignancies, however, its additional

roles in osteosarcoma tumorigenesis make it particularly applicable to this disease.

VX15/2503 is a humanized IgG4 monoclonal antibody that binds specifically to the SEMA4D (CD100) antigen, blocking the binding of SEMA4D to its high affinity receptor, plexin B1 (PLXNB1), plexin B2 (PLXNB2), and a low-affinity receptor, CD72. It has strong affinity for SEMA4D with an antibody-antigen dissociation constant (K_d) ranging from 1-5 nM.[10] Treatment of osteosarcoma cell lines with VX15/2503 resulted in decreased cell migration and colony formation as compared to controls. Additionally, a syngeneic mouse model of osteosarcoma treated with MAb67-2, a mouse analog of VX15/2503, had significantly reduced tumor growth compared to controls.[10]

2.2 Preclinical Studies

2.2.1 Antitumor Activity

VX15/2503 and the surrogate mouse MAb67-2 have demonstrated activity in both *in vitro* and *in vivo* tumor models. *In vitro* studies have demonstrated the agent's ability to block the functional effects of SEMA4D binding to PLXNB1.[11] In preclinical models, anti-SEMA4D antibody blockade regulates the balance and activity of inflammatory and tolerance inducing cells and cytokines. This results in specifically increasing cytotoxic T-cell infiltration and activity resulting in delayed tumor growth and durable tumor rejection in syngeneic murine tumor models.[12]

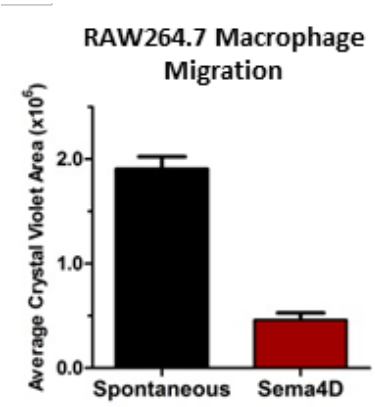


Figure 1. rSEMA4D (1 µg/ml) added to the lower chamber of a transwell inhibits spontaneous migration of mouse macrophage cell line, RAW264.[7]

Treatment with a murine monoclonal antibody to SEMA4D (MAb67-2) was evaluated in a syngeneic murine model of colorectal cancer using Colon26 cells. Mice were treated weekly with 10 mg/kg of MAb67-2 (aSEMA4D) or isotype control (Control Ig) intraperitoneally for 30 days. Treatment with anti-SEMA4D antibody promoted infiltration of activated macrophage and cytotoxic T-cells, with a reduction in infiltration of immune-suppressive T-regulatory and Myeloid Derived Suppressor Cells (MDSC) (Figure 2).

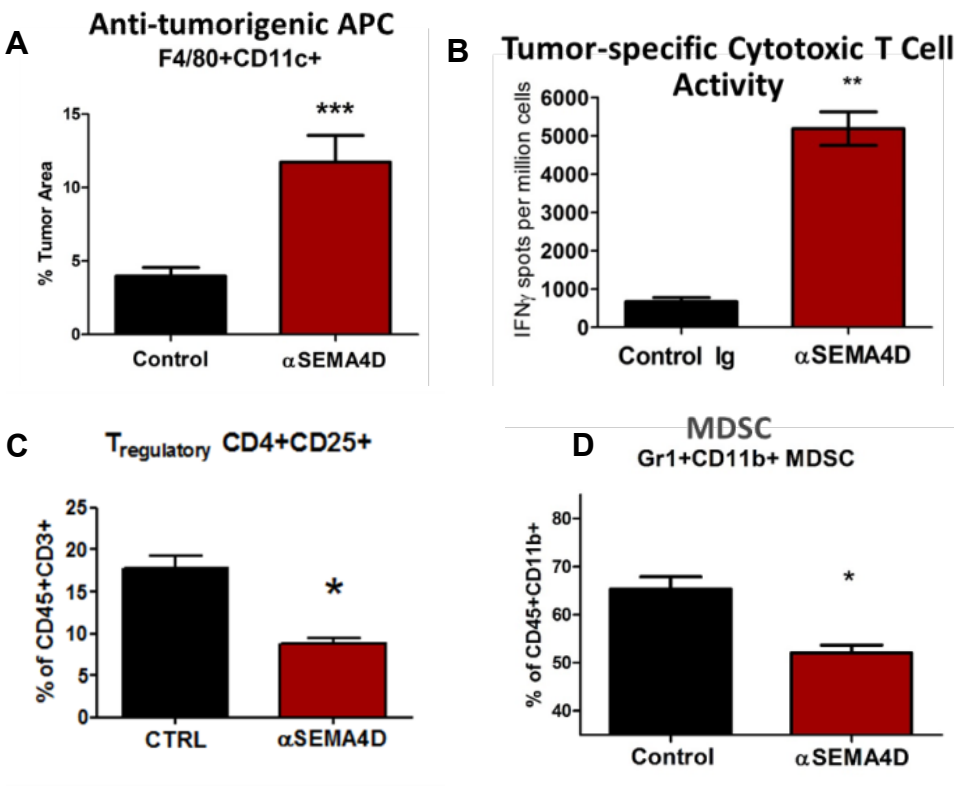


Figure 2. Changes in immune function after treatment with infiltration and rSEMA4D.

Preclinical models have demonstrated the importance of saturation of SEMA4D in that loss of saturation on circulating T-cells correlates with the minimal drug concentration needed for efficacy.

Through work at the University of Minnesota, SEMA4D expression has been extensively evaluated in osteosarcoma. The majority of human osteosarcoma cell lines tested express high amounts of SEMA4D transcript as evaluated by RT-qPCR (Figure 3). In addition, SEMA4D expression was analyzed in human tumor tissue microarrays of synovial sarcoma, neuroblastoma, and rhabdomyosarcoma. There was low level expression in 8/30 neuroblastoma tumors, 2/50 synovial sarcoma tumors, and 1/104 rhabdomyosarcoma tumors, while SEMA4D was strongly expressed on immune infiltrate in these samples.

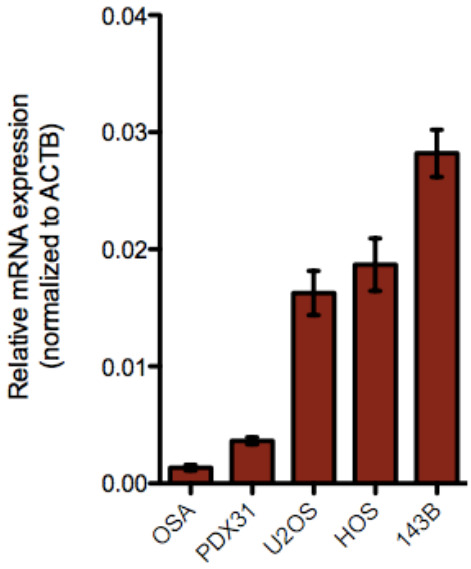


Figure 3. RT-PCR analysis of SEMA4D transcript levels in osteosarcoma cell lines, PDXs, and immortalized osteoblasts.

The effect of treatment with anti-SEMA4D (VX15/2503) on osteosarcoma growth, migration, and proliferation has been studied in three human osteosarcoma cell lines (143B, MG-63, and HOS), one Ewing sarcoma (RD-ES), and two murine osteosarcoma cell lines (K12, K7M2) with encouraging results. Treatment with increasing concentrations of anti-SEMA4D (VX15/2503) in 143B and MG-63 osteosarcoma cells reduces cellular migration as compared to anti-CD20 isotype control antibody (Figure 4). Treatment of 143B and HOS cells with 5 microgram/mL and 1 microgram/mL of VX15/2503 respectively demonstrated statistically significant decreases in colony formation as compared to control treatment. Similarly, treatment with 5 micrograms/mL also reduced colony formation in a human Ewing sarcoma cell line RD-ES when compared to anti-CD20 isotype control antibody (Figure 5). Finally, cellular proliferation was evaluated via the MTS proliferation assay in MG-63 and 143B osteosarcoma cell lines. Treatment of 5 micrograms/mL and 1 microgram/mL in MG-63 and 143B cells significantly reduced cellular proliferation on day 3 and days 2 and 3 post-plating, respectively (Figure 6). Interestingly, exposure to soluble SEMA4D (CD100) markedly increased migration in three osteosarcoma cell lines (Figure 7) (data courtesy of Dr. Branden Moriarity, University of Minnesota).

Figure 4. Osteosarcoma cell migration assays

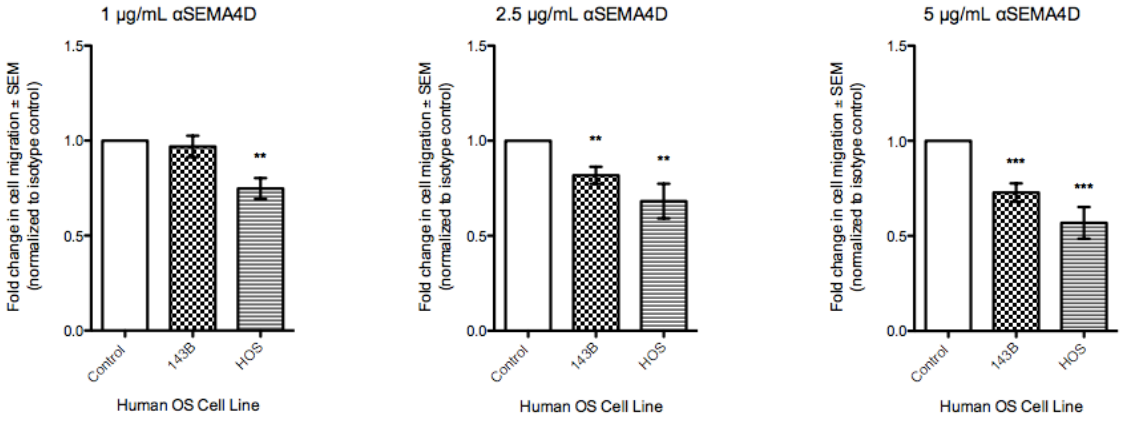


Figure 5. Osteosarcoma colony formation assays

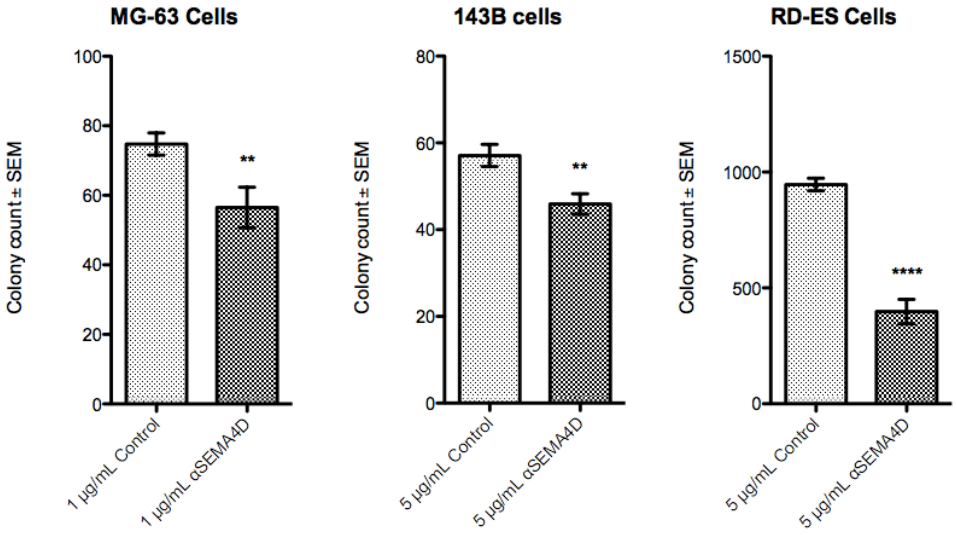


Figure 6. Osteosarcoma proliferation (MTS) assay

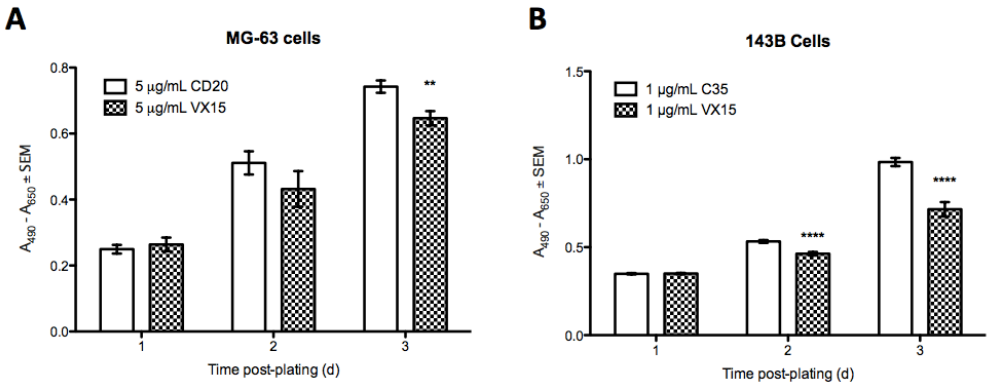


Figure 7. Osteosarcoma cell migration in response to soluble SEMA4D exposure

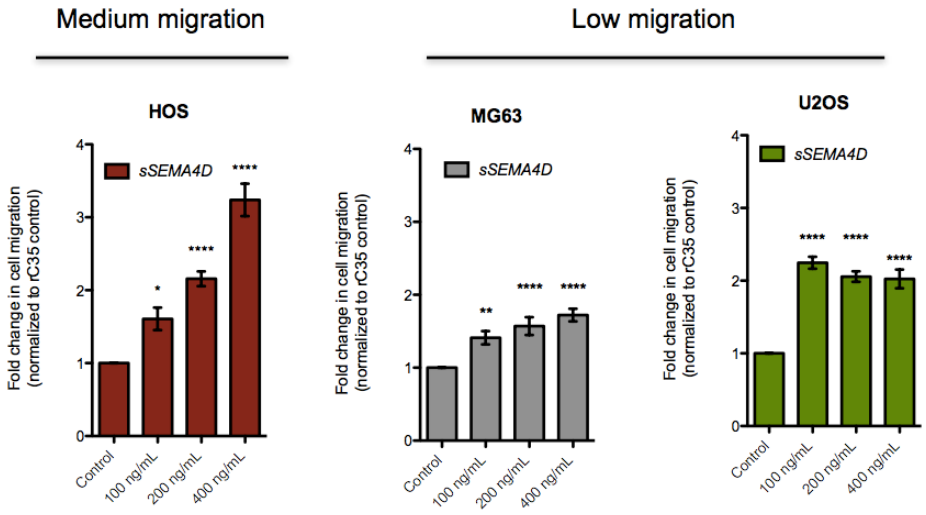
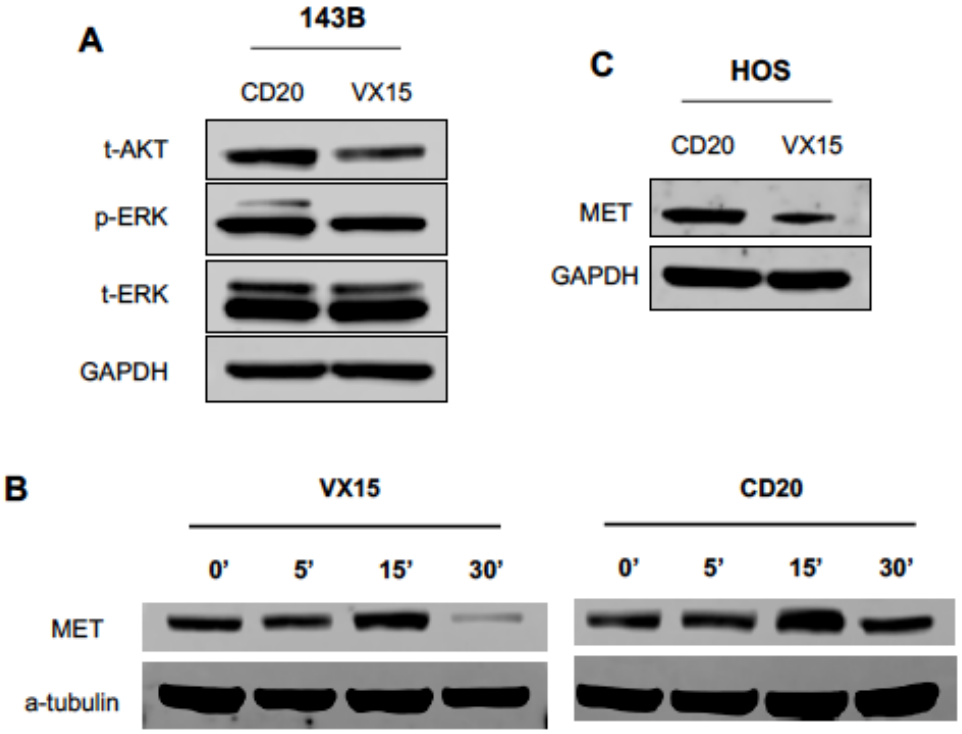


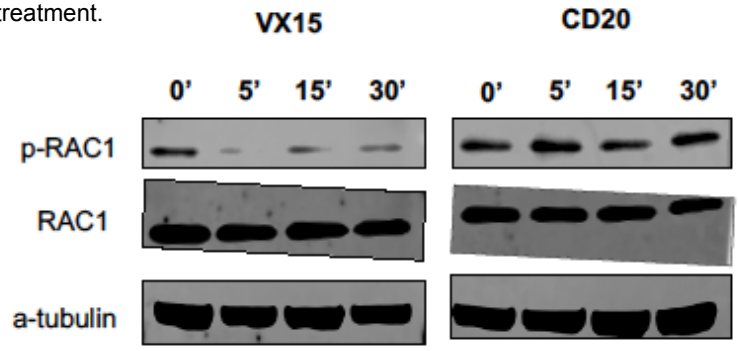
Figure 8. Reduced expression of SEMA4D signaling pathway members following treatment with VX15.



Downstream signaling mediators as well as a co-receptor of SEMA4D, MET, were probed in 143B (Figs. 8A & B) and HOS (Fig. 8C) osteosarcoma cell lines following 30' of treatment with either CD20 isotype control or VX15/2503 anti-SEMA4D antibody. Treatment with VX15/2503 reduced total AKT, activated ERK as well as total MET levels in 143B cells 30' post administration (A &B). Similarly, treatment with

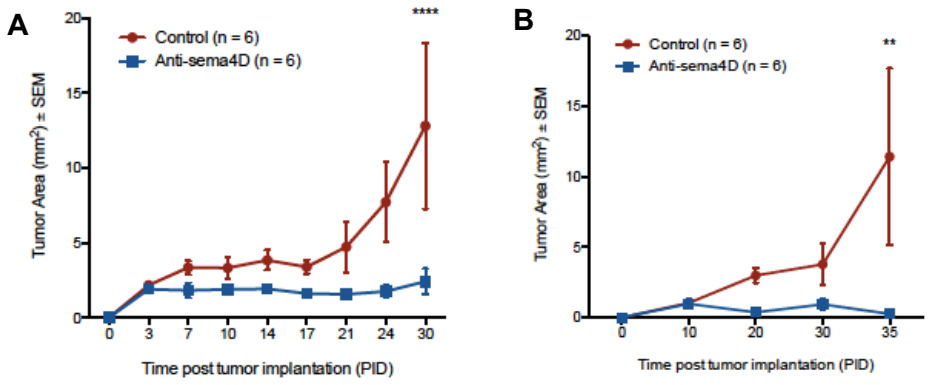
VX15 in HOS cells also reduced total MET levels (C).

Figure 9. Reduction in Rho family GTPase activation (RAC1) following VX15 treatment.



Rho family GTPases such as RAC1 are thought to play a role in PLXNB receptor localization to the surface in the presence of ligand. Activated RAC1 expression was probed in 143B osteosarcoma cell lines over a 30' time course. Treatment of 143B osteosarcoma cells with VX15, but not CD20 control reduced activated RAC1 levels (Figure 9).

Figure 10. Treatment of osteosarcoma syngeneic mouse model with mAb67-2, murine anti-sema4D antibody



Treatment with a murine monoclonal antibody to Sema4D (MAb67-2) was evaluated in a syngeneic murine model of osteosarcoma using K7M2 cells. Mice were injected with $2.5x10^5$ cells intra-calcaneally and treated with 1 mg/kg of MAb67-2 (anti-sema4D) or isotype control intraperitoneally every 2 days for 30 days (Fig. 10A) or were injected with $1x10^6$ and treated with 10 mg/kg of MAb67-2 (anti-sema4D) or isotype control intraperitoneally weekly for 30 days (Fig. 10B). Treatment with MAb67-2 resulted in reduced tumor growth beginning at post-implantation day 7 (PID 7) with continued effects observed at PID 30 when compared to control antibody (Figure 10A). Similarly, mice treated with 10 mg/kg experienced similar reductions in tumor growth (Figure

10B).

2.2.2 Animal Toxicology

No significant toxicological findings have been observed in single dose, one month, and six month GLP toxicology studies in Sprague Dawley rats and Cynomolgus macaques regardless of dose level. The no observed adverse effect level (NOAEL) was 100 mg/kg to 200 mg/kg. Immunophenotypic analysis of rat lymphocyte subsets performed prior to and at the end of the dosing regimen in the one-month study detected a statistically significant reduction in absolute and related NK levels in all treated animals.[8] Due to lack of clinical signs or histopathologic changes in the animals, decreases in NK cell levels were not considered adverse. In addition, a host-resistance study using rats challenged with flu virus after five weekly doses showed that antibody treatment was not immunosuppressive.

[13]

Additional studies exploring whether the absence of SEMA4D alters the development of fetal mice demonstrated functional defects in their immune system, without apparent abnormalities in other tissues.[13] Furthermore, Vaccinex has bred CD100-deficient mice and has not noted any bony malformations. (personal communication from Vaccinex)

2.2.3 Preclinical Pharmacokinetic Studies

Formal pharmacokinetic analyses have been conducted through both single and multiple dose studies in Sprague Dawley rats and Cynomolgus macaques. In general, longer half-lives were estimated for higher doses and the apparent volume of distribution estimated the serum volume for each species. The half-life at 100 mg/kg was about 10 days whereas that at 10 mg/kg was about 4 days. AUC did not increase linearly with dose but rather increased more rapidly.[8]

2.3 Adult Studies

2.3.1 Phase 1 Studies

A phase 1 trial of VX15/2503 in adults with advanced solid tumors demonstrated the antibody to be well tolerated as weekly infusions up to and including doses of 20 mg/kg. All treatment related adverse events were Grade 1 or 2 with the exception of one Grade 3 GGT elevation at 15 mg/kg in a patient with progressive disease who had elevated GGT levels at baseline. The most common treatment related adverse events were nausea and fatigue.

In terms of anti-tumor response, the progression free survival (PFS) was 7.82 weeks (range: 0.57 to 54.8 weeks). One patient with papillary thyroid cancer treated at the 20 mg/kg dose level achieved a partial response. Nineteen patients (45.2%) exhibited stable disease for ≥ 8 weeks, with the longest durations of stable disease observed for patients with colorectal (48 weeks) and breast cancer (55 weeks).[14]

2.3.2 Phase 2 Studies

Phase 2 studies of VX15/2503 in adults with malignancies are in development.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

The most accurate pharmacokinetic studies to date integrate the results of the Vaccinex phase 1 oncology and multiple sclerosis (MS) studies. Pharmacokinetic studies in adult oncology were limited due to inability to collect samples over a prolonged period of time. However, more extensive data collection points were obtained in the MS study allowing for more accurate assessment of T1/2 and AUC0-infinity. Based on data collected from the MS study, the half-life appears to increase with dose (t1/2, 20 days +/- 5 for 20 mg/kg dose, 15 days +/- 5 days for 10 mg/kg/dose) and clearance appears to decrease with dose (0.0201 L/hr +/- 0.0053 for 20 mg/kg dose). This may be explained by target-mediated drug disposition, which is commonly observed with monoclonal antibodies (MAbs).

Saturation of human T-cells with cSEMA4D was analyzed in the adult phase 1 study, with the threshold estimated to be approximately 0.3 microgram/mL. The extent of T lymphocyte associated SEMA4D saturation was dose independent, with weekly doses of VX15/2503 of 1 mg/kg or above producing complete, sustained cSEMA4D saturation. The time required for T-lymphocytes to become desaturated was dose dependent. Cellular SEMA4D desaturation occurred with VX15/2503 clearance from the periphery. The mean cSEMA4D saturation value at the end of infusion for all doses studied was 88% (range 68.5 to 98.7%). At the 1 mg/kg dose level, cSEMA4D saturation fell to approximately 20% at roughly 30 days post-infusion whereas full desaturation took greater than 155 days for the 20 mg/kg dose level. Cellular SEMA4D expression levels decreased approximately 50% following VX15/2503 binding to the cell surface receptor and its internalization, and returned to baseline expression levels with antibody clearance.[11,14]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children
There have been no pediatric trials of VX15/2503.

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies
There have been no pediatric trials of VX15/2503.

2.5 Overview of Proposed Pediatric Study

This is a phase 1/2 study of VX15/2503 in pediatric patients. The goal of Part A is to determine whether the adult recommended phase 2 dose (RP2D) of 20 mg/kg is both tolerated and deemed to be an optimal biologic dose, defined by adequate and sustained T-lymphocyte saturation by VX15/2503 (≥ 80% saturation). Part A will enroll patients with relapsed/refractory solid tumors, excluding brain tumors, with either measurable or evaluable disease. Using a rolling 6 design, patients on Part A will receive 20 mg/kg of VX15/2503 IV every 14 days until disease progression or toxicity requires treatment

interruption. If this dose is found to be tolerable and T-lymphocyte saturation is adequate and sustained through dosing, this will be the RP2D. If this dose is tolerated but T-lymphocyte saturation is not adequate or sustained, the study will be suspended while further dose escalation is considered. If at any time the dose level is determined to be intolerable, T-lymphocyte saturation will be assessed ***and*** if T-cell saturation is adequate, the dose will be de-escalated. Part B will open concurrent to Part A for older patients with relapsed or refractory osteosarcoma. Once Part A is complete, Part B will expand to enroll patients of all ages with relapsed or refractory osteosarcoma and PK expansion cohort will open to further evaluate the pharmacokinetics of VX15/2503 in children of all ages with relapsed or refractory solid tumors.

Measurable disease is required for Part B. Patients will be enrolled in two stages. In the first stage, 19 disease control and RECIST response evaluable patients will be enrolled. Each patient will be evaluated for both (1) disease control success and (2) RECIST response (CR or PR versus not CR or PR). Stage 2 will open if there are 5 or more disease control successes or 2 or more RECIST responders. Stage 2 will enroll 10 evaluable patients.

Dose Rationale: In adult phase 1 studies, doses up to 20 mg/kg weekly were well tolerated, so we will start the study at 20 mg/kg. Modeling from adult trials suggest that lower doses, including 10 mg/kg, maintain saturation of SEMA4D on circulating T-cells throughout the dosing and follow-up periods, thus a lower dose may be biologically active. Thus, if 20 mg/kg is deemed intolerable and T-lymphocyte saturation was adequate at 20 mg/kg, we will dose de-escalate to 10 mg/kg. This is important in choosing the dose as pre-clinical studies demonstrate that loss of saturation of SEMA4D on T-cells correlates with the minimal drug concentration needed for efficacy. The dosing interval is chosen based on the half-life determined in the MS study of 15 days +/- 5 days for the 10 mg/kg dose. Dosing on the half-life, or once every 2 weeks, should achieve a steady-state in 5-6 doses. Although steady-state will not be achieved until dose 5 or 6, based on experience from Vaccinex, we anticipate T-cell saturation to occur after the first dose and be maintained throughout the dosing periods. If the half-life or T-cell saturation is determined to be different in children, we will adjust the dosing interval accordingly.[10]

At the time of Amendment #2A, the first 6 patients on Part A have completed the first cycle of treatment and no dose limiting toxicities were observed. In addition, 5 of the 6 patients had sufficient samples to be evaluable for T-cell saturation and all 5 patients had adequate and sustained saturations with ≥ 80% saturation at all time points evaluated after the first infusion. Thus, the RP2D is 20 mg/kg IV every 14 days. Given this, with Amendment #2A we will open Part B to patients ≥ 12 months and ≤ 30 years of age with relapsed and refractory osteosarcoma once the initial 6 adult patients complete toxicity assessments per Section 11.6, and we will open the PK expansion cohort to patients ≥ 12 months and ≤ 21 years of age with relapsed/refractory solid tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Oncology Patient Enrollment Network (OPEN), a web-based registration system available on a 24/7 basis. It is integrated with the NCI Cancer Trials Support Unit (CTSU) Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the RAVE database.

Access requirements for OPEN:
Investigators and site staff will need to be registered with CTEP and have a valid and active Cancer Therapy Evaluation Program-Identity and Access Management (CTEP-IAM) account (check at <https://ctepcore.nci.nih.gov/iam/index.jsp>). This is the same account (user id and password) used for credentialing in the CTSU members' web site. To perform registrations in OPEN, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. 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.

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:

1. Log in to https://open.ctsu.org/open/
2. Click the **Slot Reservation** Tab. *The Site Patient page opens.*
3. Click the **Report** Tab. *The Slot Reservation Report opens. Available Slots are detailed per study strata.*

3.2 IRB Approval

NCI Pediatric CIRB approval or local IRB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit CIRB/IRB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. 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 (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 Regulatory Tab.

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.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.
For general (non-regulatory) questions, call the CTSU General Helpdesk at 1-888-823-5923 or contact CTSU by email at ctsucontact@westat.com.

Study centers can check the status of their registration packets by accessing the Site Registration Status page on the CTSU Member's Website under the Regulatory Tab. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

3.3 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry in the OPEN system once authorization for the release of protected health information (PHI) has been obtained.

3.4 Reservation and Contact Requirements

Before enrolling a patient on study, a reservation must be made through the OPEN website and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient ID number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

Reservations may be obtained 24-hours a day through the OPEN website.

3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.6 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through one of the following mechanisms: a) the COG screening protocol, b) an IRB-approved institutional screening protocol or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.7 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.8 **Institutional Pathology Report**

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

3.9 **Study Enrollment**

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the COG Study Research Coordinator, or the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

3.10 **Dose Assignment**

The dose level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow biopsy and/or aspirate must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

4.1 Inclusion Criteria

4.1.1 Age:

- Part A: Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.
- Part B: Patients must be ≥ 22 years and ≤ 30 years of age at the time of study enrollment until part A is complete. Part B will expand to include patients ≥ 12 months and ≤ 30 years of age once Part A is complete and once the initial 6 adult patients complete toxicity assessments per Section 11.6.

4.1.2 Diagnosis:

- Part A: Patients with recurrent or refractory solid tumors are eligible, excluding CNS tumors. Patients must have had histologic verification of malignancy at original diagnosis or relapse.
- Part B: Patients with recurrent or refractory osteosarcoma are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse.

4.1.3 Disease Status:

- Part A: Patients must have either measurable or evaluable disease (see Sections 12.2 and 12.3 for definitions).
- Part B: Patients must have measurable disease (see Section 12.2 for definition).

4.1.4 Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

4.1.5 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). 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.

4.1.6 Prior Therapy

4.1.6.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

≥ 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).

b. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

d. Corticosteroids: See Section 4.2.2. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g. pegfilfrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator.

f. Interleukins, Interferons and Cytokines (other than Hematopoetic Growth Factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoetic Growth Factors)

g. Stem cell Infusions (with or without TBI):
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
- Autologous stem cell infusion including boost infusion: ≥ 42 days.

h. Cellular Therapy: ≥ 42 days after the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.)

i. XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.

j. Radiopharmaceutical therapy (e.g., radiolabeled antibody, 131I-MIBG): ≥ 42 days after systemically administered radiopharmaceutical therapy.

k. Patients must not have received prior exposure to VX15/2503

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 patients must be evaluable for hematologic toxicity for the dose-confirmation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/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
≥ 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.

4.1.7.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- (ALT) (SPGT) ≤ 135 U/L. For the purpose of this study, the ULN for ALT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

.

4.1.7.4 Adequate Pulmonary Function Defined as:

a. No clinical indications such as evidence of dyspnea at rest, or exercise intolerance due to pulmonary insufficiency.
b. If clinical indications, pulse oximetry >94% on room air.

4.1.8 Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.1.9 Tissue blocks or slides must be sent per Section 8.7. If tissue blocks or slides are unavailable, the study chair must be notified prior to enrollment.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast- Feeding
Pregnant or breast-feeding women will not be entered on this study. 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 two effective methods of birth control, including a medically accepted barrier or contraceptive method (e.g., male or female condom) for the duration of the study. Abstinence is an acceptable method of birth control.

4.2.2 Concomitant Medications

a) Corticosteroids: Patients receiving systemic corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of systemic corticosteroid (See Section 4.1.6.1.d). Note: patients who are using topical or inhaled corticosteroids are eligible.

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

c) Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible [except leukemia patients receiving hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy].

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

4.2.3 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.4 Patients who have received a prior solid organ transplantation are not eligible.

4.2.5 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.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Day 1	Day 15	Day 28
VX15/2503 IV	VX15/2503 IV	End of Cycle/Evaluation

VX15/2503 will be administered intravenously over 60 minutes on Days 1 and 15 of a 28 day cycle. Patients should be monitored for signs and symptoms of infusion reactions during the drug infusion and for 4 hours after completion of post-infusion flush (e.g., monitor vital signs every 15 minutes during VX15/2503 infusion and every 30 minutes thereafter). Precautions for anaphylaxis should be observed during VX15/2503 administration. Emergency resuscitation equipment and medications should be present for immediate use in the immediate area where patients are receiving their infusions. If a patient develops a ≥ Grade 2 infusion related reaction, the infusion should be stopped and standard institutional guidelines for management of infusion reactions should be followed. Note: If the initial dose is well tolerated subsequent doses will required patients to be monitored for 1 hour after completion of post-infusion flush.

See Section 6.2.3 for management and dose modification guidelines for infusion related reactions. If there is no evidence of an infusion related reaction during the initial 2 infusions of VX15/2503, then no observation period is required for subsequent treatment cycles. In the event an infusion related reaction occurs thereafter, the four-hour observation period should be reinstituted.

A cycle of therapy is considered to be 28 days. A cycle may be repeated for a total of 13 cycles, up to a total duration of therapy of approximately 12 months. As some of the correlatives require same-day shipping (see Section 8.5), caution should be paid to the day of the week therapy should start and drug infusion should occur so that correlative samples are able to be sent out for analysis without delay.

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

> **Update:** With the release of Amendment #2A, the dose confirmation portion of the study is complete. Given this, Part B will be open to patients ≥ 12 months and ≤ 30 years of age with relapsed and refractory osteosarcoma once the initial 6 adult patients complete toxicity assessments per Section 11.6.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0, and is eligible to continue agent administration per the requirements in Section 6.0.

5.3 Dose Confirmation Schema (Completed)

5.3.1 Inter-Patient Escalation

The starting dose will be 20 mg/kg (dose level 1)

Dose Level	Dose (mg/kg)

-1	10
1*	**20**

* Starting Dose Level

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 10 mg/kg (dose level -1). If dose level -1 is not well tolerated, further de-escalation will not occur. The study will be closed to accrual.

Update: The RP2D was determined to be 20 mg/kg.

5.3.2 Intra-Patient Escalation

Intra-patient dose escalation is not allowed.

5.4 PK Expansion Cohort and Part B

VX15/2503 will be administered intravenously over 60 minutes on Days 1 and 15 of a 28 day cycle at the RP2D of 20 mg/kg.

5.5 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.6 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. The DLT observation period for the purposes of dose-confirmation will be the first cycle of therapy.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.6.1 Non-hematological dose-limiting toxicity

a) Any Grade 3 or greater non-hematological toxicity attributable to protocol therapy with the specific exclusion of:

- Grade 3 nausea and vomiting < 3 days duration
- Grade 3 liver enzyme elevation, including ALT,that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle. See Appendix III for values that represent thresholds between CTCAE grades. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
- Grade 3 fever
- Grade 3 infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.

b) Non-hematological toxicity that causes a delay of ≥ 14 days between treatment

cycles.

c) Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.6.2 Hematological dose limiting toxicity

a) In patients evaluable for hematological toxicity (see section 4.1.7.1), hematological dose limiting toxicity is defined as:
- Day 15:
  o Grade 4 neutropenia or Grade 3 thrombocytopenia (platelets < 50,000/mm3) that does not resolve to ANC ≥ 500/mm3 and platelets ≥ 50,000/mm3 (transfusion independent) by Day 18 will be considered dose-limiting (See Section 6.2.1).
- Platelet count < 25,000/mm^3 on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7 day period
- Myelosuppression that causes a delay of > 14 days between treatment cycles.

b) Note: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

6.1 Dose Modification for Day 1 Dosing

6.1.1 Dose Modifications for Hematologic Toxicity

6.1.1.1 Patients who have dose-limiting thrombocytopenia should receive subsequent cycles at the next lower dose level.

6.1.1.2 Patients who have dose-limiting neutropenia with no other dose-limiting toxicity should receive the same dose in the next cycle with myeloid growth factor support or receive study drug at the next lower dose level. [Note: Patients MUST NOT receive prophylactic myeloid growth factor in the first cycle of therapy (See Section 7.4).] If dose-limiting neutropenia recurs after myeloid growth factor is added, then the patient should be given the next lower dose level for subsequent cycles. If dose-limiting neutropenia recurs in a patient that has received a dose level reduction but has not received myeloid growth factor, then myeloid growth factor should be administered. If, per the treating physician, addition of myeloid growth factor is not in the best interest of the patient, the patient should be removed from protocol therapy. In the case where myeloid growth factor is used, it should be initiated 24 hours after the dose. If the day 15 dose is delayed to allow for recovery, the myeloid growth factor should not be given until 24 hours after the day 15 dose is given. If the day 15 dose is omitted, myeloid growth factor can be given at the time the decision is made to omit the dose.

6.1.1.3 Patients who experience dose-limiting thrombocytopenia after one dose reduction or dose-limiting neutropenia after addition of myeloid growth factor and one dose reduction must be removed from protocol therapy.

6.1.1.4 Patients who have a dose-limiting hematological toxicity that does not resolve to eligibility parameters within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.1.2 Dose Modifications for Non-Hematological Toxicity

6.1.2.1 Patients who have any dose-limiting non-hematological toxicity (as defined in Section 5.5.1) may continue on protocol therapy upon meeting eligibility lab requirements or baseline but should receive subsequent doses at the next lower dose level.

6.1.2.2 If the patient experiences non-hematological dose-limiting toxicity after one dose reduction, the patient must be removed from protocol therapy.

6.1.2.3 Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or eligibility (whichever is higher) within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.2 Dose Modifications for Day 15 Dosing due to Toxicity on Day 15.

6.2.1 Dose Modifications for Hematological Toxicity:

6.2.1.1 Patients who have Grade 4 neutropenia or Grade 3 thrombocytopenia (platelets < 50,000/mm3) on Day 15 will have their dose withheld. If the toxicity resolves to ANC ≥ 500/mm3 and platelets ≥ 50,000/mm3 (transfusion independent) by Day 18, the dose may be given. Platelets cannot be given to achieve a platelet count >50,000/mm3 to receive the day 15 dose. If the toxicity does not resolve to ANC ≥ 500/mm3 and platelets ≥ 50,000/mm3 by Day 18, the dose will be omitted and this will be considered a DLT. Patients who require that their Day 15 dose be omitted for Grade 4 neutropenia or Grade 3 platelets (< 50,000/mm3) after a dose reduction for any reason must be removed from protocol therapy.

6.2.1.2 Patients who meet hematological DLT criteria as defined in Section 5.5.2 on Day 15 will have their Day 15 dose omitted. Patients should receive subsequent cycles of drug per Section 6.2 after their toxicity resolves, no sooner than the planned start of the subsequent cycle. Patients who require that their Day 15 dose be omitted for hematologic DLT as defined in Section 5.5.1 after one dose reduction must be removed from protocol therapy.

6.2.2 Dose Modifications for Non-Hematologic Toxicity:

6.2.2.1 Patients who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug prior to the Day 15 dose (with the exception

of the DLT exclusions in Section 5.5.1) will be considered to have had a DLT. If the toxicity resolves to meet eligibility or ≤ Grade 2 (if not part of eligibility criteria) by Day 15, the dose may be given but at the next lower dose level.

6.2.2.2 Patients who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug on Day 15 prior to dosing (with the exception of the DLT exclusions in Section 5.5.2) will have their dose withheld and this will be considered a DLT. If the toxicity resolves to meet eligibility or ≤ Grade 2 (if not part of eligibility criteria) by Day 18, the dose may be given but at the next lower dose level. If the toxicity does not resolve by Day 18, the dose will be omitted. Patients should receive subsequent cycles of drug but with dose modifications according to Section 6.2.

6.2.2.3 If the patient experiences non-hematological dose-limiting toxicity after one dose reduction, the patient must be removed from protocol therapy.

6.2.3 Dose Modifications for Infusion-Related Reactions:

For patients who have allergic or acute infusion reactions to VX15/2503, therapy modifications based on grade should be as follows

Grade (CTCAE v.5) Infusion Related Reaction	Action
Grade 1 Transient flushing or rash, drug fever < 38° C	• Monitor patient until recovery from symptoms; infusion rate may be slowed. • If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. Monitor patient closely. The following prophylactic premedications are recommended: diphenhydramine 1 mg/kg with max 50 mg (or equivalent) and/or acetaminophen 10-15 mg/kg (max 1000 mg) at least 30 minutes before additional VX15/2503 administrations, slowing infusion rate as above. Note: Prophylactic premedications should be administered upon restart of infusion, when symptoms resolve.
Grade 2 Rash, flushing, urticaria, dyspnea, drug fever ≥ 38°C	• Stop infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent) and/or acetaminophen 10-15 mg/kg (max 1000 mg); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. • If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. Monitor patient closely. • If symptoms recur, then no further VX15/2503 will be administered at that visit. Administer diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent), and remain at

	bedside and monitor the patient until resolution of symptoms. The following prophylactic premedications are recommended: diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent) and acetaminophen (10-15 mg/kg, max 1000 mg) should be administered at least 30 minutes before additional VX15/2503 administrations. If clinically indicated, corticosteroids (recommended dose: 1-2 mg/kg/day methylprednisolone IV or equivalent) may be used.
Grade 3 or 4 Symptomatic bronchospasm with or without urticaria, allergy-related edema/angioedema, hypotension; Anaphylaxis	• Immediately discontinue infusion of VX15/2503. • Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1 mg/ml solution for subcutaneous administration, 0.1 to 0.25 mg of a 0.1 mg/ml solution injected slowly for IV administration, 0.01 mg/kg of 1:1000 dilution (0.01 ml/kg/dose) for intramuscular administration, and/or diphenhydramine 1 mg/kg with max 50 mg IV with 1-2 mg/kg/day methylprednisolone IV (or equivalent), as needed. • Patient should be monitored until the investigator is comfortable that the symptoms will not recur. • VX15/2503 will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids).

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See COG Supportive Care Endorsed Guidelines at https://childrensoncologygroup.org/index.php/cog-supportive-care-endorsed-guidelines for more information.

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be

administered in accordance with Section 6.1.1.2 or for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs[12]	X	Weekly	X
Height, weight, BSA	X		X
Performance Status	X		
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[3]	Every subsequent cycle on D1[4] and D15[4]
Pharmacokinetics[1]	X	X	X
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
Tumor Disease Evaluation	X	End of Cycle 1	Every other cycle x 2 then q 3 cycles[5]
Tumor Disease Evaluation- Part B Phase 2	X		After cycles 2,4 and 6 and then q 3 cycles[5]
Bone Marrow Evaluation[7]	X	End of Cycle 1[8]	Every other cycle x 2 then q 3 cycles[8]
Pregnancy Test[2]	X	With tumor disease	With tumor disease

		evaluation[2]	evaluation [2]
Oxygen Saturation[6]	X		
Immunogenicity Study	X	X[9]	X[9]
T Lymphocyte Saturation	X	X[10]	X[10]
Total Soluble SEMA4D	X	X[11]	X[11]
Tumor Tissue	X[13]	X[14]	X[14]

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

1 See Section 8.3 for timing of PK studies.

2 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control for the duration of the study. Abstinence is an acceptable method of birth control. Pregnancy testing is required prior to tumor imaging per institutional guidelines.

3 If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

4 If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3

5 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

6 Only if there is clinical indication of inadequate pulmonary function. See Section 4.1.7.4.

7 Patients with known bone marrow disease should have baseline bone marrow evaluation

8 If bone marrow evaluation pre-study is positive for metastatic disease

9 Immunogenicity Study see section 8.4 for timing of Immunogenicity studies

10 T Lymphocyte Saturation see section 8.5 for timing of T Lymphocyte Saturation studies

11 Total Soluble SEMA4D Solubility Assay see section 8.6 for timing of SEMA4D solubility studies.

12 Monitor vital signs every 15 minutes during VX15/2503 infusion and every 30 minutes thereafter for 4 hours.

13 Tumor tissue should be obtained if available. If a patient does not have tissue available, the study chair must be notified prior to enrollment. See Section 8.7.

14 In the event a subject requires a biopsy for surgery and tumor tissue is removed, tumor tissue will be requested for analysis. Tumor biopsies will not be performed solely for research purposes. See Section 8.7.

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response: Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy will be centrally reviewed. COG Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging 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 via the ImageInBox can send the images on CD ROM or USB flash drive. Submitted imaging studies should be clearly

marked with the COG patient ID, study number (ADVL1614) and date and shipped to [redacted]

[redacted]

8.3 Pharmacology (Required)

8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of VX15/2503 in children. Serum will be collected and VX15/2503 concentration will be determined by a qualified ELISA assay. Samples will be analyzed by Covance Laboratories.

8.3.2 Sampling Schedule (See Appendix IV and Appendix IX)

a. For patients ≤ 10kg, blood samples will be obtained prior to drug administration and at the following time points:
   - Cycle 1, Day 1: prior to start of infusion [3.5 ml], at the end of infusion [2.5 ml], and 2 hours following the end of infusion [2.5 ml]
   - Cycle 1, Day 15: prior to start of infusion [2.5 ml]
   - Cycle 2, Day 1: prior to start of infusion [3.5 ml]
   - Cycle 2, Day 15: prior to start of infusion [2.5 ml]
   - Each subsequent cycle, Day 1: These samples are collected in conjunction with the immunogenicity study samples for patients ≤ 10kg. No extra blood draws or sample tubes for PK are required for these time points. See Section 8.4.2 for timing and blood volume.

b. For patients > 10kg, blood samples will be obtained prior to drug administration and at the following time points. Blood sample volumes are 2.5 ml unless otherwise indicated:
   - Cycle 1, Day 1: prior to start of infusion, at the end of infusion, and 2 hours following the end of infusion.
     - **Note:** The PK samples collected prior to infusion and at the end of infusion are collected in conjunction with the immunogenicity study samples for patients > 10kg on Cycle 1 Day 1. No extra blood draws or sample tubes for PK are required for these time points. See Section 8.4.2 for timing and blood volume.
   - Cycle 1, Days 4 (±1), 8 (±1)
   - Cycle 1, Day 15: prior to start of infusion and at the end of infusion.
   - Cycle 2, Day 1: prior to start of infusion, at the end of infusion, and 2 hours following the end of infusion.
     - **Note:** The PK sample collected prior to start of infusion is collected in conjunction with the immunogenicity study sample for patients > 10kg on Cycle 2 Day 1. No

extra blood draws or sample tubes for PK are required for this time point. See Section 8.4.2 for timing and blood volume.

- Cycle 2, Day 15: prior to start of infusion.
- Each subsequent cycle, Day 1: These samples are collected in conjunction with the immunogenicity study samples for patients > 10kg. No extra blood draws or sample tubes for PK are required for these time points. See Section 8.4.2 for timing and blood volume.

8.3.3 Sample Collection and Handling Instructions

Please refer to the lab manual. Briefly, blood samples will be collected in SST tubes at a site distant from the infusion for pharmacokinetic evaluation. Please note above which samples are 2.5 ml and which samples are 3.5 ml. For blood samples that are to be used for both pharmacokinetic analysis and immunogenicity analysis, 3.5 ml of blood will be drawn total for both analyses. See Section 8.4.2 and Section 8.4.3 for details. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered. Please include the infusion start and stop times.

8.3.4 Sample Processing

Refer to lab manual for sample processing details.

8.3.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form (see Appendix IV and Appendix IX), which must accompany the sample(s). Additional details will be provided in the Covance lab manual.

8.3.6 Sample Shipping Instructions

Samples should be batched per patient and shipped frozen on dry ice in opaque containers at the end of cycle 1 to the lab processing the samples. Primary and backup samples should not be shipped at the same time, please refer to lab manual for detailed shipping information.

Samples should be shipped to the following address:
Covance Central Laboratory Services, Inc.
8211 SciCor Dr.
Indianapolis, IN 46214-2985

8.4 Immunogenicity Study (Required)

8.4.1 Description of Studies

Serum samples will be evaluated for Anti-Drug Antibodies through a qualified ELISA assay.

8.4.2 Sampling Schedule (See Appendix V and Appendix X)

a) For patients ≤ 10kg, samples will be collected at:
- Cycle 3, Day 1 and each subsequent cycle, Day 1: prior to start of infusion.
  - **Note:** 3.5 ml of blood will be drawn and will be used for both the immunogenicity analyses and the pharmacokinetic analyses.

b) For patients > 10kg, samples will be collected at:
- Cycle 1, Day 1: prior to start of infusion and at the end of infusion.
  - **Note:** 3.5 ml of blood will be drawn and will be used for both the immunogenicity analyses and the pharmacokinetic analyses.
- Each subsequent cycle, Day 1: prior to start of infusion.
  - **Note:** 3.5 ml of blood will be drawn and will be used for both the immunogenicity analyses and the pharmacokinetic analyses.

8.4.3 Sample Collection and Handling Instructions

Please refer to the lab manual. Briefly, blood samples (3.5 ml) will be collected in SST tubes at a site distant from the infusion for both immunogenicity evaluation and pharmacokinetic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.4.4 Sample Processing

Please refer to lab manual

8.4.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form, which must accompany the sample(s). Please refer to the Covance lab manual for additional information.

8.4.6 Sample Shipping Instructions

Samples should be shipped to the following address:
Covance Central Laboratory Services, Inc.
8211 SciCor Dr.
Indianapolis, IN 46214-2985

8.5 Pharmacodynamics: T-lymphocyte saturation (Required)

8.5.1 Description of Studies

Blood samples will be evaluated for T-lymphocyte saturation by VX15/2503 utilizing a validated flow-cytometry based assay.

8.5.2 Sampling Schedule (See Appendix VI)

c) For all patients, samples will be collected at:
- Cycle 1, Day 1: prior to start of infusion and at the end of infusion
- Cycle 1, Day 15: prior to start of infusion and at the end of infusion
- Cycle 1, Day 28: prior to Cycle 2, Day 1 dose for all patients regardless of whether or not patient is proceeding to Cycle 2

- Each subsequent cycle, Day 1: prior to start of infusion

8.5.3 Sample Collection and Handling Instructions

Blood samples:

- Cycle 1 Day 1: 2 x 4mL
- Cycle 1 Day 15: 2 x 4mL
- Cycle 1 Day 28: 1 x 4mL
- Subsequent Cycles: prior to start of infusion, Day 1: 1 x 4mL

Blood samples will be collected in cyto-chex tubes at a site distant from the infusion for pharmacodynamic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.5.4 Sample Processing

Please refer to lab manual

8.5.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form, which must accompany the sample(s). Please refer to the Covance lab manual for additional information.

8.5.6 Sample Shipping Instructions

Please note that these samples are very time-sensitive and that samples are to be sent the day of collection.

Samples should be shipped to the following address:
Covance Central Laboratory Services, Inc.
8211 SciCor Dr.
Indianapolis, IN 46214-2985

8.6 Pharmacodynamics: Total soluble SEMA4D (Required)

8.6.1 Description of Studies

Blood and serum samples will be evaluated for total soluble SEMA4D through a qualified ELISA assay.

8.6.2 Sampling Schedule (See Appendix VII and Appendix XI)

d) For patients ≤ 10kg, samples will be collected at:
- Cycle 3, Day 1 and each subsequent cycle, Day 1: prior to start of infusion

e) For patients > 10kg, samples will be collected at:
- Cycle 1, Day 1: prior to start of infusion and at the end of infusion
- Each subsequent cycle, Day 1: prior to start of infusion

8.6.3 Sample Collection and Handling Instructions

Please refer to lab manual. Briefly, blood samples (3.5mL) will be collected in SST tubes at a site distant from the infusion for pharmacodynamic evaluation. Record the exact time that the sample is drawn along with the exact time that the

drug is administered.

8.6.4 Sample Processing
Please refer to lab manual

8.6.5 Sample Labeling
Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form, which must accompany the sample(s).

8.6.6 Sample Shipping Instructions
Samples should be batched per patient and shipped frozen on dry ice in opaque containers at the end of cycle 1 to the lab processing the samples. Primary and backup samples should not be shipped at the same time, please refer to lab manual for detailed shipping information.

Samples should be shipped to the following address:
Covance Central Laboratory Services, Inc.
8211 SciCor Dr.
Indianapolis, IN 46214-2985

8.7 Tumor Assessment (archival-required and biopsy-optional)

8.7.1 Description of Studies
Tumor Expression: SEMA4D, PlexinB1, and other markers of immune cell infiltration will be performed by Immunohistochemistry. Archival tumor tissue should be submitted for all patients. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

8.7.2 Sampling Schedules (See Appendix VIII)

a) Archival tumor tissue (Archival Formalin-Fixed Paraffin-Embedded (*FFPE*)) will be requested to be sent when available. Please submit a redacted copy of the pathology report along with the specimen.

b) In the event a subject requires a biopsy or surgery and tumor tissue is removed, tissue will be requested for the analysis of SEMA4D, PlexinB1, and other markers of immune cell infiltration (optional). Tumor biopsies will not be performed solely for research purposes.

8.7.3 Sample Shipping Instructions:
Samples should be shipped to the following address:
Immunochemistry Services
Covance Laboratories, Inc.
3635 Concorde Parkway, Suite# 100
Chantilly, VA 20151

8.7.4 Sample Labeling
Each specimen must be labeled with the patient's study registration number, the study I.D., and must be accompanied by a pathology report. Data should be

recorded on the Tissue Studies Form (see Appendix VIII), which must accompany the sample(s).

9.0 AGENT INFORMATION

9.1 VX15/2503

(Mab2503) NSC# 795997 IND#136181

9.1.1 Structure and molecular weight:

VX15/2503 is a humanized, IgG4 kappa monoclonal antibody that binds specifically to the semaphorin 4D (SEMA4D; CD100) antigen, a member of the semaphorin family that normally functions to regulate the motility and differentiation of multiple cell types, including those of the immune, vascular, and nervous systems. It bears a proline at position 228 of the core hinge sequence (instead of a serine) to stabilize the hinge region and prevent chain recombination from occurring. SEMA4D blockade represents a novel mechanism and therapeutic strategy to promote immune infiltration into the tumor microenvironment and inhibit tumor progression.

VX15/2503 has a molecular weight of approximately 148 kDa.

9.1.2 Supplied by: Vaccinex, Inc

9.1.3 Formulation

The agent is supplied as a sterile solution of 20 mg/ml antibody in 20 mM sodium acetate, pH5.4, containing 130 mM sodium chloride and 0.02% polysorbate 80. The formulation contains no preservatives. Each 10 mL vial of VX15/2503 contains 10 mL (200 mg) of antibody; each vial is intended for single use. The product packaging consists of 10 mL USP Type I Schott glass vials with West Pharmaceutical Services FluroTec® grey butyl rubber stoppers and a blue plastic cap with aluminum overseal. Each 10 mL product vials is packaged in a cardboard box that provides protection from light.

9.1.4 Storage

VX15/2503 is to be kept dry and refrigerated at 2-8°C (36-46ºF) until use. It should be protected from light.

9.1.5 Solution Preparation

Using aseptic technique, prepare the solution for infusion as follows:

- Drug vials should be carefully inspected for discoloration and for particulates. The solution of VX15/2503 are normally clear to slightly opalescent, colorless or faintly yellow, and may contain a small amount of visible particulates. If the solution is discolored or otherwise does not meet this description the drug should not be administered and instead the study sponsor be contacted. The solution vials contains no preservatives.

- Do not shake the solution vials.

- To prepare infusion solution, withdraw the required amount of VX15/2503 and dilute the solution with 0.9% sodium chloride injection, USP, as needed. The final concentration should be between 1-10 mg/mL after dilution. Doses of 2,000 mg and above should be diluted to a total volume of 250 mL with 0.9% sodium chloride injection, USP. Mix the diluted solution by gentle inversion; do not shake. Inspect the prepared solution visually for particulates prior to administration.

- Destroy any unused vialed material according to organizational procedures for the destruction of biologic agents. If no appropriate procedure exists, return the unused vialed solution to the study drug distributor for destruction.

9.1.6 Stability

Refer to the package labeling for vials expiration dating.

Administration of VX15/2503 should occur as soon as possible following dilution (see Section 9.1.5). If a delay is anticipated, the prepared solution may be kept at room temperature for no more than 8 hours prior to infusion, or for no more than 24 hours after dilution if stored at 2-8 ºC (36 to 46ºF). Do not freeze the diluted solution

9.1.7 Administration

See Treatment (Section 5.0) and Dose Modification (Section 6.0) of the protocol for complete details.

Administration of VX15/2503 should occur as soon as possible following dilution.

Use one of the following (or comparable) infusion sets:

- Hospira product number 12030-12 (polyvinyl chloride composition) (with or without in-line filter)

- Baxter product number 2C8875 (polyvinyl chloride composition with polyethylene lined tubing) (with or without in-line filter)

Administer the prepared intravenous solutions using an infusion pump. Infuse all doses of VX15/2503 over the time interval specified in the study protocol using a peripheral intravenous line or indwelling intravenous catheter. Flush the line with 0.9% sodium chloride injection, USP, after study drug infusion.

Do not administer VX15/2503 as an infusion with intravenous solutions of other medicinal products. Do not add other medications to solutions containing VX15/2503.

9.1.8 Toxicities

The table below lists the expected toxicity profile of VX15/2503. This list may not be comprehensive; VX15/2503 may result in events which have never been previously reported. Note: An adverse event is unexpected for sponsor IND reporting purposes if it is not listed in bold font in the table below. Please refer to Section 13.1 for protocol-

specific exceptions to CTEP-AERS expedited reporting.

Incidence	Toxicities
Common (>20% of patients)	None
Occasional (4-20% of patients)	• **Nausea** • **Fatigue** • **Arthralgia** • **Decreased appetite** • **Infusion-related reaction** • **Fever** • **Myalgia** • **Pruritus**
Rare (<3% of patients)	• Elevated gamma glutamyl transferase • Lipase increased • Neutrophil count decreased • White blood cell count decreased • Abdominal pain • Hepatitis E • Lymphadenopathy • Lymphedema • Eye pain, decreased visual acuity • Rash • Pericardial effusion
Pregnancy & Lactation	No reproductive toxicology, genotoxicity, or mutagenicity studies have been conducted with VX15/2503. Pregnant or breast-feeding women will not be entered on this study. 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.

9.1.9 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received using the appropriate NCI Drug Accountability Record Form (DARF) available on the CTEP forms page. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers.

Upon completion of preparation of an injection, used or partially used vials should be discarded per institutional standard operating procedures. Unused vials should be stored in the original carton under refrigeration at 2°C to 8°C (36°F to 46°F) protected from light in a secure, limited access area. Do not freeze. If there are unused vials remaining at the end of the study, the pharmacist or designee should destroy unused or expired vials per institutional standard operating procedures. All material containing study drug will be treated and disposed of as hazardous waste in accordance with governing regulations. Appropriate disposal confirmation will

be provided to Vaccinex.

9.1.10 Agent Ordering

VX15/2503 will be supplied by Vaccinex, Inc. Information on drug supply and management is posted on the protocol web site. VX15/2503 is for investigational use only, and is to be used only within the context of this study. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, subjects, or clinics, or allow supplies to be used other than directed by this protocol.

9.1.11 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0).
b) Adverse Events requiring removal from protocol therapy (See Section 6.0).
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 13 cycles of therapy.
f) Physician determines it is not in the patient's best interest.
g) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of VX15/2503 (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up
d) Withdrawal of consent for any required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study
f) The patient does not receive protocol treatment after study enrollment.

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

A minimum of 4 evaluable patients will be required for Part A. The expected maximum number of evaluable patients required to complete part A is 12. Once the MTD or recommended Phase 2 dose has been defined, up to 6 additional patients with recurrent or refractory solid tumors without restrictions on heme evaluability may be enrolled to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). Therefore, the maximum number of patients anticipated to be enrolled into Part A is 23 patients which allows for 6 patients at each of 2 dose levels, 6 additional patients for PK, and 20% inevaluability. Review of the enrollment rate into previous COG new agent studies indicates that 4 patients per month are expected. Therefore, the study is expected to be completed within about 6 months. In the unlikely event that both dose levels are expanded to 12 patients due to DLTs of different classes, the absolute maximum number of patients enrolled into Part A would be 38. The absolute maximum would be expected to be completed within 10 months.

Additionally once the MTD/or RP2D has been determined in Part A, the Phase 2 portion of the study (Part B) will use a Simon's optimal two-stage design. In the first stage, 19 disease control and RECIST response evaluable patients will be enrolled. Each patient will be evaluated for both outcome measures: (1) disease control success; and (2) RECIST response (CR or PR v. not CR or PR). The decision rule for the two stage study design is summarized in Section 11.6. A maximum of 37 patients are expected to be enrolled to allow for 20% inevaluability. This is expected to be completed within about 10 months. Overall, a maximum of 60 patients are expected to be enrolled into the study, and this should be completed within about 16 months. An absolute maximum of 75 patients would take up to 19 months to complete enrollment.

Strata:
a) Part A-Determination of the MTD
b) Part B- Osteosarcoma Phase 2 cohort.

11.2 Definitions

11.2.1 Evaluable For Adverse Events

Any patient who receives at least one dose of the study drug(s) or who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. Patients who do not have DLT and are not considered evaluable for toxicity will be replaced.

11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy.

- In the unlikely event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), AND all of the following conditions are met, expansion of the cohort to 12 patients will be considered:

  - One of the DLTs does not appear to be dose-related
  - The Adverse Effects are readily reversible
  - The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

  If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation will be considered.

- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥ 1/3 of the cohort of patients at the MTD (during the dose escalation plus the PK phase 2) experience DLT then the MTD will be exceeded.

11.3 Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study[15]. Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level

2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule).

In addition to determination of the MTD, a descriptive summary of all toxicities will be reported.

11.4 Inclusion of Children, Women and Minorities

CTEP PLANNED ENROLLMENT REPORT					
Race Categories	**Ethnicity Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	**1**
Asian	1	2	0	0	**3**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	5	5	0	0	**10**

White	20	29	4	4	**57**
More Than One Race	0	0	0	0	**0**
Total	**26**	**37**	**4**	**4**	**71**

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

11.5 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of VX15/2503 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).

While the primary aim of this study is to evaluate the toxicity of VX15/2503, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors, and will be reported descriptively.

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

11.6 Study Design - Part B

Data collected from patients from the dose determining portion (Part A) treated at the MTD/RP2D and who meet eligibility criteria for Part B of the study will be counted in the Phase 2 evaluation. The following Simon's optimal two stage design will be used in each stratum.

The two stage design is illustrated below:

Stage	Number of patients enrolled in stage	Cumulative response results	Decision
1	19	4 or fewer disease control successes and 1 or fewer RECIST responders	Terminate the trial with the conclusion that VX15/2503 is not associated with sufficient activity for further investigation
		5 or more disease control success or 2 or more RECIST responders	Continue to stage 2

2	10	8 or fewer disease control successes and 4 or fewer RECIST responders	Terminate the trial with the conclusion that VX15/2503 is not associated with sufficient activity for further investigation
		9 or more disease control successes or 5 or more RECIST responders	Terminate the trial with the conclusion that VX15/2503 is associated with sufficient activity for further investigation

Part B will be initially opened to 6 adult patients. The Rolling 6 design logic will be applied for assessing toxicity in the initial cohort of 6 adults. If 2 or more patients in this cohort experience a DLT in Cycle 1, then enrollment to Part B will be suspended pending study committee discussion. If Part A is complete and the initial cohort of 6 adult patients in Part B is deemed safe, up to 19 patients will be enrolled into Stage 1 with a maximum of 12 adult patients. However, if at any point the percentage of patients experiencing a Cycle 1 DLT is >33%, then the study will be suspended pending internal review. This will include DLTs observed for all younger patients from Part A that were assigned to the MTD/RP2D used in Part B of the study.

Design Characteristics: Each patient enrolled will be evaluated for: (1) complete or partial response as defined by the RECIST criteria where the first evaluation of CR or PR is made at or before the end of the sixth cycle of study therapy (denoted as R below); or (2) stable disease after four months of therapy or at the end of the sixth cycle, whichever occurs first (denoted as S below). We will not be interested in promoting the agent for further investigation if the probability of response in any particular individual is less than or equal to 0.05 (P(R)≤0.05) and the probability of remaining analytic event free in any particular individual is less than or equal to 0.20 (P(S)≤0.20). We will be interested in promoting the agent for further investigation if the probability of response in any particular individual is at least 0.22 (P(R)≥0.22) **or** the probability of remaining analytic event free in any particular individual is at least 0.42 (P(S)≥0.42).

For the calculations below, it is assumed $\Pr(S \mid R) = 0.90$.

The statistical characteristics of this design are:

Probability of four month disease control	Probability of RECIST response	Probability of Stopping After Stage 1 (and concluding the drug is ineffective)	Probability of Concluding the Drug is Ineffective at the Conclusion of the Trial	Probability of Concluding the Drug is Effective at the Conclusion of the Trial
0.20	0.05	0.56	0.89	0.11
0.42	0.22	0.014	0.05	0.95
0.42	0.05	0.044	0.096	0.904
0.20	0.22	0.056	0.21	0.79

We will concurrently enroll on the Phase 1 and Phase 2 studies. While the Phase 1 study is accruing we will limit the Phase 2 enrollment to osteosarcoma patients greater than 21 years of age to ensure the completion of the phase 1 portion of this study. After the Phase 1 study is complete, patients less than or equal to 21 will be enrolled into the Phase 2

portion of this study. The Phase 2 study will cap the number of older patients (>21 years) enrolled into Stage 1 at 12 patients to ensure a representative number of patients in both age groups. Without this cap, it may be possible to open Stage 2 of the Phase 2 study without having enrolled any younger patients and stage 2 would have opened based on information collected solely in older patients. Osteosarcoma patients enrolled in Phase 1 will also be included in the Phase 2 part of the study.

11.7 Method of Analysis – Phase 2

Response in Part B osteosarcoma patients will be determined as defined in Section 12.0. A report on the efficacy assessment will be posted on the completed disease stratum as part of the semi-annual study committee meeting book report.

Toxicities for patients will be described separately. Every effort will be made to accrue the number of patients needed to evaluate efficacy according to the schema in Section 11.6. For strata not appropriately filled, descriptive statistics will be employed to describe outcomes.

Which Patients will be Considered Evaluable for RECIST Response:
Any eligible patient who receives at least one dose of VX15/2503 will be considered evaluable for response with the following exception: if a patient receives non-protocol anti-cancer therapy 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 VX15/2503 after the 1st 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.

Which Patients Will Be Considered Evaluable for Disease Control Success:
Any eligible patient who receives at least one dose of VX15/2503 will be considered evaluable for response with the following exception: if a patient receives non-protocol anti-cancer therapy during the first four months of therapy or first six cycles of therapy, whichever occurs first, 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 disease control success endpoint.

Which Patients Will be Considered a Disease Control Success:
Any patient who is evaluated free of all detectable disease (complete response) or is considered as having a partial response or is considered as having stable disease ('at least stable disease') after four months of therapy or at the end of the sixth cycle, whichever occurs first.

Which Patients Will be Considered Not a Disease Control Success:
Any evaluable patient who does not meet the criteria for disease control success (complete response, partial response or stable disease) will be considered to not have experienced disease control success.
In particular, any patient who dies because of treatment-related toxicity during the first six cycles of therapy and within the first four months since starting treatment will be considered not to have experienced disease control success. Also, any patient who is eligible, receives one dose of VX15/2503 and is lost to follow-up at (for example) the end of cycle 2 will be considered not a disease control success (complete response, partial

response or stable disease)

Patients who are not evaluable for both disease control and response evaluation may be replaced for the purposes of the statistical rule.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

12.2 Response Criteria for Patients with Solid Tumors

See the table in section 8.0 for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained on the next consecutive cycle following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.2.1 Definitions

a) Evaluable for objective response: Eligible patients who receive at least one dose of protocol therapy will be considered evaluable for response. Evaluable patients who demonstrate a complete or partial response confirmed by central review before receiving non-protocol anti-cancer therapy will be considered a responder. All other evaluable patients will be considered non-responders.

b) Evaluable Non-Target Disease Response: Eligible patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease and have received at least one dose of protocol therapy will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2.2 Disease Parameters

12.2.2.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

12.2.2.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

12.2.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.2.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

12.2.2.5 Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.2.3.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.2.3.2 Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

12.2.3.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

12.2.3.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

12.2.3.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.2.3.6 Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

12.2.3.7 FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET

scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.2.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.2.4.1 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit

discontinuation of therapy

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

12.2.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

12.2.5 Overall Response Assessment

Table 1: For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 28 days Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 28 days Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 28 days from baseline
PD	Any	Yes or No	PD	

Any	PD**	Yes or No	PD	no prior SD, PR or CR
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 2: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Table 4: Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	**MIBG**	**Bone Scan**	**Bone Marrow**	**Catechol**	**Overall**
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

12.2.6 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.6 from a sequence of overall response assessments.

12.3 Response Criteria for Patients with Solid Tumors and Evaluable Disease

12.3.1 Evaluable Disease

The presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

12.3.2 Complete Response

Disappearance of all evaluable disease.

12.3.3 Partial response
Partial responses cannot be determined in patients with evaluable disease

12.3.4 Stable Disease (SD)
That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

12.3.5 Progressive Disease
The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

12.3.6 Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.6 from a sequence of overall response assessments.

12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.4.1 MIBG Positive Lesions
Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

12.4.2 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
Progressive disease:	Development of new MIBG positive lesions

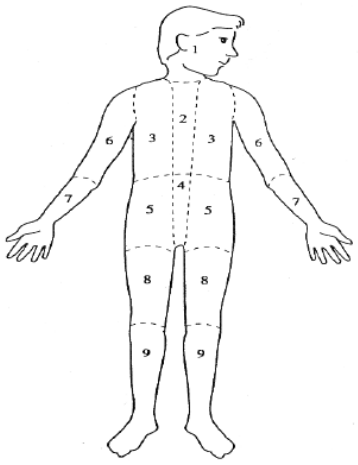
12.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

NOTE: This scoring should also 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 10th 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 21 days apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 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.

12.4.4 Overall Response Assessment

Table 5: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only
If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow	Catechol	Overall
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-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR

CR	No New Lesion	CR	CR	Normal	CR

12.4.5 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 3 in Section 12.6.

12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.5.1 Bone Marrow Involvement

Bone marrow obtained within 28 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by H&E Staining of bilateral bone marrow biopsies and aspirates.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: In 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 ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

In 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 21 days apart.

Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

12.5.2 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Section 12.6.

12.6 Best Response

12.6.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the

treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 3. Sequences of overall response assessments with corresponding best response.

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

12.6.2 Duration of Response

12.6.2.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

12.6.2.2 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); 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.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Step 2: Grade the adverse event using the NCI CTCAE.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Table A: Phase 1 and Early Phase 2 Studies: 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 [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

- Grade 1 and 2 adverse events listed in the table below do not require expedited reporting via CTEPAERS, unless it is associated with hospitalization

Category	Adverse Events
GASTROINTESTINAL DISORDERS	Nausea
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia
GASTROINTESTINAL DISORDERS	Decreased appetite
IMMUNE SYSTEM DISORDERS	Infusion-related reaction
INFECTIONS AND INFESTATIONS	Fever
MUSCULOSKELETAL AND CONNECTIVE TISSU DISORDERS	Myalgia
SKIN AND SUBCUTANEOUS DISORDERS	Pruritus

As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A to NCI via the web at http://ctep.cancer.gov (email the ADVL1614 COG assigned study Research Coordinator within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited Reporting System (CTEP-AERS) that can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-

based application located at https://eapps-ctep.nci.nih.gov/ctepaers/. If prompted to enter a sponsor email address, please type in: PEPCTNAERS@childrensoncologygroup.org.

Send supporting documentation by email to the ADVL1614 COG study assigned Research Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

13.4 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG case report forms and do not alter the guidelines for CTEP-AERS reporting.

13.4.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.4.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.4.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.4.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.4.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.3) should be reported at the end of each cycle using the forms provided in the CRF packet (See Section 14.1).

13.5.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

13.5.3 Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

13.6 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients following their chemotherapy for cancer must be reported via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for

this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after protocol treatment for cancer.

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 secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

1) Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2) Myelodysplastic syndrome (MDS)
3) Treatment-related secondary malignancy.

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

Second Malignancy:

A *second malignancy* is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

13.7 Reporting Pregnancy, Fetal Death, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and emailed to the ADVL1614 COG Study Assigned Research Coordinator along with any additional medical information. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.7.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which 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" System Organ Class (SOC)**.

- Pregnancy should 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.

13.7.2 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 conditions"* SOC.** Do NOT report a pregnancy loss as a Grade 5 event

since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.7.3 Death Neonatal

- Neonatal death, defined in CTCAE as ***"Newborn deaths occurring during the first 28 days 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 as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

  Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all follow-ups. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

14.3 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

2. Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the PEP-CTN scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG PEP-CTN Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

3. Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the COG PEP-CTN Chair, Vice Chair and Statistician on a weekly conference call.

REFERENCES

1. Giraudon P, Vincent P, Vuaillat C: T-cells in neuronal injury and repair: semaphorins and related T-cell signals. Neuromolecular Med 7:207-16, 2005
2. Worzfeld T, Offermanns S: Semaphorins and plexins as therapeutic targets. Nat Rev Drug Discov 13:603-21, 2014
3. Takamatsu H, Takegahara N, Nakagawa Y, et al: Semaphorins guide the entry of dendritic cells into the lymphatics by activating myosin II. Nat Immunol 11:594-600, 2010
4. Mendes-da-Cruz DA, Lepelletier Y, Brignier AC, et al: Neuropilins, semaphorins, and their role in thymocyte development. Ann N Y Acad Sci 1153:20-8, 2009
5. Basile JR, Castilho RM, Williams VP, et al: Semaphorin 4D provides a link between axon guidance processes and tumor-induced angiogenesis. Proc Natl Acad Sci U S A 103:9017-22, 2006
6. Campos M, SG DEC, Ribeiro GG, et al: Ki-67 and CD100 immunohistochemical expression is associated with local recurrence and poor prognosis in soft tissue sarcomas, respectively. Oncol Lett 5:1527-1535, 2013
7. Ch'ng E, Tomita Y, Zhang B, et al: Prognostic significance of CD100 expression in soft tissue sarcoma. Cancer 110:164-72, 2007
8. Leonard JE, Fisher TL, Winter LA, et al: Nonclinical Safety Evaluation of VX15/2503, a Humanized IgG4 Anti-SEMA4D Antibody. Mol Cancer Ther 14:964-72, 2015
9. Moriarity BS, Otto GM, Rahrmann EP, et al: A Sleeping Beauty forward genetic screen identifies new genes and pathways driving osteosarcoma development and metastasis. Nat Genet 47:615-24, 2015
10. Vaccinex: VX15/2503 Investigator's Brochure v. 3, 2015
11. Fisher TL, Reilly CA, Winter LA, et al: Generation and preclinical characterization of an antibody specific for SEMA4D. MAbs:1-13, 2015
12. Evans EE, Paris M, Smith ES, et al: Immunomodulation of the tumor microenvironment by neutralization of Semaphorin 4D. Oncoimmunology 4:e1054599, 2015
13. Shi W, Kumanogoh A, Watanabe C, et al: The class IV semaphorin CD100 plays nonredundant roles in the immune system: defective B and T cell activation in CD100-deficient mice. Immunity 13:633-42, 2000
14. Patnaik A, Weiss GJ, Leonard JE, et al: Safety, Pharmacokinetics, and Pharmacodynamics of a Humanized Anti-Semaphorin 4D Antibody, in a First-In-Human Study of Patients with Advanced Solid Tumors. Clin Cancer Res 22:827-36, 2016
15. Skolnik JM, Barrett JS, Jayaraman B, et al: Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 26:190-5, 2008

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: CORRELATIVE STUDIES GUIDE

FOR PATIENTS ≤ 10KG

Correlative Study	Appx	Sample volume				Tube Type
		Volume per sample	Total Cycle 1	Total Cycle 2	Subsequent Cycles	
Pharmacokinetic Study	IX	2.5-3.5ml	11ml	6ml	Included with Immunogenicity Samples	SST Tubes
Immunogenicity Study (Anti-Drug Antibody)	X	3.5ml	0ml	0ml	3.5ml	SST Tubes
Pharmacodynamics- T lymphocyte saturation/cellular SEMA4D assay	VI	4ml	20ml	4ml	4ml	Cyto-Chex Tubes
Pharmacodynamics- Total Soluble SEMA4D	XI	3.5ml	0ml	0ml	3.5ml	SST Tubes
Total Blood Volume			**31ml**	**10ml**	**11ml**	

FOR PATIENTS > 10KG

Correlative Study	Appx	Sample volume				Tube Type
		Volume per sample	Total Cycle 1	Total Cycle 2	Subsequent Cycles	
Pharmacokinetic Study	IV	2.5ml	12.5ml	7.5ml	Included with Immunogenicity Samples	SST Tubes
Immunogenicity Study (Anti-Drug Antibody)	V	3.5ml	7ml	3.5ml	3.5ml	SST Tubes
Pharmacodynamics- T lymphocyte saturation/cellular SEMA4D assay	VI	4ml	20ml	4ml	4ml	Cyto-Chex Tubes
Pharmacodynamics- Total Soluble SEMA4D	VII	3.5ml	7ml	3.5ml	3.5ml	SST Tubes
Total Blood Volume			**46.5ml**	**18.5ml**	**11ml**	

APPENDIX III: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN - ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN - 3.0 x ULN
Grade 3:	> 3.0 x ULN - 10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: For the purpose of this study, the ULN for SGPT is 45 U/L regardless of baseline.

Grade 1:	> 45 U/L - ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

AST: For the purpose of this study, the ULN for SGOT is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L - ≤ 150 U/L
Grade 2:	151 U/L - 250 U/L
Grade 3:	251 U/L - 1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN - 20.0 x ULN
Grade 4:	> 20.0 x ULN

APPENDIX IV: PHARMACOKINETIC STUDY FORM FOR PATIENTS > 10KG

COG Pt ID # _____ Cycle # _____ Date: _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg VX15/2503 Dose Level: _____mg/kg VX15/2503 Total Daily Dose: _____mg

Blood samples (2.5 ml) will be collected in SST tubes at the following time points during Cycle 1: Day 1 (2 hrs. after the infusion), Day 4 (at any time point), Day 8 (at any time point), and Day 15 (pre-infusion, and at the end of infusion). For cycle 2, blood samples (2.5 ml) will be collected in SST tubes at the following time points: Day 1 (at the end of infusion, and 2 hrs. after the infusion), and Day 15 (pre-infusion). On Cycle 1 Day 1 (pre-infusion, and at the end of infusion), and Cycle 2 Day 1 (pre-infusion), pharmacokinetic blood samples (3.5 ml) will be collected in conjunction with immunogenicity samples in SST tubes. For subsequent cycles pharmacokinetic samples (3.5 ml) will be collected in conjunction with immunogenicity samples in SST tubes on Day 1 prior to infusion.

Record the exact time the sample is drawn along with the exact time VX15/2503 is given on Days 1 and 15.

Blood Sample No.	Cycle 1 Timepoint	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to Cycle 1 Day 1 VX15/2503 infusion	___/___/___	|__|__| : |__|__|
VX15/2503 on Cycle 1 Day 1		**Date:**___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|		
2	**Day 1**	At the end of infusion on Cycle 1 Day 1 VX15/2503	___/___/___	|__|__| : |__|__|
3	**Day 1**	2 hrs. following infusion on Cycle 1 Day 1 VX15/2503 infusion	___/___/___	|__|__| : |__|__|
4	**Day 4 (+/ - 1 Day)**	Any time point	___/___/___	|__|__| : |__|__|
5	**Day 8 (+/ - 1 Day)**	Any time point	___/___/___	|__|__| : |__|__|
6	**Day 15**	Prior to Day 15 VX15/2503 infusion		
VX15/2503 on Cycle 1 Day 15		**Date:**___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|		
7	**Day 15**	At the end of infusion on Cycle 1 Day 15 VX15/2503	___/___/___	|__|__| : |__|__|
Blood Sample No.	**Cycle 2 Timepoint**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Sample Collected (24-hr clock)**
8	**Day 1**	Prior to Day 1 VX15/2503 infusion	___/___/___	|__|__| : |__|__|
VX15/2503 on Cycle 2 Day 1		**Date:**___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|		
9	**Day 1**	At the end of infusion on Cycle 2 Day 1 VX15/2503	___/___/___	|__|__| : |__|__|
10	**Day 1**	2 hrs. following infusion on Cycle 2 Day 1 VX15/2503 infusion	___/___/___	|__|__| : |__|__|
11	**Day 15**	Prior to Cycle 2 Day 15 VX15/2503 infusion		
VX15/2503 on Cycle 2 Day 15		**Date:**___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|		

Subsequent Cycles (cycle 3 onwards)				
Blood Sample No.	**Timepoint**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Collected (24-hr clock)**
1	Cycle #_____	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 Infusion on Day 1 Date: ___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.3.6. See Section 8.3 for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX V: IMMUNOGENICITY STUDY FOR PATIENTS > 10KG

COG Pt ID # _____ Cycle # _____ Date: _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg VX15/2503 Dose Level: _____mg/kg VX15/2503 Total Daily Dose: _____mg

Blood samples (3.5 ml) will be collected in consenting patients in SST tubes during Cycle 1 at the following time points: Day 1 (pre-infusion and at the end of infusion) and each subsequent cycle on Day 1 prior to infusion. All of these blood draws will be used for both immunogenicity and pharmacokinetic analysis.

Record the exact time the sample is drawn along with the exact time VX15/2503 is given on Days 1 and 15.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Collected (24-hr clock)
1	Cycle 1, Day 1	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 Infusion on Day 1 Date:___/___/___ Infusion Start Time: |__|__| : |__|__| **Infusion End Time:** |__|__| : |__|__|				
2	Cycle 1, Day 1	At the end of VX15/2503 infusion		|__|__| : |__|__|

Subsequent Cycles (Cycle 2 onwards)				
Blood Sample No.	**Time Point/Cycle Number**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Collected (24-hr clock)**
1	Cycle #_____	Prior to VX15/2503 infusion		|__|__|:|__|__|
VX15/2503 Infusion on Day 1 Date:___/___/___ Infusion Start Time: |__|__| : |__|__| **Infusion End Time:** |__|__| : |__|__|				

One copy of this Immunogenicity Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.4.6 . See Section 8.4 for detailed guidelines for packaging and shipping PD samples.

Record any notes for Sample Storage Conditions below.

Notes_____
_____
_____
_____
_____
_____
_____

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX VI: PHARMACODYNAMICS T-LYMPHOCYTE SATURATION (FOR ALL PATIENTS)

COG Pt ID # _____ Cycle # _____ Date: _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg VX15/2503 Dose Level: _____mg/kg VX15/2503 Total Daily Dose: _____mg

Blood samples (4 ml) will be collected in consenting patients in cyto-chex tubes during Cycle 1 at the following time points: Day 1 (pre-infusion and at the end of infusion), Day 15 (pre-infusion and at the end of infusion), and Day 28 (at any time point). Blood samples (4 ml) will be collected in consenting patients prior to infusion on Day 1 for each subsequent cycle.

Record the exact time the sample is drawn along with the exact time VX15/2503 is given on Day 1 and Day 15.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Collected (24-hr clock)
1	Cycle 1, Day 1	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				
2	Cycle 1, Day 1	At the end of VX15/2503 infusion		|__|__| : |__|__|
3	Cycle 1, Day 15	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				
4	Cycle 1, Day 15	At the end of VX15/2503 infusion		|__|__| : |__|__|
5	Cycle 1, Day 28	Any time point		|__|__| : |__|__|

Subsequent Cycles (Cycle 2 onwards)				
Blood Sample No.	**Time Point/Cycle Number**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Collected (24-hr clock)**
1	Cycle #_____	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				

One copy of this Pharmacodynamic T-Lymphocyte Saturation Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.5.6. See Section 8.5 for detailed guidelines for packaging and shipping PD samples.

Record any notes for Sample Storage Conditions below.

Notes:

_____
_____
_____
_____
_____

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX VII: PHARMACODYNAMICS TOTAL SOLUBLE SEMA4D FOR PATIENTS > 10KG

COG Pt ID # _____ Cycle # _____ Date: _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg VX15/2503 Dose Level: _____mg/kg

VX15/2503 Total Daily Dose: _____mg

Blood samples (3.5 ml) will be collected in consenting patients in SST tubes during Cycle 1 at the following time points: Day 1 (pre-infusion and at the end of infusion) and each subsequent cycle on Day 1 prior to infusion.

Record the exact time the sample is drawn along with the exact time VX15/2503 is given on Days 1 and 15.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Collected (24-hr clock)
1	Cycle 1, Day 1	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				
2	Cycle 1, Day 1	At the end of VX15/2503 infusion		|__|__| : |__|__|

Subsequent Cycles (cycle 2 onwards)				
Blood Sample No.	**Time Point/Cycle Number**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Collected (24-hr clock)**
1	Cycle #_____	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				

One copy of this Pharmacodynamic Total Soluble SEMA4D Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.6. See Section 8.6.6 for detailed guidelines for packaging and shipping PD samples.

Record any notes for Sample Storage Conditions below.

Notes_____
_____
_____
_____
_____
_____

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX VIII: TISSUE STUDIES FORM

COG Pt ID # _____ **ACC #** _____ **Date:**_____ Part of Study # ____
(Please do not write patient names on this form or on samples)

Sample Labeling:
Samples should be labeled with the following information:

Protocol number: **ADVL1614**
Institution: _____
Patient ID #: _____
Accession #: _____
Sample Date: _____
Site of Acquired Tissue: _____

Tissue obtained at (check one option below):
☐Diagnosis ☐Relapse ☐Subsequent Resection/Biopsy

Tissue sample is from a:
☐ Resection or ☐ Biopsy

Shipment of Tumor Tissue:
Tissue is requested from original diagnosis, relapse, or any subsequent resection or biopsy prior to treatment with VX15/2503. Archived tissue samples should be in the form of a paraffin-embedded tissue block or 8-10 unstained slides from the tissue block accompanied by a copy of the pathology report. Fine needle aspirate samples or other cytology samples are not acceptable and tumor samples obtained from bone metastases are generally not considered acceptable.

All blocks or slides must be labeled with the patient's study registration number (COG Patient ID #), the study I.D. (ADVL1614), and the sample collection date. Data should be recorded on this Tissue Studies Form, which must accompany the sample(s) to the address provided in Section 8.7.3.

1. **If sending paraffin block (PREFERRED):**
   a. Place appropriate sample ID label on back of cassette
   b. Place labeled cassette in a Zipper lock bag
   c. Paraffin blocks are shipped to the lab at **ambient temperature**. It is acceptable to send blocks refrigerated if sending blocks and slides together.

2. **If sending slides:**
   If slides will be cut from tissue block, recommended thickness of tissue sections for slides is 4 microns. Positively charged slides are required (Superfrost Plus is recommended). After cutting, the slides should be kept in refrigerator (2-5°C).
   a. Place slides in the plastic slide holder and place sample ID label provided on the slide holder
   b. Place the slide holder in the Zipper lock bag and eliminate as much air (and therefore moisture) as possible prior to sealing the Zip-lock bag
   c. Slides are shipped to the lab **at refrigerated temperature on a cold gel pack**. It is acceptable to send blocks refrigerated if sending blocks and slides together.

One copy of this form should be uploaded into RAVE.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX IX: PHARMACOKINETIC STUDY FORM FOR PATIENTS ≤ 10KG

COG Pt ID # _____ Cycle # _____ Date: _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg VX15/2503 Dose Level: _____mg/kg VX15/2503 Total Daily Dose: _____mg

Blood samples will be collected in SST tubes at the following time points during Cycle 1: Day 1 (pre-infusion [3.5 ml], at the end of infusion [2.5 ml], and 2 hrs. after the infusion [2.5 ml]), and Day 15 (pre-infusion [2.5 ml]). For Cycle 2, blood samples will be collected in SST tubes at the following time points: Day 1 (pre-infusion [3.5 ml]) and Day 15 (pre-infusion [2.5 ml]). For subsequent cycles pharmacokinetic blood samples (3.5 ml) will be collected in conjunction with immunogenicity samples in SST tubes on Day 1 prior to infusion.

Record the exact time the sample is drawn along with the exact time VX15/2503 is given on Days 1 and 15.

Blood Sample No.	Cycle 1 Timepoint	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	Day 1	Prior to Cycle 1 Day 1 VX15/2503 infusion	___/___/___	|__|__| : |__|__|
VX15/2503 on Cycle 1 Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				
2	Day 1	At the end of infusion on Cycle 1 Day 1 VX15/2503	___/___/___	|__|__| : |__|__|
3	Day 1	2 hrs. following infusion on Cycle 1 Day 1 VX15/2503 infusion	___/___/___	|__|__| : |__|__|
4	Day 15	Prior to Day 15 VX15/2503 infusion		
VX15/2503 on Cycle 1 Day 15 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				

Blood Sample No.	Cycle 2 Timepoint	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
5	Day 1	Prior to Day 1 VX15/2503 infusion	___/___/___	|__|__| : |__|__|
VX15/2503 on Cycle 2 Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				
6	Day 15	Prior to Cycle 2 Day 15 VX15/2503 infusion		
VX15/2503 on Cycle 2 Day 15 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				

Subsequent Cycles (cycle 3 onwards)				
Blood Sample No.	**Timepoint**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Collected (24-hr clock)**
1	Cycle #_____	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 Infusion on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.3.6. See Section 8.3 for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX X: IMMUNOGENICITY STUDY FOR PATIENTS ≤ 10KG

COG Pt ID # _____ Cycle # _____ Date: _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg VX15/2503 Dose Level: _____mg/kg VX15/2503 Total Daily Dose: _____mg

Blood samples (3.5 ml) will be collected in consenting patients in SST tubes during Cycle 3 and each subsequent cycle on Day 1 prior to infusion. All of these blood draws will be used for both immunogenicity and pharmacokinetic analysis.

Record the exact time the sample is drawn along with the exact time VX15/2503 is given on Day 1 of Cycle 3 and each subsequent cycle.

Cycle 3 Onwards				
Blood Sample No.	**Time Point/Cycle Number**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Collected (24-hr clock)**
1	Cycle #_____	Prior to VX15/2503 infusion		|__|__|:|__|__|
VX15/2503 Infusion on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **Infusion End Time:** |__|__| : |__|__|				

One copy of this Immunogenicity Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.4.6 . See Section 8.4 for detailed guidelines for packaging and shipping immunogenicity samples.

Record any notes for Sample Storage Conditions below.

Notes_____
_____
_____
_____
_____
_____

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX XI: PHARMACODYNAMICS TOTAL SOLUBLE SEMA4D FOR PATIENTS ≤ 10KG

COG Pt ID # _____ Cycle # _____ Date: _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg VX15/2503 Dose Level: _____mg/kgVX15/2503

Total Daily Dose: _____mg

Blood samples (3.5 ml) will be collected in consenting patients in SST tubes during Cycle 3 and each subsequent cycle on Day 1 prior to infusion.

Record the exact time the sample is drawn along with the exact time VX15/2503 is given on Day 1 of Cycle 3 and each subsequent cycle.

Cycle 3 Onwards				
Blood Sample No.	**Time Point/Cycle Number**	**Scheduled Collection Time**	**Actual Date Sample Collected**	**Actual Time Collected (24-hr clock)**
1	Cycle #_____	Prior to VX15/2503 infusion		|__|__| : |__|__|
VX15/2503 on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				

One copy of this Pharmacodynamic Total Soluble SEMA4D Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.6. See Section 8.6.6 for detailed guidelines for packaging and shipping PD samples.

Record any notes for Sample Storage Conditions below.

Notes_____
_____
_____
_____
_____
_____

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX XII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1614
(for children from 7 through 12 years of age)

A study of VX15/2503 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 VX15/2503. You will also have regular tests and exams done more often while you are in this study. The doctors want to see if VX15/2503 will make children with your type of cancer get better. We don't know if VX15/2503 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 VX15/2503 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 VX15/2503 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 VX15/2503 works.

APPENDIX XIII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1614
(for teens from 13 through 17 years of age)

A study of VX15/2503 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.

3. Children and teens who are part of this study will be given a cancer-fighting medicine called VX15/2503. VX15/2503 is an antibody (a protein that makes up part of the immune system) that binds to an antigen (a substance that activates the immune system) and therefore blocks the antigen from working to increase tumor growth. We are using VX15/2503 in this study because it seems to work against certain types of cancer cells in test tubes and animals. VX15/2503 is considered experimental because the Food and Drug Administration (FDA) has not approved this drug. The dose of VX15/2503 used in this study was found to be well-tolerated in adults.

4. You will get VX15/2503 by IV on Days 1 and 15 of a 28-day period. This entire 28-day period is called a cycle. You may continue to receive VX15/2503 for up to about 12 months (up to 13 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 VX15/2503. The doctors want to see if VX15/2503 will make children with your type of cancer get better. We don't know if VX15/2503 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 VX15/2503 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 VX15/2503 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 VX15/2503 works. The samples will come from leftover tissue so there would be no extra procedures.