CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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A National Cancer Institute-supported member group of the National Clinical Trials Network

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Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

The Study Committee for **ACNS1022**, *A Phase II Randomized Trial of Lenalidomide (NSC # 703813) in Pediatric Patients with Recurrent, Refractory or Progressive Juvenile Pilocytic Astrocytomas and Optic Pathway Gliomas*, has provided Amendment #6 for CTEP review.

The submission of this amendment is in response to an RRA from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). Revisions to the protocol are detailed in the summary of changes below.

The ACNS1022 Study Committee looks forward to approval of this amendment. Please contact me with any questions or concerns.

Sincerely,

Nina Butingan, MBS, Protocol Coordinator (for)
Katherine Warren, MD, ACNS1022 Study Chair
Peter Adamson, MD, Children's Oncology Group Chair

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General		The amendment number has been updated.
2.	General		The version date has been updated.
3.	General		The Study Chair's phone number has been updated.
4.	Table of Contents	2-4	The Table of Contents has been updated.
5.	6.1	30-37	The drug monograph for lenalidomide has been updated.
6.	11.0	51-55	Changes have been made to the section based on CTCAE version 5.0.

Activated: March 19, 2012
Closed: January 18, 2017
Version Date: 6/1/2018
Amendment #: 6

CHILDREN'S ONCOLOGY GROUP

ACNS1022

A Phase II Randomized Trial of Lenalidomide (NSC # 703813) in Pediatric Patients with Recurrent, Refractory or Progressive Juvenile Pilocytic Astrocytomas and Optic Pathway Gliomas

NCI Supplied Agent: Lenalidomide (NSC# 703813)

A Groupwide Phase II Study

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AGENT NSC# AND IND#'s
Lenalidomide NSC#703813

SEE SECTION 13 FOR SPECIMEN SHIPPING ADDRESSES

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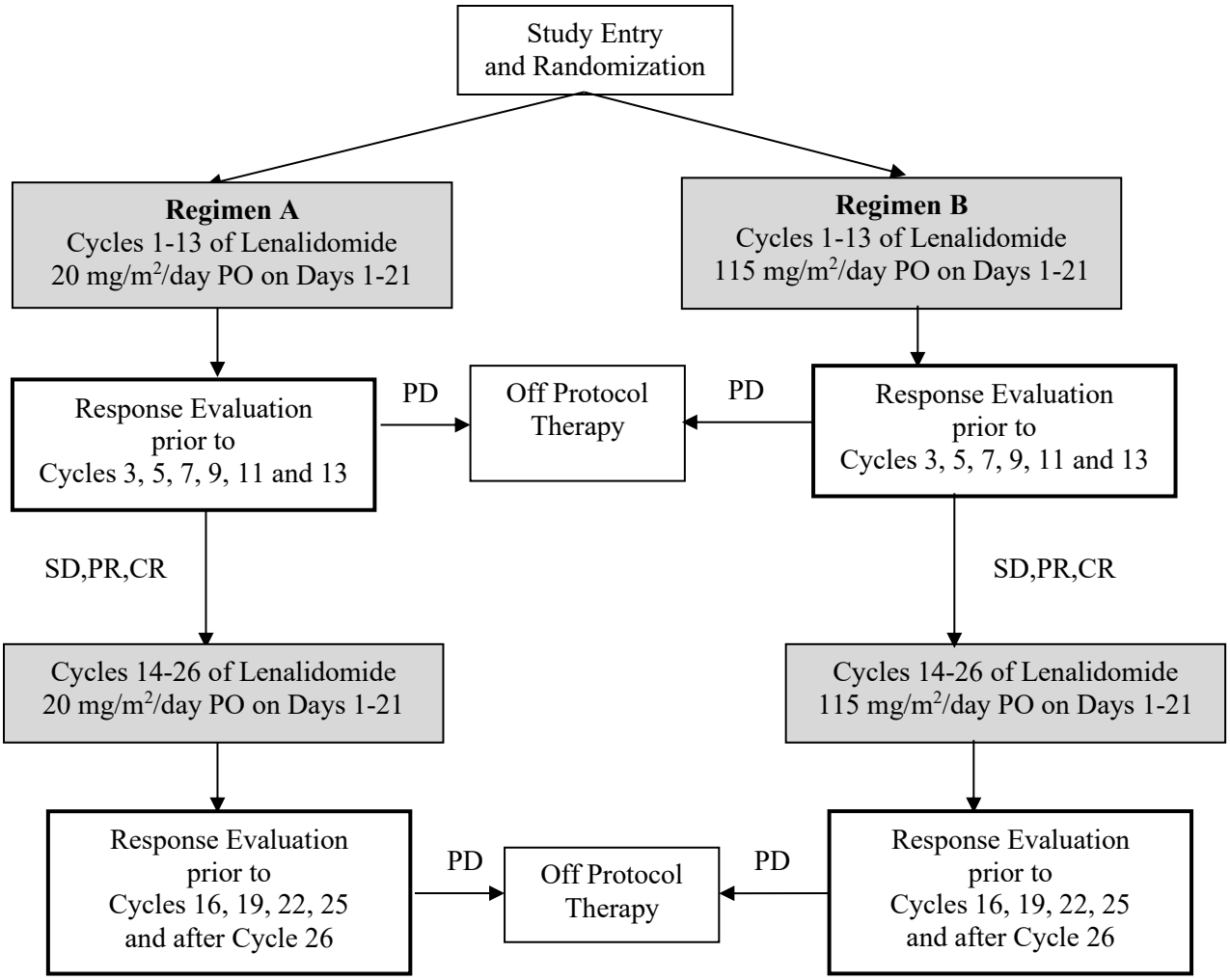
ABSTRACT

Given the poor outcome of patients with recurrent or refractory gliomas and the limited activity of most cytotoxic agents, new agents with novel mechanisms of action are needed. Inhibition of angiogenesis offers a new approach based upon the dependence of tumor growth on angiogenesis. Lenalidomide is an oral agent with both antiangiogenic and immunomodulatory activity that is well-tolerated in adults and children, and appears to have some activity in childhood CNS tumors.

This study is a randomized comparison of response rate among patients with recurrent, refractory or progressive juvenile pilocytic astrocytomas and optic pathway gliomas who are treated with lenalidomide. Lenalidomide will be given either as a low dose (20 mg/m^2/dose) or high dose (115 mg/m^2/dose) regimen PO for 21 days of each 28 day cycle. Treatment will continue for a maximum of 26 cycles in the absence of disease progression or unacceptable side effects. Response will be evaluated prior to every other cycle for the first 13 cycles and prior to every third cycle for cycles 14-26. Correlation of steady state pharmacokinetic levels with patient outcome will be performed.

EXPERIMENTAL DESIGN SCHEMA



Note: Each cycle is 28 days
PD = Progressive Disease
SD = Stable Disease
PR = Partial Response
CR = Complete Response

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objective

To determine the objective response rate of children with recurrent, refractory or progressive juvenile pilocytic astrocytomas and optic pathway gliomas who are treated with Regimen A low-dose
(20 mg/m^2/dose) or Regimen B high-dose (115 mg/m^2/dose) lenalidomide.

1.2 Secondary Objectives

1.2.1
To estimate the event-free survival (EFS) (based on standard two-dimensional tumor measurements, determined by each institution) of children with recurrent, refractory or progressive juvenile pilocytic astrocytomas and optic pathway gliomas who are treated with lenalidomide.

1.2.2
To compare response categories and EFS across the 3 MR sequences (T2-weighted, FLAIR, T1-weighted post-contrast).

1.2.3
To correlate steady state pharmacokinetics of lenalidomide (1 sample obtained between Days 5-21) with objective response and EFS.

1.2.4
To evaluate toxicities of long term lenalidomide use.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Brain tumors are the most common solid tumors of childhood, with an annual incidence of 33 per 1,000,000 children. Low-grade gliomas are the most common, representing 1/3 of all childhood primary CNS tumors. While treatment of these lesions is somewhat controversial, the general consensus is that these lesions are best treated with surgical resection if this can be performed without significant sequelae. Frequently, complete resection is not feasible without significant morbidity. Five- and ten-year progression-free survival rates for children with incomplete resections are 50% and 38%, respectively.[1, 2] Radiation therapy and chemotherapy are utilized in the setting of incomplete resection, but radiation may be associated with significant side effects. In addition, in a recent analysis, adults with low-grade gliomas who received postoperative radiation therapy had an improved 5 year progression-free survival (PFS), but overall survival (OS) was not significantly different.[3] In pediatric patients, particularly those younger than 10 years and those with neurofibromatosis type I (NF1), chemotherapy is frequently utilized in an effort to postpone radiation therapy and its accompanying neurotoxic effects.

Low-grade gliomas are a histologically heterogeneous group of tumors. Significant interobserver variability has been documented for pathologic diagnosis and grading.[4,5] This is further complicated by the fact that some tumors are diagnosed by biopsy alone, which may not be representative of the entire tumor. The course of the disease in patients with

low-grade gliomas can be unpredictable. While some patients are symptomatic, some lesions, particularly those associated with NF1, represent incidental findings and the disease may be indolent.

The major goals for treating unresectable lesions are therefore prevention of tumor progression and ablation of associated symptoms, while minimizing side effects of treatment. Radiation therapy has been shown to have efficacy, but is associated with cognitive deficits, cerebrovascular sequelae, endocrinologic dysfunction and second malignancies. Many low-grade gliomas are chemosensitive tumors and chemotherapeutic regimens have been used to delay or avoid radiation therapy. Chemotherapeutic regimens that have resulted in objective responses and increased PFS for patients with low-grade gliomas include vincristine and carboplatin, and the combination procarbazine, lomustine, vincristine dibromodulcitol and 6-thioguanine.[6,7] In a study of children with newly diagnosed low-grade gliomas with evidence of progression, 56% had an objective response to vincristine/carboplatin and PFS was 68 ± 7% at 3 yrs.[8] In children with recurrent low-grade gliomas, 52 ± 10% of assessable patients had an objective response to this chemotherapy regimen.[6] However, these chemotherapeutic regimens are associated with significant toxicities, including allergic reactions to carboplatin.

Temozolomide and weekly vinblastine are alternative chemotherapeutic regimens. In the COG Phase II study of temozolomide given on a 5-day every 28 day schedule to children with recurrent CNS tumors (A09701), 1/21 patients with low-grade glioma had an objective response.[9] Despite this low objective response rate, 41% of patients remained on study for 12 courses with no evidence of progression. In a second study of children with progressive or recurrent low-grade gliomas treated with temozolomide on a 5/28 day cycle, 11% of patients with optic pathway/pilocytic astrocytomas had a partial response and 38% had stable disease.[10] Although it appears to have modest activity, temozolomide is associated with hematologic toxicity and a potential risk of second malignancy. In A09701, 25% of patients had Grade 3 or 4 thrombocytopenia and 19% had Grade 3 or 4 neutropenia during cycle 1.

Weekly vinblastine has also been studied in the recurrent setting. In a Phase II study of weekly vinblastine in children with recurrent or refractory low-grade gliomas, 57% completed 52 weeks of chemotherapy.[11] Objective responses occurred in 40% of patients. Patients in this study were eligible at the time of first recurrence, and disease progression was defined radiographically by either 2 dimensional (≥ 25% increase) or 3-dimensional (≥ 40% increase) criteria, confirmed at 8 weeks. More than 50% of these patients required a dose reduction for toxicity. It is important to note that these Phase II studies were performed in a heterogeneous group of patients with small numbers, different eligibility requirements and different definitions of progression. Toxicity was fairly significant.

Juvenile pilocytic astrocytomas are the most common low-grade glioma in the pediatric age group[12,28,] but, historically, low-grade gliomas have been consolidated into one diagnostic category for the purposes of clinical trials. Biological data on low-grade astroctytomas has recently emerged, challenging this concept.

2.2 Angiogenesis in Childhood CNS Tumors

Angiogenesis plays a role in tumor growth, including tumors of the CNS. Brain tumors have demonstrated intense neovascularization and produce potent angiogenic mediators.[13,14] Several types of childhood CNS tumors, including low-grade astrocytic,

high-grade astrocytic, and embryonal tumors exhibit significant angiogenic activity.[15] Over the last decade, several of the mechanisms involved in tumor-induced angiogenesis have been elucidated. The most direct of these mechanisms is the secretion of cytokines with angiogenic properties by the tumor cells. Examples of such cytokines include acidic and basic fibroblastic growth factor (α,β-FGF), angiogenin, vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNF-α).[16-17] Alternately, tumor cells can release angiogenic peptides through the production of proteases and the subsequent breakdown of the extracellular matrix where some cytokines are stored (i.e. βFGF). Angiogenesis can also be induced indirectly through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (i.e. TNF-α, βFGF).[18]

2.3 Thalidomide

Thalidomide is a drug with a broad spectrum of activity, including anti-angiogenic properties. It inhibits growth factor-mediated neovascularization, is a known inhibitor of TNF-α, and has demonstrated inhibition of tumor growth in solid tumor models. Thalidomide costimulates T cells *in vitro*, inducing cytokine production (including IL-2 and IFN-γ) and cytotoxic responses.[19] In clinical trials of this agent in adults with recurrent high-grade gliomas, some anti-tumor activity was observed (4/36 objective radiographic responses in one study, with 12/36 stable disease (SD) for minimum of 2 months), although the overall response rate was low.[20,21]

2.4 Lenalidomide (CC-5013)

Lenalidomide is a potent analog of thalidomide and is classified as an immunomodulatory agent. Like thalidomide, it exerts a broad spectrum of pharmacologic and immunologic effects. Lenalidomide has been shown to be more potent than thalidomide in stimulating proliferation of T cells following primary induction by T-cell receptor (TCR) activation, and more potent than thalidomide in augmenting production of IL-2 and IFN-γ following TCR activation of PBMC (IL-2) or T-cells (IFN-γ). Lenalidomide also exhibits dose-dependent inhibition of LPS-stimulated production of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 by PBMC, and increased production of the anti-inflammatory cytokine IL-10 by LPS-stimulated PBMC. Lenalidomide up-regulates caspase 8 and down-modulates leukocyte adhesion molecules. In contrast to thalidomide, lenalidomide stimulates activity of NK cells and induces G1 growth arrest of tumor cells. Lenalidomide exhibits significant antiangiogenic properties. It inhibits vascularization by inhibiting endothelial cell migration, rather than endothelial cell proliferation, and is an inhibitor of βFGF, VEGF, and TNF-α. (Investigator Brochure)

Lenalidomide has been studied for use in patients with multiple myeloma, MDS, solid tumors and congestive heart failure. In Phase I clinical trials of lenalidomide in patients with multiple myeloma treated for 28 days at doses of 5 mg-50 mg per day, neutropenia and thrombocytopenia were the most common toxicities.[22] Grade 4 neutropenia was observed in 1 patient at dose level 5 mg, 1 patient at dose level 25 mg; grade 3 neutropenia was observed in 2 patients at dose level 10 mg, 2 patients at dose level 25 mg and 4 patients at dose level 50 mg. Grade 3 thrombocytopenia was observed in 1 patient at each of the dose levels (5 mg, 10 mg, 25 mg, 50 mg). In an adult study of patients with solid tumors, 16 patients with various solid tumors were enrolled at doses ranging from 5 mg/day –150 mg/day for six weeks. [24,30] The majority of patients treated above 25 mg/day developed dose-limiting neutropenia or thrombocytopenia. Additional adverse events considered possibly, probably or definitely related to lenalidomide were mild to moderate in severity

and included rash, paresthesias, peripheral neuropathy, leg or hand cramps, taste disturbance, dry mouth, fever, nausea, vomiting, achiness, myalgias, generalized pains, bone pain, headache, itchy eye, constipation, bloating, cough, aphasia, tinnitus, pharyngitis, epistaxis, lightheadedness, shortness of breath, depression, night sweats, insomnia, dry skin, sinus congestion, urinary frequency, elevated SGOT, hyperuricemia, hyperglycemia, and elevated creatinine.

In a Phase I study of lenalidomide administered daily to adults with refractory metastatic cancer (median age 66 yrs), an episode of thrombosis (dose-limiting) and Grade III hypotension was observed at a dose of 20 mg/day.[23] Other toxicities (nausea, vomiting, diarrhea, rash, dizziness, peripheral neuropathy, fatigue, bone marrow suppression) were mild. In a second study of lenalidomide in adults with solid tumors (primarily melanoma and renal cell carcinoma), daily doses of 5-150 mg/day were well tolerated. Grade 4 neutropenia was observed in 2 patients receiving > 50 mg/day.[24] In a Phase I study in adults with recurrent high-grade gliomas, lenalidomide at doses of 40 mg/day x 21 days was well tolerated and no MTD was defined. This dose of 40 mg daily was predetermined to be the maximum dose to be tested in the adult glioma population based on some, but not all, prior Phase I adult studies which demonstrated myelosuppression at doses ≥ 50 mg/day.

A Phase I study of lenalidomide was recently performed within the COG in pediatric patients with relapsed or refractory solid tumors or myelodysplastic syndrome. (ADVL0319) The primary objectives were to determine the maximum tolerated dose and recommended Phase II dose for children with refractory solid tumors and describe the toxicities in this population. Doses up to 70 mg/m^2/day x 21 days followed by a 7-day rest were evaluated. Although 6 episodes of dose-limiting toxicity (DLT) were observed, they were sporadic and not clearly associated with dose. These DLTs included Grade 3 hypercalcemia, Grade 3 hypophosphatemia, Grade 3 hypokalemia, Grade 4 neutropenia, Grade 3 somnolence, and Grade 3 urticaria and occurred at doses ranging from 15 mg/m^2 to 55 mg/m^2. [29] No MTD was reached. The majority of patients on this study did not receive more than one course of therapy.

A Phase I trial of lenalidomide in pediatric patients with recurrent, refractory or progressive CNS tumors performed within the Pediatric Brain Tumor Consortium (PBTC-018) has recently closed to accrual.[25] Fifty-one patients were enrolled; 44 patients are evaluable for toxicity and response. Patients were treated at doses of 15-116 mg/m^2/day for 21 days followed by a 7 day rest period (one course is 21 days of therapy + 7 day break). A maximum tolerated dose has not been reached. The agent has been well tolerated. Two DLTs were reported with an unclear association with lenalidomide. One patient treated at the 20 mg/m^2/day dose level had cardiac dose limiting toxicity with a presumed myocardial infarct and elevated troponin. This patient had multiple risk factors for thromboembolism. One patient at dose level 68 mg/m^2/day had dose-limiting fatigue but had concurrent disease progression. Twenty-three patients, representing all dose levels, received 6 or more courses of treatment and 9 patients have received 12 or more courses to date.

On this study (PBTC-018), myelosuppression was the primary toxicity and occurred sporadically. No patient had Grade 4 myelosuppression during Course 1. Myelosuppression for patients treated for ≥ 6 cycles was also sporadic and not clearly associated with dose, although data at the higher dose levels shows a possible trend toward more frequent episodes of Grades 3 and 4 myelosuppression at dose levels ≥68 mg/m^2/day. Other common toxicities include fatigue (30%), gastrointestinal symptoms including

nausea (10%), emesis (4%), diarrhea (16%), and constipation (8%), as well as rash (14%) and muscle cramping (10%). It is also unclear if responses were dose-related. Objective responses (two partial responses, diagnoses JPA, OPG) were reported at doses of ≥ 88 mg/m^2/day. Of note, nine patients with recurrent, refractory or progressive optic pathway gliomas enrolled on study have received 8, 12+, 24, 24, 12, 13, 11 and 11+ cycles of therapy to date. Dose levels for these patients ranged from 15-116 mg/m^2/day. Of 12 patients with JPA, 8 have received ≥ 6 courses to date at doses ranging from 68-116 mg/m^2/day. Other patients with low-grade gliomas, including third ventricular astrocytomas (2 patients) and ganglioglioma (1 patient) have received 22, 24 and 12 courses, respectively. No patient with glioblastoma (n=4) received more than one course of therapy. Results from pharmacokinetic analysis show a linear relationship between lenalidomide dose and C_{max} and $AUC_{24\ hrs}$.

Early phase clinical trials of noncytotoxic (eg, antiangiogenic) agents in patients with brain tumors are complicated by several issues. Conventional endpoints in phase I trials are defined by predetermined toxicity criteria in order to define a maximum tolerated dose (MTD), or, more recently, by biologic endpoints in order to define a biologically effective dose. Standard phase I studies are designed to best identify acute, rather than long-term toxicities. Antiangiogenic agents frequently have little acute toxicity and may need to be administered chronically. They may be effective at doses well below the MTD and therefore dose escalations to the MTD may be unnecessary. However, defining a biologically effective dose is difficult as there is a lack of validated biological surrogate markers. Although objective responses were observed in the Pediatric Phase I trial at the higher dose levels and preliminary PK data suggests increasing exposure with increasing dose, it is unclear if response to this agent is dose related. We will therefore estimate activity in two cohorts, with patients receiving Regimen A low-dose (20 mg/m^2/day) or Regimen B high-dose (115 mg/m^2/day) lenalidomide.

Efficacy of an agent in patients with brain tumors is historically defined in phase II trials by measuring response of the tumor based upon two-dimensional measurements using post-contrast MRI scans. These endpoints are neither ideal, nor applicable, when evaluating cytostatic agents, such as antiangiogenic agents, in patients with CNS tumors, especially with tumors such as low grade gliomas, that have variable and sometimes heterogeneous enhancing patterns and frequently contain cystic areas. Time-dependent endpoints, such as time to tumor progression, may be more appropriate for this group of agents in this patient population. However, this can be complicated by the erratic growth patterns of low-grade gliomas. The majority of clinical studies estimating activity report objective response rate as the primary objective. We will therefore evaluate both objective response rate and event-free survival in this study.

In summary, lenalidomide is a well-tolerated, novel agent that appears to have some activity in childhood CNS tumors. Although it has immunomodulatory, anti-inflammatory and antiangiogenic activity, its exact antitumor mechanism is unclear. It is unclear if a dose-response relationship exists or if the primary toxicity (myelosuppression) is dose-related. Long-term toxicities have not been fully evaluated. Given its apparent activity profile in children with low-grade gliomas enrolled on the pediatric Phase I study (PBTC-018), we are proposing a Phase II trial of lenalidomide in a subset of this population. Initial dosing will be 20 mg/m^2/day on Regimen A and 115 mg/m^2/day on Regimen B, which is the maximum dose evaluated in the PBTC-018 Phase I study. Two dose reductions will be allowed as long as the patient is deriving clinical benefit. Response as defined in this trial

will include the objective response rate and long term stable disease; EFS will also be determined and compared to the objective response rate. It is expected that a number of these patients will remain on therapy for an extended period of time and therefore the long-term hematologic tolerability of this agent will be evaluated.

2.5 Rationale for Pharmacokinetic Studies

In order to obtain more information regarding a potential dose-response relationship and to further determine if myelosuppression is dose-related, pharmacokinetic studies will be performed in all patients in this study. Steady state PK levels of lenalidomide will be performed prior to administering the daily dose any day between Days 5-21 on Cycle 1 and again between Days 5-21 on any cycle following a dose reduction. Correlation of steady state levels and best response at the patient dose will be performed. A single blood sample (2 ml in a heparinized tube) will be collected at up to three time-points and pharmacokinetic analyses will be performed using HPLC.

2.6 Rationale for Imaging Studies

To date, there are no reliable biologic surrogate markers established in humans for the effect of lenalidomide in children with CNS tumors. It is unclear if objective response in patients with low grade gliomas correlates with progression-free survival. In this study, standard COG MRI sequences, including T2-weighted, FLAIR, and T1-weighted post contrast, will be retrospectively reviewed to compare response categories with event-free survival.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

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

Please see Appendix X for detailed CTEP Registration Procedures for Investigators and Associates, and CTSU Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the Cancer Trials Support Unit (CTSU) Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional

CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

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

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

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

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

CRAs/Site Investigators should refer to the COG website to determine if the study is currently open for accrual. **If the study is active, a reservation can be made by following the steps below**:

1) Log in to https://www.ctsu.org and enter your CTEP IAM user name and password to access the CTSU members area. Then, click on the following link: https://www.ctsu.org/OPEN_SYSTEM/.
2) Then, click on 'Connect to OPEN' link, and finally on 'Create New Registration' link.
3) After entering your Institution CTEP ID and protocol number, click on the 'Slot Availability Information' link to see how many reservations are available for that study.
4) If one or more is available, select step 0 under registration step and complete the remaining questions to obtain a reservation.

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

3.1.4 Study Enrollment

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

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff and the results from the rapid central pathology screening review have confirmed the patient is eligible.

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

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

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

3.1.5 Timing

Female patients of childbearing potential must have negative serum or urine pregnancy test (sensitivity of at least 25 mIU/mL) results performed within 10-14 days and again within 24 hours prior to the anticipated start of protocol therapy. (Refer to Appendix II for definition of female children of childbearing potential [FCCBP]) Also see Exclusion Criteria in Section 3.2.9.3 regarding the requirement for female patients of childbearing potential to commit to complete abstinence or to be on two forms of effective birth control prior to, during, and following protocol therapy.

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 who are started on protocol therapy on this Phase II study prior to study enrollment will be considered ineligible**.

3.1.5.1 Required Counseling

FDA requires that each clinical trials site have two counselors (Investigators are not eligible) trained by Celgene through the Celgene Pregnancy Prevention Counselor Program-Pediatric (CPPCP-PED). The CPPCP-PED is available on the internet for each person who has completed the site counselor identification form (Appendix I) and registered with Celgene prior to completing the CPPCP-PED. Each patient/guardian must be counseled prior to dispensing lenalidomide and

documentation is kept in the patient's records. Both the training certificates and the completed Lenalidomide Education and Counseling Guidance Documents are auditable documents and must be produced upon request. Counselors who wish to counsel patients for different protocols at the same site or for the same protocol at different silts should indicate this on the site counselor form. Please not that counselor training for pediatric patients is separate from training for adult patients. Counselors who previously obtained CPPCP certificates must complete pediatric version. CPPCP-PED, in order to counsel patients in NCI-sponsored pediatric studies.

Examples of healthcare professionals that may be trained counselors include nurses, pharmacists and physicians. Investigators may not serve as designated, trained counselors for the purpose of this study. Trained counselors must complete training using the online program provided free by Celgene. After the training is complete, the counselors must generate a training certificate and provide it to the CTSU for documentation. Sites may not order lenalidomide until documentation for two trained counselors is provided to the appropriate office as instructed in the email from Celgene. Because it may take up to 7 days for training, it is suggested that counselors be identified at the onset of the protocol and receive training as soon as possible after IRB protocol approval.

Following completion of training, the designated counselors will be responsible for counseling subjects prior to any treatment or the dispensing of lenalidomide to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing and that the subject understands the risks associated with lenalidomide. Information pertinent to the risks of lenalidomide that should be used as part of training can be found in the document entitled "Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods" (Appendix II). All investigators should be familiar with this document and the risks associated with lenalidomide. Counseling must be documented by the completion of a Lenalidomide Education and Counseling Guidance Document (Appendix III). No drug will be dispensed until counseling and completion of this document occurs. A copy of this document must be maintained in the patient's medical record. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. Pregnancy test results should be documented on the Lenalidomide Patient Card for Pediatric Patients (Appendix IV). A Lenalidomide Information Sheet (Appendix V) will be supplied with each medication dispense.

Please Note: The counseling requirements for investigational use of lenalidomide are separate from the RevAssist program requirements in the United States and the RevAid^{SM} program in Canada. Participation in these two programs is not required, nor sufficient for use of the investigational lenalidomide product.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.6 Randomization

Randomization will take place at the time a patient is entered On Study via eRDE. Patients will be assigned to receive one of two lenalidomide doses with equal probability: 20 mg/m^2/day (Regimen A – low dose) or 115 mg/m^2/day (Regimen B – high dose). Patients will be stratified according to the number of prior regimens (2 or less regimens versus greater than 2 regimens).

3.2 Patient Eligibility Criteria

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/research record which will serve as the source document for verification at the time of audit.

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Age
Patients must be less than 22 years of age at the time of enrollment.

3.2.2 Body Surface Area (BSA)
Patients must have a BSA ≥ 0.4 m^2 at the time of study enrollment.

3.2.3 Diagnosis
Patients must have a pilocytic astrocytoma or optic pathway glioma that has relapsed, progressed or become refractory to conventional therapy. Patients with neurofibromatosis (NF-1) are eligible.

3.2.3.1
Patients must have histologic verification of malignancy. Histologic confirmation for patients with optic pathway gliomas will not be required.

3.2.3.2
Patients must have measurable residual disease, defined as tumor that is measurable in two perpendicular diameters on MRI. For a lesion to be considered measurable, it must be at least twice the slice thickness on MRI (i.e visible on more than one slice).

3.2.3.3 Brain and Spine MRI
To document the degree of residual tumor, the following must be obtained (see Section 14.0 for complete details):

3.2.3.3.1
All patients must have a brain MRI with and without contrast (gadolinium) within 1 week prior to study enrollment. For patients on steroids, baseline MRI scans must be performed after at least 1 week at a stable or decreasing dose of steroids.

3.2.3.3.2

All patients with a history of spinal or leptomeningeal disease, and those patients with symptoms suspicious of spinal disease, must have a spine MRI with and without contrast (gadolinium) performed within 2 weeks prior to study enrollment.

3.2.4 Performance Level

Patients must have a Lansky or Karnofsky performance status score of ≥ 60%. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

3.2.5 Prior Therapy

3.2.5.1

Patients must have been treated with at least one prior treatment regimen that included carboplatin. Patients who have received prior radiation therapy for this tumor are eligible.

3.2.5.2

Patients must have recovered (to CTC v.4.0 ≤ Grade 1 unless indicated below) from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study, with the exception of alopecia, weight changes and Grade I or II lymphopenia.

a. Myelosuppressive chemotherapy: Must not have received within 3 weeks of entry onto this study (6 weeks if prior nitrosourea or mitomycin-C).
b. Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. 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.
c. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.
d. Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody. (See table on DVL homepage listing monoclonal antibody half-lives.)
e. Radiation therapy (RT): Patients must have had their last fraction of craniospinal RT ≥ 6 months prior to study entry and their last fraction of focal RT ≥ 4 weeks prior to study entry. If the lesion used for on-study criteria is in the radiation field, there must be evidence of tumor progression after radiation therapy was completed.
f. Study specific limitations on prior therapy:
    1) Patients who have received thalidomide are eligible if all acute thalidomide-related toxicity has resolved.
    2) Patients must not have received lenalidomide previously.

3.2.6 Concomitant Medications Restrictions

(Please see Section 4.2 for the concomitant therapy restrictions for patients during treatment.)

a. Growth factor(s): Must not have received within 2 weeks of entry onto this study.

b. Steroids: Patients who are receiving corticosteroids must be on a stable or decreasing dose for at least 1 week prior to baseline MRI.

3.2.7 Organ Function Requirements

3.2.7.1 Adequate Bone Marrow Function Defined As:

- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

3.2.7.2 Adequate Renal Function Defined As:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
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.

3.2.7.3 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

3.2.7.4 Adequate Pulmonary Function Defined As:

- No evidence of dyspnea at rest and a pulse oximetry > 94% if there is clinical indication for determination.

3.2.8 Patients must be able to swallow intact capsules.

EXCLUSION CRITERIA

3.2.9 Pregnancy and Breast Feeding

3.2.9.1
Female patients who are pregnant are not eligible due to risks of fetal and teratogenic adverse events as seen in animal studies of lenalidomide. Lenalidomide is structurally related to thalidomide, which is known to cause severe life-threatening birth defects in humans.

3.2.9.2
Lactating females are not eligible unless they have agreed not to breastfeed their infants while receiving protocol therapy and for 28 days after the last dose of lenalidomide.

3.2.9.3
Female patients of childbearing potential are not eligible unless they commit to complete abstinence or have been on 2 methods of birth control, including 1 highly effective method and 1 additional method at the same time (unless committing to complete abstinence of heterosexual intercourse) at least 28 days (4 weeks) prior to study enrollment. Sexually active females must also agree to remain on 2 methods of birth control, during treatment (including during dose interruptions), and continuing for at least 28 days after the completion of protocol therapy. Examples of methods of contraception are as follows:

- Highly effective methods (must use at least 1):
    - Intrauterine device (IUD)
    - Hormonal (prescription birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy

- Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical cap

The two methods of birth control requirement applies to all sexually active females unless they have undergone a hysterectomy or bilateral oophorectomy.

3.2.9.4
Female patients of childbearing potential (including those who commit to complete abstinence) are not eligible unless they agree to ongoing pregnancy testing (see Section 4.1 for details) and counseling every 28 days about pregnancy precautions and risks of fetal exposure.

3.2.9.5
Male patients of child fathering potential are not eligible unless they have agreed to use latex condoms during intercourse with a woman of childbearing potential while receiving treatment and for 28 days thereafter.

3.2.10 Pre-existing conditions

3.2.10.1
Patients with a history of thromboembolism unrelated to a central line, or patients with a known predisposition syndrome for thromboembolism are not eligible.

3.2.10.2
Patients who have an uncontrolled or untreated infection are not eligible.

3.2.10.3
Patients with known overt cardiac disease, including but not limited to a history of myocardial infarction, severe or unstable angina, clinically significant peripheral vascular disease, Grade 2 or greater heart failure, or serious and inadequately controlled cardiac arrhythmia are not eligible.

3.2.10.4
Patients with a significant systemic illness that is not well-controlled in the opinion of the treating physician are not eligible.

REGULATORY

3.2.11
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.12
All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Upon enrollment, patients will be randomized to receive one of two treatments with lenalidomide; Regimen A (low dose) versus Regimen B (high dose). Please note there is a requirement for contraception for female patients of childbearing potential, such that they must commit to complete abstinence or agree to use two forms of effective contraception beginning at least 28 days prior to the first dose of lenalidomide and continuing until 28 days after the last dose of lenalidomide. (See Section 3.2.9.4 and Appendix II). The primary study endpoint is objective response. Therapy may continue for a maximum of 26 cycles, in the absence of disease progression (see Section 10.4 for definition) if off protocol criteria have not yet been satisfied (see Section 8.1).

Each cycle of therapy will last 28 days. Lenalidomide will be administered daily for the first 21 days of each cycle followed by a 7 day rest period. The lenalidomide dose for Regimen A will be 20 mg/m^2/day by mouth daily and the dose for Regimen B will be 115 mg/m^2/day by mouth daily. The dose will be rounded to within 10% of the prescribed dose for convenience of capsule size. The calculated dose should be rounded in a manner to minimize the daily number of capsules.

Patients or their guardians will keep a diary to document the intake of each dose of lenalidomide and potential side effects (see Appendix VI). Please instruct patient/parents to record each dose on the diary immediately rather than waiting until a later time. Errors on the diary should be crossed out and initialed. The patient diary should be reviewed with the patient and family at the completion of each treatment cycle, and drug should be accounted for at this time.

Brain MRI will be performed at baseline (within 1 week prior to study enrollment and ≥ 1 week on a stable or decreasing dose of steroids for those patients receiving steroids) and prior to each odd-numbered cycle (ie, prior to cycles 3, 5, 7, 9, 11, and 13) for the first 13 cycles. During cycles 14-26, imaging will be performed prior to every third cycle (ie, prior to cycles 16, 19, 22, and 25), after cycle 26, and as clinically indicated. See Section 14.0 for imaging requirements. Patients with spine disease will also have spine MRI performed at the same timepoints after enrollment, (ie, prior to cycles 3, 5, 7, 9, 11, and 13) for the first 13 cycles. During cycles 14-26, imaging will be performed prior to every third cycle (ie, prior to cycles 16, 19, 22, and 25), after cycle 26, and as clinically indicated.

Pharmacokinetic Study
For all patients, a blood sample must be obtained prior to the daily dose between Day 5-21 of cycle 1 at the time of routine safety lab monitoring. In the event of a dose reduction, a blood sample must also be obtained between Day 5-21 of the first cycle following each dose reduction. Please see Section 13.1 for details on pharmacokinetic sample collection and shipping.

Required Pregnancy Testing During Study Participation
Pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for female patients of childbearing potential, including those who commit to complete abstinence. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, when the patient is taken off protocol therapy, and at Days 14 and 28 following the last dose of lenalidomide. All other female patients of childbearing potential must have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at the time the patient is taken off protocol therapy, and at Day 28 following the last dose of lenalidomide. If pregnancy or a positive pregnancy test does occur during protocol therapy, lenalidomide must be immediately discontinued. Pregnancy testing and counseling must be performed if a patient misses her period, if her pregnancy test is positive, or if her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation.

Pregnancies and suspected pregnancies (including in the partner of a male study patient during study participation) must be reported as an adverse event. See Section 11.0 for adverse event expedited reporting guidelines for pregnancies and suspected pregnancies.

Required Patient Education and Counseling
Counseling about pregnancy precautions and the potential risks of fetal exposure will be conducted every 28 days, on Day 1 of each cycle. See Section 3.1.5.1 for counselor training requirements. Counseling must be completed prior to each dispensing of lenalidomide, and the counseling of each subject must be documented using the Lenalidomide Education and Counseling Guidance Document (Appendix III).

See Section 7.1 for required observations prior to starting protocol therapy.

4.2 Concomitant therapy restrictions

4.2.1
Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients while on this study. The use of alternative or complementary therapies is discouraged.

4.2.2
Radiotherapy is not permitted.

4.2.3
Filgrastim (G-CSF) may be used at the treating physician's discretion in patients with severe neutropenia (i.e. ANC <500/μL) to enhance neutrophil recovery when clinically indicated (for culture proven bacteremia or invasive fungal infections). Prophylactic or routine use of filgrastim in clinically well patients awaiting count recovery is not recommended.

4.2.4
Corticosteroid therapy is permissible only for the treatment of increased intracranial pressure or physiologic replacement. The lowest dose consistent with good medical management should be used. Corticosteroids should NOT be used as an antiemetic due to their effect on the blood brain barrier. Patients on steroids who require an increase in steroid dose for worsening neurologic symptoms should have an MRI performed within 72 hours to rule out tumor progression.

4.2.5
Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Antiemetics should not be given prophylactically for cycle 1.

4.2.6
Anticonvulsants may be administered as clinically indicated. However, it is unclear what effect, if any, lenalidomide has on anticonvulsant pharmacokinetics. It is strongly recommended that anticonvulsant levels be checked at least weekly during the first course of therapy.

4.2.7
Drugs known to be pro-thrombotic (i.e. erythropoietic stimulating agents) should be avoided.

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.3 Lenalidomide Administration

The lenalidomide cycle will be repeated every 28 days. Each cycle will be comprised of lenalidomide orally once daily for 21 days followed by 7 days without lenalidomide. Lenalidomide should be taken at approximately the same time each day. One cycle of lenalidomide is described below. **Lenalinomide is distributed by the NCI DTCD. Do not use commercially available drug.**

Begin Cycle 1 on Day 1 if ANC ≥ 1,000/μL, platelet count ≥ 100,000/μL (transfusion independent), and upon the following:

- confirmation of negative serum or urine pregnancy test (sensitivity of at least 25 mIU/mL) in female patients of childbearing potential,
- confirmation of the use of 2 forms of effective birth control for female patients of childbearing potential OR confirmation of commitment to complete abstinence, and
- completion and documentation of required lenalidomide education and counseling (all patients)

Dose calculations should be based on actual BSA and adjusted as necessary prior to each cycle. There is no maximum dosing.

Lenalidomide: PO once daily
Days: 1 through 21.
Dose: Regimen A (Low Dose): 20 mg/m^2/dose (See Appendix X for Dosing Tables)
Regimen B (High Dose): 115 mg/m^2/dose

Note: The calculated dose should be rounded to within 10% of the prescribed dose for convenience of capsule size. The calculated dose should be rounded in a manner to minimize the daily number of capsules. The dose should be given without food when possible, although this is not mandatory. If a patient vomits a dose within 10 minutes of administration and the capsules are clearly visible, the dose may be repeated. The capsules should be swallowed whole and not opened or chewed.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery maps (TDMs) for this cycle are on the next two pages. See Section 4.3.1 for the Regimen A (Low Dose: 20 mg/m^2/dose) therapy delivery map and Section 4.3.2 for the Regimen B (High Dose: 115 mg/m^2/dose) therapy delivery map.

Following completion of the first cycle, the lenalidomide cycle is repeated for up to a total of 26 cycles, as tolerated and in the absence of disease progression (see Section 10.4 for Response Evaluation). If disease progression occurs, the patient will be taken off protocol therapy.

Susbequent lenalidomide cycles should begin on Day 29 or when ANC ≥ 1,000/µL, platelet count ≥ 100,000/µL (transfusion independent), whichever occurs later, AND once the following criteria have been met:

- confirmation of negative serum or urine pregnancy test (sensitivity of at least 25 mIU/mL),
- confirmation of the use of 2 effective methods of birth control for female patients of childbearing potential OR confirmation of commitment to complete abstinence,
- completion and documentation of required lenalidomide education and counseling (all patients).

4.3.1 **Lenalidomide Cycle – Regimen A (Low Dose: 20 mg/m^2)** Four consecutive weeks (28 days) will constitute one cycle (Lenalidomide daily x 21 days followed by 7 day rest). This therapy delivery map relates to all cycles of Regimen A. Use a copy of this page once for each cycle. *(Please note cycle number below.)*	_____ Patient name or initials _____ DOB

Criteria to start this cycle: ANC ≥ 1,000/µL and platelet count ≥ 100,000/µL (transfusion independent), confirmation of negative pregnancy test and the use of 2 methods of effective birth control for female patients of childbearing potential or commitment to complete abstinence, completion and documentation of required counseling. Details are in Section 4.0 (Treatment Overview). The Therapy Delivery Map for this cycle is on **1** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Lenalidomide NSC#703813	PO	20 mg/m^2/dose	1-21	See admin guidelines in Section 4.3. (See Appendix IX for Dosing Tables)	a. History, PE (Ht, Wt, VS), Performance Status b. CBC (differential, platelets) c. Urinalysis d. Electrolytes (inc BUN, Calcium, PO_4, Magnesium) e. Creatinine; Total protein; Albumin, ALT, AST, bilirubi f. Pregnancy test (female pts of childbearing potential only) g. Brain MRI with and without gadolinium h. Spine MRI with and without gadolinium i. Pharmacokinetic study (see Section 13.0) j. Required Education and Counseling; Confirmation of birth control/abstinence **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Please Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Lenalidomide ___mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below		
		1	___mg	a, b@, c, d, e, f*, g#, h^, j	
		2	___mg		
		3	___mg		
		4	___mg		
		5	___mg	i$	
		6	___mg		
		7	___mg		
		8	___mg	b, d, f*	
		9	___mg		
		10	___mg		
		11	___mg		
		12	___mg		
		13	___mg		
		14	___mg		
		15	___mg	b, d, f*	
		16	___mg		
		17	___mg		
		18	___mg		
		19	___mg		
		20	___mg		
		21	___mg	b, d, f*	
		29	Start next cycle on Day 29 or when blood count parameters are met (whichever occurs later). For end of therapy observations, see Section 7.1.		

@ Obtain weekly. If patient develops hematologic toxicity as defined in Section 5.2, CBCs should be checked every 3 to 4 days until recovery to Grade 3.

*Obtain within 24 hours prior to starting each cycle and weekly during cycle 1. If menstrual cycles are known to be irregular, pregnancy testing must occur every 14 days beginning with Day 1 of Cycle 2. If a patient misses her period or menstrual bleeding becomes irregular, hold lenalidomide and perform pregnancy testing and counseling immediately.Only for females of childbearing potential.

#Obtain prior to each odd-numbered cycle of therapy (ie, prior to cycles 3, 5, 7, 9, 11 and 13) for the first 13 cycles. During cycles 14-26, obtain every third cycle (ie, prior to cycles 16, 19, 22 and 25), after cycle 26 and as clinically indicated.

^ Obtain at same time points as brain MRI, for patients with known or suspected spinal disease.

$ For PK study, obtain 2 mL blood in heparinized tube (green top) any day between Days 5-21 of Cycle 1 and any day between Days 5-21 of the first cycle following a dose reduction at the time of safety lab monitoring. See Section 13.0

See Section 5.0 for Dose Modifications for Toxicities. For COG Supportive Care Guidelines see: https://members.childrensoncologygroup.org/prot/reference_materials.asp.

4.3.2 **Lenalidomide Cycle – Regimen B (High Dose: 115 mg/m^2)** Four consecutive weeks (28 days) will constitute one cycle (Lenalidomide daily x 21 days followed by 7 day rest). This therapy delivery map relates to all cycles of Regimen B. Use a copy of this page once for each cycle. *(Please note cycle number below.)*	_____ Patient name or initials _____ DOB

Criteria to start this cycle: ANC ≥ 1,000/µL and platelet count ≥ 100,000/µL (transfusion independent), confirmation of negative pregnancy test and the use of 2 methods of effective birth control for female patients of childbearing potential or commitment to complete abstinence, completion and documentation of required counseling. Details are in Section 4.0 (Treatment Overview). The Therapy Delivery Map for this cycle is on **1** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Lenalidomide NSC#703813	PO	115 mg/m^2/dose	1-21	See admin guidelines in Section 4.3.	a. History, PE (Ht, Wt, VS), Performance Status b. CBC (differential, platelets) c. Urinalysis d. Electrolytes (inc BUN, Calcium, PO_4, Magnesium) e. Creatinine; Total protein; Albumin, ALT, AST, bilirubin f. Pregnancy test (female pts of childbearing potential only) g. Brain MRI with and without gadolinium h. Spine MRI with and without gadolinium i. Pharmacokinetic study (see Section 13.0) j. Required Education and Counseling; Confirmation of birth control/abstinence **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Please Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Lenalidomide ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below		
		1	____mg	a, b@, c, d, e, f*, g#, h^, j	
		2	____mg		
		3	____mg		
		4	____mg		
		5	____mg	i$	
		6	____mg		
		7	____mg		
		8	____mg	b, d, f*	
		9	____mg		
		10	____mg		
		11	____mg		
		12	____mg		
		13	____mg		
		14	____mg		
		15	____mg	b, d, f*	
		16	____mg		
		17	____mg		
		18	____mg		
		19	____mg		
		20	____mg		
		21	____mg	b, d, f*	
		29	Start next cycle on Day 29 or when blood count parameters are met (whichever occurs later). For end of therapy observations, see Section 7.1.		

@ Obtain weekly. If patient develops hematologic toxicity as defined in Section 5.2, CBCs should be checked every 3 to 4 days until recovery to grade 3.

*Obtain within 24 hours prior to starting each cycle and weekly during cycle 1. If menstrual cycles are known to be irregular, pregnancy testing must occur every 14 days beginning with Day 1 of Cycle 2. If a patient misses her period or menstrual bleeding becomes irregular, hold lenalidomide and perform pregnancy testing and counseling immediately. Only for females of childbearing potential.

#Obtain prior to each odd-numbered cycle of therapy (ie, prior to cycles 3, 5, 7, 9, 11 and 13) for the first 13 cycles. During cycles 14-26, obtain every third cycle (ie, prior to cycles 16, 19, 22 and 25), after cycle 26 and as clinically indicated.

^ Obtain at same time points as brain MRI, for patients with known or suspected spinal disease.

$ For PK study, obtain 2 mL blood in heparinized tube (green top) any day between Days 5-21 of Cycle 1 and any day between Days 5-21 of the first cycle following a dose reduction at the time of safety lab monitoring. See Section 13.0.

See Section 5.0 for Dose Modifications for Toxicities. For COG Supportive Care Guidelines see: https://members.childrensoncologygroup.org/prot/reference_materials.asp.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

Lenalidomide dose reductions will not be re-escalated, even if there is minimal or no toxicity with the subsequent reduction in dose. Patients who experience significant toxicity (as listed in Sections 5.1 and 5.2) will have the dose reduced by 25% on subsequent cycles. Two dose reductions are allowed, as long as there is no evidence of disease progression (see Section 10.0). Each dose reduction will be a reduction of 25% of the starting dose; therefore the first dose reduction will be to 75% of the starting dose (either to 15 mg/m^2/dose for patients on Regimen A or to 86 mg/m^2/dose for patients on Regimen B), and a second reduction will be to 50% of the starting dose (either to 10 mg/m^2/dose for patients on Regimen A or to 58 mg/m^2/dose for patients on Regimen B). See Appendix IX for Regimen A dosing tables. Patients who again experience dose modifying toxicity after two dose reductions will be taken off protocol therapy.

If a dose reduction occurs, a blood sample for pharmacokinetic study should be drawn during the cycle subsequent to the reduction. See Section 13.0 for details of pharmacokinetic sample collection.

5.1 Non-Hematologic Toxicities

The dose of lenalidomide will be reduced for any of the following toxicities at least possibly attributed to lenalidomide:

- Any Grade 4 non-hematological toxicity
- Any Grade 3 non-hematological toxicity with the specific exclusion of:
  - Grade 3 nausea and vomiting controlled by antiemetics
  - Grade 3 fever or infection
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation.
- Any Grade 2 non-hematologic toxicity that persists for > 3 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption
- Any other adverse event attributed to lenalidomide that requires treatment interruption for > 3 days or which recurs upon drug rechallenge and requires treatment interruption.
- Non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles.

Patients who experience non-hematologic toxicity should have appropriate laboratory testing at least twice weekly (3-4 days apart) until the toxicity has resolved.

Lenalidomide will be held for any patient experiencing any Grade hemorrhagic or bullous skin rash until a specific evaluation to exclude toxic epidermal necrolysis (TEN) has been performed. Any patient with evidence of TEN or Stevens-Johnson syndrome will not be retreated with lenalidomide.

If the patient experiences a thromboembolic event unrelated to a central line, lenalidomide will be discontinued and the patient will be taken off protocol therapy.

5.2 Hematologic Toxicities

The dose of lenalidomide will be reduced for any of the following toxicities:

- Grade 4 decreased neutrophil count (neutropenia) > 3 days duration
- Grade 4 decreased platelet count (thrombocytopenia)

- ≥ 2 platelet transfusions per cycle for platelet counts < 50,000/μL
- ≥ 14 day delay in starting subsequent cycles due to low ANC (< 1,000/μL or low platelet count (< 100,000/μL.
- If ANC < 500/μL and platelets <100,000/μL during the 21 day dosing period, the lenalodomide should be held until recovery. Counting of cycle days should continue uninterrupted.

Patients who experience hematologic toxicity should have appropriate laboratory testing at least twice weekly (3-4 days apart) until the toxicity has resolved (i.e. ANC > 1000/μL and platelets >100,000/μL) .

6.0 DRUG INFORMATION

6.1 LENALIDOMIDE (Revlimid™, CC-5013, CDC-501) NSC# 703813 (05/15/18)

Source and Pharmacology: Lenalidomide is a thalidomide analogue with the chemical name 3-(4'-amino-1,3-dihydro-1-oxo-2*H*-isoindol-2-yl) -2,6-piperidinedione. The molecular weight of lenalidomide is 259.25.

Lenalidomide is an immunomodulatory agent with a mechanism of action that remains to be fully characterized. Lenalidomide inhibits proliferation of certain hematopoietic tumor cells (including MM plasma tumor cells and those with deletions of chromosome 5), enhances T cell- and natural killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments fetal hemoglobin production by CD34+ hematopoietic stem cells, and inhibits secretion of proinflammatory cytokines (eg, TNF-α and IL-6) from monocytes. Lenalidomide also inhibited the expression of cycoloxygenase-2 (COX-2) but not COX-1 *in vitro*.

Following oral administration, lenalidomide is rapidly absorbed with maximum plasma concentrations occurring between 0.5 and 1.5 hours postdose. Co-administration with food does not alter the extent of lenalidomide absorption (area under the concentration time curve, AUC) but does reduce the maximal plasma concentration (C_{max}) by 36%. The Cmax and AUC increase proportionally (linearly) with increases in dose and multiple dosing (up to 100 mg twice daily) does not cause a significant drug accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 55% and 45%, respectively.

Lenalidomide binding to plasma proteins is low with mean plasma protein binding around 30% (22.7% and 29.2% in multiple myeloma patients and healthy volunteers, respectively). Lenalidomide is neither metabolized by nor inhibited or induced by the cytochrome P450 pathway. In healthy volunteers, lenalidomide undergoes limited metabolism and the parent compound is the predominant circulating component. Approximately 65% to 85% of lenalidomide is eliminated unchanged in the urine. The half-life of elimination is approximately 3 hours at the clinically relevant doses and steady-state levels are achieved within 4 days. Pharmacokinetic analyses in patients with impaired renal function indicate that as renal function decreases, the total drug clearance decreases proportionally resulting in an increase in AUC. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with creatinine clearance < 50 mL/min; therefore, patients with inadequate renal function are ineligible for this study.

With regards to potential drug interactions, the periodic monitoring of digoxin plasma levels is recommended due to increased Cmax with concomitant administration of lenalidomide. Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of venous thromboembolic events. Therefore, erythropoietic agents should not be used while patients are receiving lenalidomide on this trial. Other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in patients receiving lenalidomide.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (CC-5013, NSC 703813)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4081 patients.* Below is the CAEPR for Lenalidomide (CC-5013).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.7, March 14, 2018[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Blood and lymphatic system disorders - Other (pancytopenia)		
	Febrile neutropenia		
	Hemolysis		
CARDIAC DISORDERS			
		Atrial fibrillation	
		Heart failure	
		Myocardial infarction[2]	
EAR AND LABYRINTH DISORDERS			
	Vertigo		

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
ENDOCRINE DISORDERS			
		Hyperthyroidism	
	Hypothyroidism		***Hypothyroidism (Gr 3)***
EYE DISORDERS			
	Blurred vision		
	Cataract		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
Constipation			***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		
	Dyspepsia		
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 3)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (cholestasis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Anaphylaxis	
		Immune system disorders - Other (angioedema)	
		Immune system disorders - Other (graft vs. host disease)[3]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
	Fall		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Blood bilirubin increased		
	GGT increased		

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Investigations - Other (C-Reactive protein increased)		
		Lipase increased	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		
	Hyperglycemia		
	Hyperuricemia		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		
	Hypophosphatemia		
	Iron overload		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Bone pain		
	Generalized muscle weakness		
	Muscle cramp		***Muscle cramp (Gr 2)***
	Pain in extremity		
		Rhabdomyolysis[5]	
	Myalgia		***Myalgia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy[6]	
		Myelodysplastic syndrome[6]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[7]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies)	
		Treatment related secondary malignancy[6]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Depressed level of consciousness		

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dysesthesia		
	Dysgeusia		
	Headache		
	Paresthesia		
	Peripheral motor neuropathy		
	Peripheral sensory neuropathy		
		Stroke[2]	
	Syncope		
	Tremor		
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		***Insomnia (Gr 2)***
	Psychiatric disorders - Other (mood altered)		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
		Erythema multiforme	
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])	
	Skin and subcutaneous tissue disorders - Other (pyroderma gangrenosum)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
SURGICAL AND MEDICAL PROCEDURES			
		Surgical and medical procedures - Other (impaired stem cell mobilization)[8]	
VASCULAR DISORDERS			
	Hematoma		
	Hypertension		
	Hypotension		
	Peripheral ischemia		
	Thromboembolic event[9]		***Thromboembolic event[9] (Gr 3)***
	Vasculitis		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Myocardial infarction and cerebrovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomde and dexamethasone.

[3]Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5]The rare adverse event of rhabdomyolysis has been observed with lenalidomide. The reports of rhabdomyolysis were confounded by concurrent use of statins and dexamethasone, concurrent viral and bacterial infections, trauma, and serotonin syndrome. Statins, infections, trauma, and serotonin syndrome are known risk factors for rhabdomyolysis.

[6]There has been an increased frequency of secondary malignancies (including ALL, AML, and MDS) in multiple myeloma patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant.

[7]Serious tumor flare reactions have been observed in patients with chronic lymphocytic leukemia (CLL) and lymphoma.

[8]A decrease in the number of stem cells (CD34+ cells) collected from patients treated with >4 cycles of lenalidomide has been reported.

[9]Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

[10]Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[11]Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[12]Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®).

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Adverse events reported on lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (monocytosis); Disseminated intravascular coagulation; Eosinophilia
CARDIAC DISORDERS - Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Cushingoid
EYE DISORDERS - Dry eye; Flashing lights; Retinopathy
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Ascites; Colonic perforation; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[10]; Gastrointestinal obstruction[11]; Ileus; Mucositis oral; Pancreatitis; Rectal mucositis; Small intestinal mucositis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Cholecystitis
INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (opportunistic infection associated with >=Grade 2 Lymphopenia); Myelitis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Hip fracture; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypoglycemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Joint effusion; Muscle weakness lower limb; Neck pain; Osteonecrosis of jaw[12]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (hyporeflexia); Spinal cord compression; Seizure; Somnolence; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Psychosis
RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Urticaria
VASCULAR DISORDERS - Hot flashes; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

Note: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Effect in Pregnancy and Lactation:
Lenalidomide is **Pregnancy category X**. It can cause fetal harm when administered to a pregnant woman and is contraindicated in women who are or may become pregnant. There are no adequate and well-controlled studies in pregnant women. However, in an embryofetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis at doses approximately 0.17 times the adult maximum recommended human dose (MRHD) of 25 mg, based on BSA. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryolethality in rabbits and no adverse reproductive effects in rats. In another study, pregnant rats received lenalidomide from organogenesis through lactation; some delay in sexual maturation occurred in male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryofetal developmental effects for lenalidomide.

The requirements of this study and the requirements to receive the commercially available supply are slightly different. For the purpose of this study, female of childbearing potential (FCBP) is a sexually mature (at least Tanner 2) female who: 1) has achieved menarche or breast development in Tanner Stage 2 or greater, and 2) has not undergone a hysterectomy or bilateral oophorectomy and must use effective means of contraception for 28 days before therapy, during lenalidomide therapy and dose interruptions, and for 28 days following discontinuation of lenalidomide therapy or continually abstain from reproductive heterosexual intercourse. Venous thromboembolism (VTE) has been seen in patients with multiple myeloma receiving lenalidomide plus dexamethasone and patients with myelodysplastic syndrome receiving lenalidomide monotherapy (to a lesser extent). Because oral contraceptives may also place the patient at risk of VTE, physicians should discuss this increased risk and the risk/benefit of contraceptive methods with patients receiving lenalidomide.

Male patients must agree to completely abstain from sexual contact with women who are pregnant or are able to become pregnant or use a latex condom every time he engages in sexual contact with women who are pregnant or who may become pregnant.

If a pregnancy occurs during treatment, the drug must be immediately discontinued and the suspected fetal exposure should be reported to CTEP via CTEP-AERS. Refer to Section 11.9.

It is not known whether lenalidomide is excreted in human milk. Since many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

Formulation and Stability:
Lenalidomide is available in 2.5 mg, 5 mg, and 25 mg capsules for oral administration for the purpose of this study. **Lenalidomide 10 mg capsules will not be used in this study.**

Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsules are supplied in tamper-evident, child-resistant, opaque,

high density polyethylene (HDPE) bottles) with polypropylene caps. Each bottle contains 100 capsules. Lenalidomide should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.
Each subject must receive counseling regarding the use and risks of lenalidomide by a healthcare professional who has received specific training by Celgene. Additional information about the training of these healthcare professionals can be found in Section 3.1.5.1 and Appendix I. The counseling of each subject must be documented using the Lenalidomide Education and Counseling Guidance Document (Appendix III). Once documentation has been confirmed, a pharmacist may dispense the investigational lenalidomide to the patient. Pharmacists may only dispense up to a 28-day supply at one time (1 cycle, or a 21-day supply for the purpose of this study). A Lenalidomide information sheet (Appendix V) must be provided each and every time the medication is dispensed. Prescriptions may not be mailed to the patient.

Lenalidomide capsules should not be opened or crushed. If lenalidomide powder contacts the skin, it must be washed immediately and thoroughly with soap and water. If lenalidomide contacts mucous membranes, flush thoroughly with water.

Lenalidomide should be taken by mouth with a full glass of water and without food at approximately the same time each day for 21 consecutive days. If nausea occurs after taking the dose, administer with food as this may decrease nausea. If a dose is forgotten but remembered within 8 hours, the missed dose should be taken/given immediately. If more than 8 hours have passed since the time the dose was due, that day's dose should be skipped. If a dose is vomited within 10 minutes of taking the dose and the capsules are visible in the emesis, the dose should be repeated and the patient's provider should be notified.

Procedures for the proper handling and disposal of hazardous/anticancer drugs should be considered.

Supplier: Supplied by Celgene and distributed by the NCI DTCD. **Do not use commercially available drug.**

Agent Ordering
NCI supplied agent may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. One additional dose of lenalidomide may be ordered and dispensed so it is readily available in the event the patient vomits the capsules.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs for the Procedures for Drug Accountability and Storage and http://ctep.cancer.gov/forms/default.htm to obtain a copy of the DARF and Clinical Drug Request form.)

Agent Returns

Investigators/Designees must return unused DCTD supplied investigational agent to the NCI clinical repository as soon as possible when: the agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another DCTD sponsored protocol; the agent is outdated or the agent is damaged or unfit for use. Regulations require that all agents received from the DCTD, NCI be returned to the DCTD, NCI for accountability and disposition. Return only unused vials/bottles. Do NOT return opened or partially used vials/bottles unless specifically requested otherwise in the protocol. See the CTEP web site for Policy and Guidelines for Investigational agent Returns at: http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs. The appropriate forms may be obtained at: http://ctep.cancer.gov/forms/default.htm.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. **Obtain other studies prior to start of subsequent cycles and as otherwise indicated.**

STUDIES TO BE OBTAINED	Baseline	Prior to Each Cycle	During Each Cycle	When Patient is Removed from Protocol Therapy
History	X	X		
Physical Exam (Ht, Wt, VS)	X	X		X
Performance Status	X	X		X
CBC (differential, platelets)	X	X	Weekly[A]	X
Urinalysis	X	X		X
Electrolytes (including BUN, Calcium, PO_4, Magnesium)	X	X	Weekly	X
Creatinine	X	X		
Total protein, AST, ALT, albumin, bilirubin	X	X		X
Pregnancy test (serum or urine, with sensitivity of 25 mIU/mL) (for females of childbearing potential)	X[B]	X[B]	Weekly[C]	X[D]
Confirmation of use of 2 effective methods of birth control OR confirmation of complete abstinence (for female patients of childbearing potential)	X	X		
Education and Counseling (all patients)[E]		X		X
Brain MRI with and without gadolinium	X[F]	X[G]		X
Spine MRI with and without gadolinium[F,H]	X	X[G]		X
Pharmacokinetic studies (see Section 13.0)			X[I]	

[A] If patient develops hematologic toxicity as defined in Section 5.2, CBCs should be checked every 3 to 4 days until recovery.

[B] Obtain 2 weeks prior to study enrollment and again within 24 hours prior to Day 1 of each cycle.

[C] Obtain weekly during cycle 1. Females with irregular menstruation must have a pregnancy test every 14 days while receiving protocol therapy (including breaks in treatment). Pregnancy test is also required if patient misses her period or has unusual menstrual bleeding.

[D] Pregnancy testing must also occur at Day 28 (and at Day 14 if female has irregular menstruation) after lenalidomide discontinuation).

[E] The Lenalidomide Education and Counseling Document (Appendix III) must be completed and signed by a trained counselor at the site prior to each dispensing of lenalidomide.

[F] Obtain brain MRI within 1 week prior to study enrollment. Spine MRI (if necessary) may be obtained within 2 weeks prior to enrollment.

[G] Obtain prior to each odd-numbered cycle of therapy (ie, prior to cycles 3, 5, 7, 9, 11 and 13) for the first 13 cycles. During cycles 14-26, imaging will be performed every third cycle (ie, prior to

16, 19, 22 and 25), after cycle 26, and as clinically indicated. See Section 14.0 for imaging requirements.

[H] Obtain in patients with a history of spinal or leptomeningeal disease, or those patients with symptoms suspicious of spinal disease. Obtain spine MRI at same time points as brain MRI.

[I] PK blood sample must be obtained prior to the daily dose between Day 5-21 of cycle 1 at the time of routine safety lab monitoring. In the event of a dose reduction, a blood sample must also be obtained between Day 5-21 of the cycle following the dose reduction.

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.2 Follow-up

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule. This includes required pregnancy testing for all female patients of childbearing potential on Day 28 following the last dose of lenalidomide. Patients with irregular menstrual cycles must have pregnancy testing completed on Day 14 and Day 28 following the last dose of lenalidomide.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease (see definition in Section 10.0).

b) Significant toxicity at least possibly attributed to lenalidomide despite two dose reductions (as stated in Section 5.0).

c) Refusal of further protocol therapy by patient/parent/guardian.

d) Completion of 26 cycles of protocol therapy.

e) Physician determines it is in patient's best interest.

f) Development of a second malignancy.

g) Patient becomes pregnant while on study.

h) Refusal to cooperate with required birth control methods or to commit to complete abstinence.

i) Development of a thromboembolism, unrelated to central line.

j) Evidence of toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death.

b) Lost to follow-up.

c) Patient enrollment onto another COG study with tumor therapeutic intent.

d) Withdrawal of consent for any further data submission.

e) The fifth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

Approximately 45 patients per year less than 10 years of age with progressive/recurrent and high-risk LGA were enrolled on COG-A9952, *Chemotherapy for Progressive Low Grade Astrocytoma in Children Less Than Ten Years Old*. About half of these children (22 patients) would be expected to progress and would be eligible for the current study.

The total accrual of newly diagnosed LGA patients on CCG-9891/POG-9130, *Treatment of Newly Diagnosed Low Grade Astrocytomas*, was 713 over a period of 5 years. About 40% of these patients were older than 10 years of age and 20% progressed within 6 years of diagnosis. This corresponds to about 11 patients per year older than 10 years with progressive LGA. Adding to this those who will be entered because of symptomatic, incomplete resections, we would expect approximately 20 patients per year older than 10 years of age.

Adding together patients who are younger than and those older than 10 years of age (22 + 20 = 42), and taking into account patients who may opt for other treatments and the eligibility criteria of at least 1 prior therapy including carboplatin, we expect a total of 30 patients with recurrent or progressive low-grade glioma per year.

This study will enroll only patients with pilocytic astrocytoma and progressive optic pathway gliomas. Based on prior COG enrollment, we estimate 70% of low grade glioma patients to be in this subset (30*0.7=21/yr). The total accrual target for this study is 74 patients enrolled in 3.5 years. Considering that some patients enrolled may be found to be ineligible, the maximum number of patients expected to be accrued is 80 patients.

9.2 Study Design

This is a randomized study to estimate the response rate of children with recurrent or progressive pilocytic astrocytoma and optic pathway gliomas who are treated with lenalidomide assigned to either Regimen A low dose (20 mg/m^2/dose) or Regimen B high dose (115 mg/m^2/dose).

9.3 Methods of Analysis

9.3.1 Endpoints

9.3.1.1 Primary Endpoint

- Objective response – best response determined from the sequence of the objective statuses described in Section 10.0 'Response Criteria.'

9.3.1.2 Secondary Endpoints

- Time to treatment failure (Event-free survival, EFS) – the time from study enrollment to tumor progression, tumor recurrence, death from any cause, or occurrence of a second malignant neoplasm.

- Time to death (Overall survival, OS) – the time from study enrollment to death from any cause.

9.4 Analysis of Efficacy

A total of 74 eligible patients will be enrolled on this trial. Patients will be randomly assigned to either the low dose (Regimen A) or the high dose arm (Regimen B). Each patient will be classified according to their 'best response' for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described in Section 10.0 'Response Criteria.' A responder is defined as a patient who achieves a best overall response of CR or PR at any time on the study. If a patient achieves a PR or CR and later has progressive disease or relapse, then the patient will be counted as a responder. The response rate will be calculated as the ratio of the number of patients who demonstrate response (CR or PR) divided by the number of patients evaluable for response. The 95% confidence bounds for response rate are shown in the table below for several different outcomes. The computation is based on the binomial distribution, assuming the availability of 30 evaluable patients (7 inevaluable patients) for response in each arm (each dose level). All patients eligible for study who receive any study drug will be considered evaluable for response. Any patient who goes off protocol therapy for any reason (patient/parent/physician choice, adverse event profile, etc.) prior to the first response evaluation will be considered a non-responder. For example, an observed response rate of 33% (10/30) will be consistent with the view that 17% or more patients will respond to the treatment.

Outcome (#Response/#Patients)	95% Exact Confidence Bound on Response Rate
20/30	(0.47, 0.83)
15/30	(0.31, 0.69)
10/30	(0.17, 0.53)
5/30	(0.06, 0.35)

There would be modest power to compare the response rates for the 2 dose cohorts. With 74 patients, we would have 80% power to detect a response rate difference of 35% vs. 15%, at the 1-sided 20% significance level.

Disease progression will be based on the results of institutional review. Standard survival methods will be used for analysis of EFS and OS. Analyses include log rank tests and the product-limit (Kaplan-Meier) estimate for estimation of EFS and OS probability. Comparison of EFS between the two dose levels will primarily be exploratory. With 74 patients, we will have only approximately 69% power to detect a 15% increase in long-term EFS (30% to 45%) with 50% patients receiving high dose vs. 50% receiving low dose, based on a one-sided logrank test with 20% Type I error rate.

9.5 Monitoring for Efficacy

Patients will be randomly assigned to either the low dose or the high dose treatment. Of the 37 patients on each treatment, we will closely monitor the first 20 patients enrolled. For each regimen, the early stopping criterion and the decision regarding ultimate further interest in this agent will be based on the number of objective responses and disease progressions in the first 6 months of treatment. If the early stopping rule is met for one treatment, that particular arm will be closed and the other arm will continue as planned.

A true response rate of 5% and a true early (6-month) progression rate of 40% are considered inadequate, whereas a true response rate of 20% and a true early (6-month) progression rate of 25% would be sufficient for further interest in this agent.

The study will be a 2-stage design, with 20 evaluable patients in the first stage and 17 evaluable patients in the second stage (37 patients total per treatment regimen), with decisions made as follows:

Number of Evaluable Patients Enrolled	Results	Decision
Stage I: 20 evaluable patients	Zero or one responders or 10 or more with early progression	Terminate enrollment with the conclusion the regimen does not demonstrate sufficient disease control
	All other configurations of response or early progression	Continue to the next stage and enroll 17 more patients
Stage II: 17 additional evaluable patients (Total of 37: 20 from Stage I and 17 from Stage II)	Cumulatively 3 or fewer responders or 15 or more with early progression	Conclude the regimen does not demonstrate sufficient disease control
	All other configurations of response or early progression	Conclude the regimen demonstrates sufficient disease control for further investigation

A summary of the operating characteristics of this design are provided below:

Response Probability	**Early Progression Probability**	**Probability of Stopping at First Stage**	**Probability Accept Regimen**
0.05	0.40	0.78	0.05
0.10	0.40	0.51	0.24
0.20	0.30	0.11	0.81
0.15	0.25	0.18	0.73
0.20	0.25	0.08	0.88

9.6 Monitoring for Toxicity

"Toxic events" will be defined as one in which a patient has two dose reductions and then experiences another significant toxicity as defined in Section 5.0, irrespective of attribution. A two-stage stopping rule will be used to monitor for an excessive number of these toxic events. All patients described below must be evaluable for toxicity. All patients who receive at least one dose of lenalidomide will be evaluable for toxicity. A review of treatment feasibility and patient safety will be undertaken if we observe at least 5/18 or 8/36 toxic events. The rule will be met about 4% of the time if the true incidence of toxic event is 10%, and 90% of the time if the true incidence is 30%.

9.7 Interim Monitoring of Toxic Death

Toxic death is death predominantly attributable to treatment-related causes. The occurrence

of toxic death at any time will be a primary endpoint for safety monitoring. Any toxic death on study will be reviewed with CTEP and the DMSC prior to continuing enrollment on study. The study will be stopped if there are two toxic deaths on study.

9.8 Analysis of Toxicity

Estimates will be obtained using life-table methods, with an event defined as the first occurrence of a primary toxicity. Time scale used in the time to first occurrence of a key acute and subacute toxicity is time in days since the start of therapy. Patients who have progression or recurrence of disease will be censored in these analyses. The rates of individual toxicities in each course of treatment, the number of patients who require a dose reduction and number of patients who come off protocol therapy due to toxicity will be summarized using standard descriptive statistical methods. To evaluate hematologic toxicity of long term lenalidomide administration adverse event data will be collected using CTCAE version 4 toxicity coding. Grade 3 or greater hematologic toxicities will be recorded per reporting period and compared between 2 lenalidomide doses

9.9 Analysis of Lenalidomide Pharmacokinetic Parameters

Correlation of lenalidomide concentration obtained from the steady-state sample and the number of cycles received prior to the occurrence of disease progression will be performed using Pearson's correlation coefficient. Cox regression analysis will be used to assess the association between outcome and steady state levels at a particular cycle.

9.10 Analysis of Standard MR Sequences

To compare the methods of MRI sequence, the response categories (complete response, partial response, stable disease, and progression) will be determined from the following three standard MR sequences, T2-weighted, FLAIR, T1-weighted post-contrast. Percent agreement between the sequences will be estimated as the number of follow-up scans in which the corresponding sequence agreed divided by the total number of follow-up scans. Standard error will be estimated by use of the bootstrap method[28] to account for the correlated dependent response data, and these values will be used to estimate the 95% confidence intervals. The event-free survival distributions will be compared across the MR sequences, with a proportional hazards model developed for dependent survival data by Wei et al (1989).[29]

9.11 Effect of the Stratification on Response Rate

At enrollment, the number of prior therapies, classified as 2 or fewer versus more than 2 will be required to complete the treatment assignment process. The efficacy rule described in Section 9.5 will be executed as written regardless of the number of prior therapies that a patient has received. The risk for EFS-event and death associated with receiving more than 2 prior regimens will be assessed using the stratified 1-sided log-rank test, with randomized regimen as the stratification factor. Only patients enrolled after approval of the proposed amendment will be considered in the analysis. If the resulting p-value is not significant at the 0.10 level or less, the EFS and OS results will be presented without regard to stratification factor.

The following logistic regression model will be utilized:

$$\Pr\left(CR\ or\ PR \mid \underline{x}_i\right) = \frac{e^{\underline{x}_i'\underline{\beta}}}{1+e^{\underline{x}_i'\underline{\beta}}};$$

where: x_{i1} *is* 1

x_{i2} *is the random treatment assignment*

x_{i3} *is* 1 *if the patient received three or more prior regimens and* 0 *otherwise*

The value and p-value associated with the estimate of β_3 will be used to infer whether there evidence of an association between response rate and number of prior regimens

9.12 Gender and Minority Accrual Estimates

Both males and females of all races and ethnic groups are eligible for this study. The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	1	3
Not Hispanic or Latino	37	40	77
Ethnic Category: Total of all subjects	39	41	80
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	1	1	2
Black or African American	4	3	7
Native Hawaiian or other Pacific Islander	1	1	2
White	32	36	68
Racial Category: Total of all subjects	39	41	80

This distribution was derived from CCG 9891/POG 9130.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

10.2 Methodology to Determine Tumor Measurement

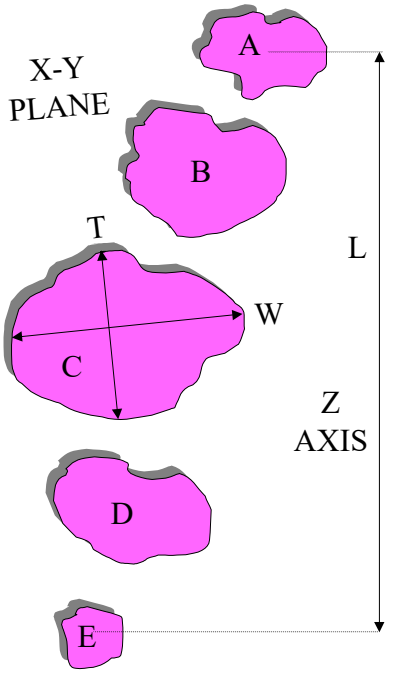
Tumor dimensions are determined by measurement of the longest tumor dimension and its perpendicular for each target lesion. Regarding MRI imaging, the radiologist at each institution may select whatever sequence best highlights the tumor (T1 enhanced or T2

weighted or FLAIR images) and the same sequence should be used for serial measurements. Response determination will be based on a comparison of an area (W x T – see below) between the baseline assessment and the study date designated in the follow-up Report Form. Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Non-target lesions or newly occurring lesions should also be enumerated in these reports, and changes in non-target lesions should be described.

Tumor response criteria are determined by changes in size using the longest tumor dimension, and its perpendicular. Either T1 or T2 weighted images are used - which ever gives the best estimate of tumor size. The following section describes the methodology. (See Figure 10.1 below for illustration)

1. For MRI imaging (preferred), the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups. This longest measurement of the tumor is referred to as the width (W). Longest diameter of target lesion(s) should be selected in the axial plane only for CT.
2. The perpendicular measurements should be determined - transverse (T) measurement, perpendicular to the width in the selected plane.
3. The cystic or necrotic components of a tumor are <u>not</u> considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis composes the majority of the lesion, the lesion may not be "measurable".
   Options:
   - if the cyst/necrosis is eccentric, the W and T of the solid portion should be measured, the cyst/necrosis excluded from measurement
   - if the cyst/necrosis is central but represents a small portion of the tumor (< 25%), disregard and measure the whole lesion
   - if the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured
4. Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted and change in extent/thickness assessed on follow up studies.

Figure 10.1: COG Guidelines for Measurement of Tumor Size



COG GUIDELINE: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

• A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
• W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
• Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice thickness + gap) and the number of slices showing the tumor

5. Overall Response Assessment

The overall response assessment takes into account response in both the target and non-target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	**CR**
CR	IR/SD	No	**PR**
PR	CR, IR/SD	No	**PR**
SD	CR, IR/SD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

CR – Complete Response
PR – Partial Response
SD – Stable Disease
PD – Progressive Disease
IR – Incomplete Response

The sections that follow discuss the selection and evaluation of each of these types of lesions.

10.3 Selection of Target and Non-Target Lesions

1. For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response.
2. If multiple measurable lesions are present, up to 3 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions (including CSF positive for tumor cells).
3. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g. 8 mm lesion for a 4 mm slice).
4. Any change in size of non-target lesions should be noted, though does not need to be measured.

10.4 Response Criteria for Target Lesions

1. Response criteria are assessed in 2 dimensions – the product of W x T.
2. To assess response/progression, the ratio is calculated:

$$\frac{W \times T \text{ (current scan)}}{W \times T \text{ (reference scan)}}$$

3. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g. when multiple lesions show opposite responses, the progressive disease takes precedence.
4. For purposes of this study, response criteria for target lesions are:

Complete Response (CR): Complete disappearance of all known disease for at least 4 weeks. Complete response is dated from the time all lesions have disappeared.

Partial response (PR): A reduction of at least 50% in the size of all measurable tumor as quantitated by the sum of the products of the largest diameters of measurable lesions and maintained for at least 4 weeks. Partial response is dated from the time of first observation. In addition, there can be no appearance of new lesions or progression of any lesion.

Stable Disease (SD): A decrease of <50% or an increase of <25% in the sum of the products of the largest diameters of measurable lesions and no evidence of new lesions.

Progressive Disease (PD): ≥ 25% increase in the sum of the products of the largest diameters of the measurable lesions or the appearance of one or more new lesions. Two-dimensional measurements (using WHO criteria) of an existing tumor will be compared to the study baseline or best response scan (whichever is smaller) compared side-by-side.

Local progression is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Distant progression is defined as the appearance of tumor at sites other than known prior sites of disease. Distant progression most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure. Combined local and distant progression is defined when evaluation of the entire neuraxis reveals local and distant progression.

10.5 Response Criteria for Non-target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Incomplete Response/Stable Disease (IR/SD): The persistence of one or more non-target lesions.

Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

10.6 Retrospective Response Review

MRI imaging for all patients on study will undergo retrospective central review following the completion of treatment. See Section 14.4 for imaging central review requirements.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

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

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
7) Pregnancy (See Section 11.9)

11.3 Specific Examples for Expedited Reporting

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

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

11.3.2 Persistent or Significant Disabilities/Incapacities

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

11.3.3 Death

Reportable Categories of Death

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

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

11.3.4 Secondary Malignancy

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

The NCI 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:

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

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

11.3.4 Second Malignancy

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

11.3.5 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.3.5.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the **"*Pregnancy, puerperium and perinatal conditions"*** SOC.

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

11.3.5.2 **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.

11.3.5.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days of birth*", should be reported expeditiously, as **Grade 4 "*Death neonatal*" under the *"General disorders and administration"* SOC when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in

partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4 Reporting Requirements for Specialized AEs

11.4.1 Baseline AEs

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

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

11.4.2 Persistent AEs

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

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

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

11.4.3 Recurrent AEs

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

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

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

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

11.5 Exceptions to Expedited Reporting

11.5.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.5.2 Special Situations as Exceptions to Expedited Reporting

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

11.6 Reporting Requirements - Investigator Responsibility

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

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

11.7 General Instructions for Expedited Reporting via CTEP-AERS

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 at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

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

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is strongly recommended for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: **301-230-0159** (back-up: 301-897-7404).

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax# 626-303-1768; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

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

11.8 Reporting Table for Late Phase 2 and Phase 3 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]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

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. Additional Special Situations as Exceptions to Expedited Reporting are listed below (see Section 11.10).

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 notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.9 Protocol Specific Additional Instructions and Reporting Exceptions

- **Grades 1–4 myelosuppression do not require expedited reporting unless unexpected.**
- Grades 1–3 of the following do not require expedited reporting: nausea, diarrhea, constipation, headache, rash and muscle cramps.
- **Expedited reporting guidelines for occurrence of pregnancy or suspected pregnancy**

Pregnancy
Females of Childbearing Potential:

- Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the partner of a male subject occurring while the subject is on lenalidomide or within 28 days after the subject's last dose, are considered immediately reportable events. Lenalidomide must be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported via CTEP-AERS as a **grade 4** event under: SOC pregnancy, puerperium and perinatal conditions; adverse event: **pregnancy, puerperium and perinatal conditions-other, fetal exposure.**
    - *The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*
- The Investigator will follow the female subject until completion of the pregnancy, and must make an amendment to the initial pregnancy report immediately regarding the outcome of the pregnancy and neonatal status (either normal or abnormal outcome).
- If the outcome of the pregnancy was abnormal (including spontaneous or therapeutic abortion, fetal demise and congenital abnormalities), the Investigator should report the abnormal outcome as an amendment to the initial pregnancy report as soon as the as the Investigator has knowledge of the outcome.
- All neonatal deaths and neonatal complications that occur within 28 days of birth should be reported, without regard to causality, as an amendment to the initial pregnancy report. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the lenalidomide should also be reported as an amendment within 24 hours of the Investigator's knowledge of the event.

Male Subjects

- If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

11.10 Routine Reporting of Adverse Events

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

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

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

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

12.2 Data and Safety Monitoring Committee

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

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

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

12.3 CRADA/CTA

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

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

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

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

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and

proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

13.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

13.1 Steady State Pharmacokinetic Study

Participation in the pharmacokinetic study is required. Peripheral blood will be collected from all patients, for correlation of steady state pharmacokinetic levels of lenalidomide with best response and EFS at the patient dose.

Serum samples will be assayed for lenalidomide by a validated high performance liquid chromatography assay with MS detection that has been developed for the quantitative determination of lenalidomide in biological matrices[30].

13.1.1 Sampling Schedule

Plasma samples will be obtained prior to drug administration at the following three time-points:

- any day between Days 5-21 on Cycle 1,
- any day between Days 5-21 on the cycle following a first dose reduction
- any day between Days 5-21 on the cycle following a second dose reduction.

Patients do not need to be NPO for the samples. Whenever possible, institutions are encouraged to collect samples at the same time other labs are collected (eg, weekly CBC).

13.1.2 Sample Collection and Processing Instructions

Draw 2 mL of blood into a green top (sodium heparin) tube for pharmacokinetic evaluation, and immediately place on wet ice. Centrifuge whole blood at room temperature within 30 minutes to 1 hour at 2000G X 5 minutes. Transfer serum to individually labeled tubes and store at -70° C to -80° C.

Label all serum specimens and the accompanying paperwork with the patient's COG ID number, patient's BPC number, the specimen collection date and time, the designated time point that the sample represents (eg, Cycle 1, Day X) and the COG study number (ACNS1022).

13.1.3 Sample Handling and Shipping Instructions

Sample kits and shipping containers are not provided.

Sample shipments should be made Monday through Thursday only, for delivery Tuesday through Friday. Weekend deliveries should be avoided. Sites should call Dr. Brigitte Widemann's Laboratory (details below) to notify her of the shipment and provide the courier and tracking number. Ship all serum specimens on dry ice, with a completed ACNS1022 Pharmacokinetic Sample Collection Form for each sample shipment (see Appendix VII) to:

Widemann Laboratory
Pediatric Oncology Branch, NCI, CCR
10 Center Dr. 10-CRC, Rm 1-5750 MSC 1101
Bethesda, MD 20892-1928
Phone: 301-496-7387

14.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

14.1 Timing of MRIs

To document the degree of residual tumor, standard whole brain MRI with and without contrast (gadolinium) and spine MRI with and without contrast (gadolinium) must be performed at the following time points:

- within 1 week preceding enrollment into the study
- at the following timepoints during protocol therapy:
  - within 1 week prior to each odd-numbered treatment cycle (ie, prior to cycles 3, 5, 7, 9, 11, 13) for the first 13 cycles,
  - within 1 week prior to every third treatment cycle (ie, prior to 16, 19, 22, 25) for cycles 14-26.
- when patient is removed from protocol therapy (upon completion of therapy or at progression)

In addition, for patients who have undergone surgical tumor debulking prior to protocol therapy, pre-operative and post-operative imaging must be obtained preferably within 48 hours of surgery.

14.2 MRI Guidelines for Brain/Spine Tumors

Juvenile pilocytic astrocytomas and optic pathways gliomas are generally measured on the sequence that best demonstrates tumor (usually FLAIR or T2), although this sometimes varies. For the purposes of this study, tumors will be measured two-dimensionally using the sequence that best demonstrates tumor as determined by the institutional neuroradiologist. No additional measurements will be required from the institution.

For recommended brain/spine imaging, required and optional sequences and technical details, see the COG CNS Imaging Guidelines posted on the COG member website at: https://members.childrensoncologygroup.org/_files/reference/RefMaterial/COGCNSImagingGuidelines6_4_10.pdf.

14.3 Tumor Response Assessment

For the response assessments, MRI scans obtained at the time-points during protocol therapy (see Section 14.1) will be compared to the baseline MRI scan. **Exception:** In cases of progressive disease, the reference scan should be the MRI with the smallest product observed since the start of treatment).

14.4 Retrospective Central Review

A retrospective central review of imaging will be performed for all patients enrolled on ACNS1022 for determination of best response. Results of the retrospective review will not be returned to the site. Submit the following studies with their corresponding reports for central review at the completion of treatment or when the patient is removed from protocol therapy:

- Initial (pre-operative) scan
- Post operative scan (if applicable)
- Recurrence scan (baseline scan)
- Removal from protocol therapy
- Best response (if different from end of treatment scan) (Subsequent evaluations do not need to be submitted if no change from earliest best response)

For each study sent to IROC RI (QARC), all imaging sequences obtained (e.g. Precontrast T1, FLAIR, T2, diffusion, post contrast T1, etc.) must be submitted.

14.4.1 Address Information

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP. Information for obtaining a sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC RI (QARC) at the address below. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Sites using Dicommunicator may submit imaging via that application. Contact IROC RI (QARC) with questions or for additional information.

Copies of scans of the required studies for central review should be forwarded to:

IROC RI (QARC)
640 George Washington Highway
Buildig B, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

Imaging will then be uploaded by IROC RI (QARC) for review by the National Cancer Institute (Drs Warren and Patronas). Measurements on T2, FLAIR and T1 post gadolinium will be taken to determine correlation between sequences and patient outcome.

APPENDIX I: SITE COUNSELOR IDENTIFICATION FORM

Celgene Corporation	**Celgene Pregnancy Prevention & Counseling Program** **Site Counselor Identification Form** **NCI Protocol #: _____**

- **Please identify at least two (2) counselors There must be two persons at your institution trained. Previous trainings for lenalidomide counseling ARE NOT accepted in lieu of the current training.**
- **Please fax the request for training form to Celgene at 888-314-2392**
- **Use one form per counselor.**
- **Identified counselors must be licensed healthcare professionals (e.g. RN, PA, RPh, PhD, LPN, CNP, or MD) and must not be the principal investigator.**
- **You may list all the protocols and sites that you are requesting training for on the bottom of the form. Please add the NCI protocol number(s).**
- **You will receive e-mail instructions on accessing and completing the training from Celgene.**
- **Please note: There may be a delay if the handwriting is unclear. Celgene will contact the counselor at the phone numbe provided if this is the case.**
- **Please allow adequate time for Celgene to process your request (3-5 business days) most forms are processed withinthe week they are received. If training instructions are no received within this timeframs, please e-mail coop_ma@celgene.com to inquire.**
- **After taking the training, print and fax the Certificate of Completion and your training request form to the CTAU at 1-888-691-8039 to ensure the training is applied appropriately to all studies and sites you are covering. The CTSU ONLY needs the Certificate of Completion and does no need the additional "risk minimization plan" certificates.**
- **For questions on the training content and scheduling of trainings contact Celgene at coop_ma@celgene.com and someone will respond within 24 to 48 hours.**
- **For questions on study status and CTSU processing of the form contact the CTSU Help Desk at ctsucontact@westat.com or 1-888-823-5923.**

General Information

Principal Investigator: _____ Institution Name: _____

Counselor Information

CTEP person ID: _____ CTEP site ID: _____

First Name: _____ Middle Initial:_____ Last Name: _____

License Type: (circle one) MD PhD PA CNP RN LPN RPh Other:_____

Email Address:_____

Phone: _____ Fax:_____

Institution Street Address: _____

City: _____ State/Region: _____

Zip/Post Code: _____ Country: _____

Which training will you require? ☐ Adult ☐ Pediatric

Were you previously approved as a Counselor? ☐ No ☐ Yes (Previous training) ☐ Adult ☐ Pediatric

If no, please list all the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) that you *plan to provide* counseling for:

If yes, please list the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) *for protocols Celgene has already associated you with*:

Protocol#:	CTEPsiteID	Institution

APPENDIX II: LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

Lenalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If Lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Definition of female children of childbearing potential (FCCBP)

A FCCBP is a female child who:

- Has achieved menarche and/or breast development in Tanner stage 2 or greater
    - Onset of fertility typically occurs within 3-12 months after menarche. Menarche varies considerably from person to person, and thus no age cut off can be attributed. One of the primary tools used to follow a girl's progress through puberty is the Tanner staging system which describes the pattern of development of the secondary sex characteristics. Tanner stage 2 corresponds to the beginning of breast development, which is the first visible sign of puberty in girls. Breast development is estrogen stimulated, and since ovulation cannot occur without estrogen, Tanner stage 2 will be a reliable marker for the definition of fertility.
- Has not undergone a hysterectomy or bilateral oophorectomy.

Note: Amenorrhea following cancer therapy does not rule out childbearing potential

Definition of Female Children NOT of Childbearing Potential (FCNCBP)

A FCNCBP is a female child who:

- has **not** yet experienced menarche or breast development has not reached Tanner stage 2 or
- has undergone a hysterectomy or bilateral oophorectomy.

Counseling

Female Children of Childbearing Potential (FCCBP)

For a, FCCBP lenalidomide is contraindicated unless all of the following are met (i.e., all female children of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need to commence the study treatment as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this protocol and in the Informed Consent.

For FCCBP who do not commit to complete abstinence or plan not to commit to complete abstinence, the following are required prior to the start of lenalidomide:

- She understands the need for effective contraception, without interruption, 28 days (4 weeks) before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The investigator must ensure that:

- A FCCBP complies with the conditions of the PPP, including confirmation that she has an adequate level of understanding
- A FCCBP and/or her parent/guardian acknowledge the aforementioned requirements

Female Children Not of Childbearing Potential

For a FCNCBP, lenalidomide is contraindicated unless all of the following are met (i.e., all FCNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She and/or her parent/guardian acknowledge an understanding of the hazards lenalidomide can cause to an unborn fetus and necessary precautions associated with the use of lenalidomide
- She and/or her parent/guardian will inform site staff as soon as possible regarding new onset of menarche

Male Children

The effect of lenalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time. Male subjects taking lenalidomide (and/or his parent/guardian) must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.
- Understand the potential teratogenic risk if the subject donates semen or sperm.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days (4 weeks) before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Male children must practice complete abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCCBP.

Before starting study drug

Female Patients:

FCCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10-14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Female children of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Female children of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

Male Patients:
Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for at least 28 days following study drug discontinuation

Female Patients:

- FCCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation.
- Female children of childbearing potential with irregular menstrual cycles, must agree to have pregnancy tests weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit the Investigator must confirm with the FCCBP that she is continuing to use two reliable methods of birth control
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days (once per cycle).
- If a FCCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.

- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.

- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

- Female children must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a female of childbearing potential while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

  - Must not donate semen or sperm while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

  - Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days (once per cycle).

  - If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

Patients should be instructed never to give lenalidomide to another person and to return any unused capsules to the Investigator at the end of treatment.

Patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.

Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of lenalidomide.

APPENDIX III A: LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: ACNS1022

COG Patient ID#: _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

☐ FCCBP (Female children of childbearing potential): female child who: 1) has achieved menarche or breast development in Tanner Stage 2 or greater, and 2) has not undergone a hysterectomy or bilateral oophorectomy.

Note: Amenorrhea following cancer therapy does not rule out childbearing potential

☐ FCNCBP (Female Children Not of Childbearing Potential): female child who: 1) has not experienced menarche or breast development has not reached Tanner Stage 2 or 2) has undergone a hysterectomy or bilateral oophorectomy.

Female Child of Childbearing Potential and/or Parent/Guardian:

1. I have verified and counseled the subject and/or parent/guardian regarding the following:

☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Female children of childbearing potential must agree not to become pregnant while taking lenalidomide.

☐ That the required pregnancy tests performed are negative.

☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).

One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

Examples of highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
- Tubal ligation
- Partner's vasectomy

Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.

Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.

Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.

If the subject missed a period or has unusual menstrual bleeding.

When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

- ☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.
- ☐ The subject has not and will never share lenalidomide with anyone else.
- ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

Female Child Not of Childbearing Potential:

1. I have verified and counseled the female child NOT of childbearing potential and/or her parent/guardian regarding the following:

- ☐ The need to be aware of signs of menarche and inform site staff as soon as possible regarding onset, if it occurs.
- ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- ☐ The subject has not and will never share lenalidomide with anyone else.
- ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

<u>Do Not Dispense Lenalidomide if:</u>

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**

- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____Date:_____/_____/_____

**Maintain a copy of the Education and Counseling Guidance Document in the patient records. **

APPENDIX III B: LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: ACNS1022

COG Patient ID#: _____ DOB: _____/_____/_____ (mm/dd/yyyy) \

1. I have verified and counseled the male subject and/or his parent/guardian regarding the following:

   ☐ Potential risks of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.

   ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

   ☐ The subject confirmed that he has not impregnated his female partner while in the study.

   ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.

   ☐ The subject has not and will never share lenalidomide with anyone else.

   ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.

   ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

   ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

   ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____Date: _____/_____/_____(dd/mmm/yyyy)

**Maintain a copy of the Education and Counseling Guidance Document in the subject's records. **

APPENDIX IV: LENALIDOMIDE PATIENT CARD FOR PEDIATRIC PATIENTS

Protocol Number: ACNS1022

Subject COG ID#: _____ DOB: _____/_____/_____ (mm/dd/yyyy)
Investigator to complete each section.

1. Status of Patient (check one)

Female Children NOT of childbearing potential*
(*no monitoring of pregnancy tests required. Retain card in records) ☐

Male ☐

Female children of child bearing potential ☐

2. Counseling regarding the potential teratogenicity of lenalidomide and the need to avoid pregnancy has been provided before first dose dispensed.

Investigator's Signature

Date

3. For Female Children of Childbearing potential – If all fields have been used below, print additional Lenalidomide Patient Cards as needed to collect and document results.

Date of Visit	Date of NEGATIVE pregnancy test	Confirmed no risk of pregnancy	Date lenalidomide prescribed	Investigator's signature

APPENDIX V: LENALIDOMIDE INFORMATION SHEET

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply, since there may be new information. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby. Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Lenalidomide was found to cause birth defects when tested in pregnant rabbits.

If you are a female who is able to become pregnant:

- **Do not take lenalidomide if you are pregnant or plan to become pregnant**
- **You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**
  - for 28 days before starting lenalidomide
  - while taking lenalidomide
  - during dose interruptions of lenalidomide
  - for 28 days after stopping lenalidomide
- **You must have pregnancy testing done at the following times:**
  - within 10 – 14 days and again 24 hours prior to the first dose of lenalidomide
  - weekly for the first 28 days
  - every 28 days after the first month or every 14 days if you have irregular menstrual periods
  - if you miss your period or have unusual menstrual bleeding
  - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
- **Stop taking lenalidomide if you become pregnant during lenalidomide treatment**
  - **If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to the NCI.**
- **Do not breastfeed while taking lenalidomide and for at least 28 days after thee last dose of lenalidomide**
  - The study doctor will be able to advise you where to get additional advice on contraception

If you are a female child not able to become pregnant:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant. Any awareness of menstrual periods must be reported to site staff.

If you are a male:

The effect of lenalidomide on sperm development is not known and has not been studies. The rsik to an unborn baby in females whose male partneris receiving lenalidomide is unknown at this time.

1. Male children, (including those who have had a vasectomy), must either not have any sexual relations with a pregnant female or a female who can become pregnant, or must use a condom during sexual contact with a pregnant female or a female who that can become pregnant:
    - While you are taking lenalidomide
    - During dose interruptions of lenalidomide
    - For 28 days after you stop taking lenalidomide
2. **Male children should not donate sperm or semen** while taking lenalidomide and for 28 days after stopping lenalidomide.
3. **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to the National Cancer Institute. Your partner should call her healthcare provider immediately if she gets pregnant.**

All subjects:

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not give blood** while you take lenalidomide and for 28 days after stopping lenalidomide.
- **Do not break, chew, or open lenalidomide capsules.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

APPENDIX VI: PATIENT DIARY FOR LENALIDOMIDE CAPSULE ADMINISTRATION

Date: From _____ To _____ (4 weeks) Cycle _____

COG Patient ID _____ ACC#: _____ Institution: _____
Please do not write patient name on this form.

My daily dose of lenalidomide is:_____ mg, (____ 2.5 mg capsule, _____ 5 mg capsule, _____ 25 mg capsule) once a day for 21 days.

1. Take/give lenalidomide dose by mouth with a full glass of water. The lenalidomide capsules should not be opened, broken or chewed.
2. Take/give the medication at a convenient time approximately the same time each day for 21 days (THREE weeks). You should take/give the medication without food. If nausea occurs after taking the dose, try taking/giving it with food as administration with food may decrease nausea.
3. Write down date, number of capsule(s) you gave/took. Wash your hands if you touch the pills.
4. If you forget to take/give the dose on time and you remember that a dose is missed within 8 hours, take the missed dose. If more than 8 hours have passed then skip that dose. Notify the clinic that a dose was taken late or skipped at the next visit.
5. If you vomit within 10 minutes of taking the dose and you can see the capsules, take another dose and notify the clinic. You may need to obtain additional supply of drug to finish the cycle.
6. Write down any side effects (like diarrhea, constipation, nausea) in the comments column.
7. Bring your capsule bottle and this form to your doctor when you return to your next appointment.

Date	Day	# Capsules (list strength and quantity)	Comments (example: diarrhea, constipation, nausea)	Date	Day	# Capsules (list strength and quantity)	Comments (example: diarrhea, constipation, nausea)
	1				15		
	2				16		
	3				17		
	4				18		
	5				19		
	6				20		
	7				21		
	8				22	Rest period of 7 days	
	9				23		
	10				24		
	11				25		
	12				26		
	13				27		
	14				28		

Patient's/Caregiver Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____ Date patient was removed from study _____
2. Patient's planned daily dose _____

Physician/Nurse/Data Manager's Signature _____

APPENDIX VII: ACNS1022 PHARMACOKINETIC STUDY FORM: STEADY STATE SAMPLES

COG Pt ID # _____ **ACC #** _____

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

Cycle ____, Day_____ Date: |__/__|__/__|__/__|

Body Surface Area: |__|°|__|__| m^2 Total Dose: |__| |__| |__|°|__| |__| mg

Blood samples (2 mL) will be drawn peripherally in green top (sodium heparin) tubes. Please see protocol Section 13.1 for detailed Sample Collection, Handling, and Processing instructions**.** Record the exact time that the sample is drawn along with the exact time that the drug was administered after sample collection.

		Date Sample Collected	**Time Sample Collected**	**Administration of Lenalidomide**	
Blood Sample No.	**Collection Time (prior to drug administration)**			**Date**	**Time**
1	**Cycle 1, Between Days 5-21**	Date: _____	Time: _____	Date: ___	Time: ____
2	**Cycle following a first dose reduction, Any day between Days 5-21**	Date: _____	Time: _____	Date: ___	Time: ____
3	**Cycle following a second dose reduction, Any day between Days 5-21**	Date: _____	Time: _____	Date: ___	Time: ____

Each tube must be labeled with "ACNS1022", the patient's COG number, the date and time the sample was drawn, and the designated time point that the sample represents (eg, "Cycle 1, Day X"). Data should be recorded on this Pharmacokinetic Study Form, which must accompany the sample(s).

Please see Section 13.1 for detailed sample shipping instructions. Prior to shipping, please contact Dr. Brigitte Widemann (301-496-7387) for notification of sample shipment. **DO NOT SHIP SAMPLES ON A FRIDAY OR WEEKEND.** Refer to the following link for information regarding Federal Express Account information to use for shipping pk samples: https://members.childrensoncologygroup.org/prot/biology.asp. **Ship samples to:**

Widemann Laboratory
Pediatric Oncology Branch, NCI, CCR
10 Center Dr. 10-CRC, Rm 1-5750 MSC 1101
Bethesda, MD 20892-1928
Phone: 301-496-7387

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 who collected samples)

APPENDIX VIII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS1022
(for children from 7 through 12 years of age)

A Study of An Experimental Drug in Children and Teens with Brain Tumors That are Hard to Treat or Have Come Back after Treatment

1. We have been talking with you about your brain tumor. Your brain tumor has either come back or not gone away with the treatments you already received.

2. We are asking you to take part in a research study because other treatments did not get rid of your tumor. 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 find out if an experimental anti-cancer medicine can make your tumor get smaller or go away.

3. Children who are part of this study will be treated with the anti-cancer medicine called lenalidomide. This medicine has been used to treat children with different kinds of cancers, including brain cancer. In this study, we want to treat more children with brain cancers so we can get more information about how well lenalidomide works. This study will look at two doses of the anti-cancer medicine. Half of the children in this study will get a lower dose of the anti-cancer medicine and half will get a higher dose. Which dose you get will get is decided on by chance. This is like flipping a coin and saying, "Heads means I get the lower dose treatment, but tails means I get the higher-dose treatment." A computer decides which treatment you will get, not you or your doctor.

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 the new anti-cancer medicine will make your tumor get smaller or go away for as long as possible. But, we do not 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." One risk to you from this study is that the study treatment may not work as well as other treatments to make your tumor get smaller or go away for as long as possible. 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. We are asking your "okay" to collect extra blood. We want to see if there are ways to tell how the tumor will react to treatment. We would like to collect about ½ teaspoon of blood at up to 3 times during your treatment. We will try to collect the extra blood at the same time other standard blood tests are being done. If we can't do this, you might have up to two extra needle sticks.

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS1022
(for teens from 13 through 17 years of age)

A Study of An Experimental Drug in Children and Teens with Brain Tumors That are Difficult to Treat or Have Come Back after Treatment

1. We have been talking with you about your low grade glioma. Low grade gliomas are types of cancer that grow in the brain. Your tumor has either come back or not gone away with previous treatments.

2. We are asking you to take part in a research study because other treatments did not get rid of your low grade glioma. A research study is when doctors work together to try out new ways to help people who are sick. In this study, doctors want to try an experimental anti-cancer drug to see if this drug will work well to make your tumor get smaller or go away.

3. All children and teens who are part of this study will be treated with the anti-cancer drug called lenalidomide. This drug has been used to treat children and teens with different types of cancer, including some children and teens with brain cancer. In this study, doctors would like to treat a larger group of children and teens with brain cancers so they can get more information about how well lenalidomide works. This study will look at two doses of the anti-cancer drug. Half of the children in this study will get a lower dose of the anti-cancer drug and half will get a higher dose. Which dose you get will get is decided on by chance. This is like flipping a coin and saying, "Heads means I get the lower dose treatment, but tails means I get the higher-dose treatment." A computer decides which treatment you will get, not you or your doctor.

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 the lenalidomide will make your tumor get smaller or go away for as long as possible, 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." One risk to you from this study is that the treatment you get may not work as well as other treatments to get rid of the tumor for as long as possible. Another risk is that you may have more side effects from the drug if you get the higher dose. If you get the lower dose, there is a risk is that you may get a treatment that does not work as well as the higher dose. 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. We are asking your permission to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. We would like to collect about ½ teaspoon of blood at up to 3 times during your treatment. We will try to collect the extra blood at the same time other standard blood tests are being performed. If we can't do this, you might have up to two extra needle sticks.

APPENDIX IX: REGIMEN A LENALIDOMIDE DOSING TABLES

20 mg/m^2, Dose Level 1	
BSA (m^2)	**Daily Dose (mg)**
0.44 – 0.56	10
0.57 – 0.69	12.5
0.70 – 0.81	15
0.82 – 0.93	17.5
0.94 – 1.06	20
1.07 – 1.18	22.5
1.19 – 1.31	25
1.32 – 1.43	27.5
1.44 – 1.56	30
1.57 – 1.69	32.5
1.70 – 1.82	35
1.83 – 1.94	37.5
1.95 – 2.06	40
2.07 – 2.19	42.5
≥2.20	Round to nearest 2.5 mg

15 mg/m^2, Dose Level -1	
BSA (m^2)	**Daily Dose (mg)**
0.44 – 0.56	7.5
0.57 – 0.75	10
0.76 – 0.91	12.5
0.92 – 1.08	15
1.09 – 1.25	17.5
1.26 – 1.42	20
1.43 – 1.58	22.5
1.59 – 1.76	25
1.77 – 1.91	27.5
1.92 – 2.08	30
2.09 – 2.20	32.5
≥ 2.20	Round to nearest 2.5 mg

10 mg/m^2, Dose Level -2	
BSA (m^2)	**Daily Dose (mg)**
0.44 – 0.62	5
0.63 – 0.82	7.5
0.83 – 1.12	10
1.13 – 1.37	12.5
1.38 – 1.62	15
1.63 – 1.87	17.5
1.88 – 2.12	20
2.13 – 2.20	22.5
≥ 2.20	Round to nearest 2.5 mg

APPENDIX X: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

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

Registration requires the submission of:

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

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

CTEP Associate Registration Procedures / CTEP-IAM Account

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

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

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

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

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

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

Requirements for ACNS1022 Site Registration:

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

Submitting Regulatory Documents:

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

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:

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

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

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