SUMMARY OF CHANGES
For Protocol Amendment #36 (CTEP Amd # 36) to:

NCI Protocol #: **8317**
Local Protocol #: **10-182-B**

Protocol Date: 09/25/2019

Per CTEP recommendations the following changes were made:

#	Section	Page	Change
1.	Title Page	1	Updated the protocol version date from 03.14.2019 to 09.25.2019
2.	Protocol history	5	Updated protocol history section to change Regulatory Manager from Supriya Perambakam to Mary Harris and updated RM contact information
3.	CAEPR Lenalidomide	60	Updated CAEPR for Lenalidomide from Version 2.6, December 24, 2015 to Version 2.8, June 27, 2019

NCI Protocol #: **8317**
Local Protocol #: **10-182-B**

TITLE: Phase I/II trial of Cediranib alone or Cediranib and Lenalidomide in iodine 131-refractory differentiated thyroid cancer

Coordinating Center: **The University of Chicago for the University of Chicago Phase II Consortium**

Principal Investigator:

Chih-Yi Liao, M.D.
The University of Chicago Medical Center
5841 S. Maryland Ave., MC 2115
Chicago, IL- 60637
Tel: (773) 702 6241
Fax: (773) 702 3163
e-mail: andyliao@medicine.bsd.uchicago.edu

Lenalidomide training: Any new site has to have two trained counselors for lenalidomide dispensing. Training documentation must be kept on file at PMB per section 4 of the protocol. Sites cannot register patients or order agents until this is done. Recommend that two counselors at each site be identified and trained as early as possible. Please note as of April 10, 2015, patients on Arm B are no longer receiving lenalidomide. For further details refer to section 5.1.2.

Participating Sites:	
James L. Wade III, M.D. Decatur Memorial Hospital 2300 N. Edward St. Decatur, IL 62526 Ph: (217) 876-6600 JLWADE3@sbcgloab.net Krishna Rao, M.D. , PhD krao@siumed.edu Springfield, IL; (217) 545-5817 or (217) 545-7089	Sreenivasa Nattam, M.D. Fort Wayne Medical Oncology/Hematology, Inc. Research Department 11143 Parkview Plaza Drive, Suite 100 Ft. Wayne, IN 46815 Ph: (260) 484-8830 snattam@fwmoh.com Dr. Sunil Babu, MD Fort Wayne Medical Oncology/Hematology, Inc. 7910 West Jefferson Blvd. Suite 108 Fort Wayne, IN 46804 Ph: 260-436-0800 sunilbabumail@yahoo.com

Mark Kozloff, M.D. S. Yalavarthi, M.D. Ingalls Hospital 1 Ingalls Dr. Harvey, IL 60430-1144 Ph: (708) 339-4800 mfkozloff@aol.com sulochana2001@hotmail.com	Mark Agulnik, M.D. Northwestern Memorial Hospital 676 N St. Clair St Suite 850 Chicago, IL 60611 (312) 695-1222 m-algulnik@northwestern.edu
Bethany G. Sleckman, M.D. Saint John's Mercy Medical Center 607 S. New Ballas Road, Ste 3425 St. Louis, MO 63141 Ph: (314) 251-7057 slecbg@stlo.mercy.net	Stephanie Wagner, MD Hematology/Oncology Department IU Simon Cancer Center 535 Barnhill Drive, RT 449 Indianapolis, IN 46202 Phone: 317-962-9000 E-mail: wagnerst@iupui.edu
FrancisWorden M. D. University of Michigan Comprehensive Cancer Center C361 MIB 0848 1500 E Medical Center Drive Ann Arbor, MI 48109-0848 Ph: (734) 936-0453 fworden@umich.edu	Bruce Brockstein, M.D. NorthShore University Health System 2650 Ridge Ave. Evanston, IL 60201 Ph: (847) 570-2515 b-brockstein@northwestern.edu
Kevin J. Cullen, M.D. Marlene & Stewart Greenbaum Distinguished Professor in Oncology, Director, University of Maryland Greenbaum Cancer Center, 22 S. Greene Street,Baltimore, MD 21201 Ph: (410) 328-5506 kcullen@umm.edu	Paul A.S. Fishkin, M.D. Illinois CancerCare, P.C. 8940 N. Wood Sage Road Phone: 309-243-3000 Fax: 309-243-3049 Peoria, IL 61615 pfishkin@illinoiscancercare.com

Additional Sites:	
Naifa L. Busaidy, MD MD Anderson Cancer Center Endocrine Neoplasia and Hormonal Disorders 1515 Holcombe Boulevard, Unit 435 Houston, Texas 77030-4009 Ph: (713) 792-2841 nbusaidy@mdanderson.org	Amit Oza, MD Monika Krzyzanowska, MD Princess Margaret Hospital Division of Medical Oncology 5700, 610 University Avenue Toronto, ON, Canada M5G 2M9 PH: (416) 946-2818 Fax: (416)946-2082 amit.oza@uhn.on.ca monika.krzyzanowska@uhn.on.ca
Colleen Veloski, MD Fox Chase Cancer Center 333 Cottman Ave Room P3179C Philadelphia, PA 19111 Phone: 215-728-3591 Fax: 215-214-1525 Email: Colleen.Veloski@fccc.edu	Dr. Dean Ruether Tom Baker Cancer Centre 1331 29 St NW Calgary, AB T2N 4N2 Ph: 403-521-3093 Fax: 403-283-1651 Dean.Ruether@albertahealthservices.ca Dr. Cynthia Card Tom Baker Cancer Centre 1331 29 St NW Calgary, AB T2N 4N2 Ph: 403-521-2446 Fax: 403-283-1651 Cynthia.Card@albertahealthservices.ca
Eric Winquist M.D., MSc University of Western Ontario Clinical Cancer Research Program London Health Sciences Centre 790 Commissioners Road East London, Ontario Canada N6A 4L6 Ph: (519) 685-8600 Fax: (519) 685-8624 eric.winquist@lhsc.on.ca	Dan Sullivan, M.D. Tawee Tanvetyanon, MD Moffitt Cancer Center and Research Institute University of South Florida 12902 Magnolia Drive Tampa, FL 33612 Ph: (813) 745-3878 or (813) 745-6323 Fax: (813) 745-7265 or (813) 745-5944 dan.sullivan@moffitt.org Tawee.tanvetyanon@moffitt.org
Jared Weiss, M.D. University of North Carolina Chapel Hill Physicians Office Bldg., Third Floor, CB #7305 170 Manning Drive Chapel Hill, NC 27599-7305 Phone: (919) 843-7714 Fax: (919) 966-6735 E-Mail: jared_weiss@med.unc.edu	

Jill Gilbert, MD Vanderbilt University Medical Center 777 Preston Research Building Nashville, TN 37232-6307 Ph : (615) 343-4677 Fax: (615) 343-7602 jill.gilbert@vanderbilt.edu	Joseph Aisner, MD The Rutgers Cancer Institute of New Jersey 195 Little Albany St. New Brunswick, NJ 08901 Phone: 732-235-7464 Fax: 732-235-6797 aisnerjo@cinj.rutgers.edu

Dean Lim, MD City of Hope 1500 E. Duarte Rd. Duarte, CA 91010 Phone: 626-256-HOPE (4673) Fax: 626-301-8233 dlim@coh.org	Thomas J. Semrad, MD, MAS University of California Davis Cancer Center 4501 X Street, Sacramento, CA 95817 Phone: (916) 734-3771 Fax: (916) 734-7946 thomas.semrad@ucdmc.ucdavis.edu
Stephen Koehler, MD City of Hope Medical Group, Inc., 209 Fair Oaks Avenue South Pasadena, CA 91030 626/396-2900 Skoehler@cohmg.com	Barbara Gitlitz, M.D. USC/Norris Comprehensive Cancer Center 1441 Eastlake Avenue Los Angeles, CA 90033-0804 Phone: 323-865-3959 Fax: (323) 865-0061 gitlitz@usc.edu
Chandra P. Belani, MD Penn State Hershey Cancer Institute 500 University Drive, CH72 Hershey, PA 17033 Phone: 717-531-1078 Fax: 717-531-0002 cbelani@psu.edu	Ammar Sukari, MD Wayne State University/Karmanos Cancer Institute 4100 John R Mail code: HW04HO Detroit, MI 48201 Phone: 313 576 8778 Fax: 313 576 8767 sukaria@karmanos.org
Anne Traynor, M.D. 1111 Highland Avenue, WIMR Room 3103 Madison, WI 53705-2275 Phone: (608) 262-5092 E-mail: amt@medicine.wisc.edu	PJ Flynn, M.D. Metro-Minnesota Community Clinical Oncology Program Minnesota Oncology Hematology, PA 800 E 28th St, Suite 405 Minneapolis, MN 55407 Phone: (612) 863-8585 Fax: (612) 863-8586 E-mail: patrick.flynn@usoncology.com
Douglas R. Adkins, M.D. Washington University School of Medicine, Campus Box 8056, 660 South Euclid Avenue St. Louis MO 63110 Phone: (314) 362-5654 Fax: (314) 362- 7086 dadkins@dom.wustl.edu	Bryan R. Haugen, MD Professor of Medicine and Pathology Head, division of endocrinology, metabolism, diabetes 12801 E. 17th Ave, 8117 RC 1 South, Room 7103 Aurora, CO 80045 Phone: 303-724-3921

	Bryan.haugen@ucdenver.edu

Study team:	
Statistician: Theodore Karrison, PhD. University of Chicago 5841 S. Maryland Ave. MC 2007 Chicago, IL 60637 Ph: (773) 702-9326 tkarrison@health.bsd.uchicago.edu	**Regulatory Affairs Manager**: Mary Harris University of Chicago 5841 S. Maryland Ave., MC 1140, Chicago, IL 60637 Phone:(773) 702-0142 Email mharris7@bsd.uchicago.edu
Group Chairman: Walter Stadler, M.D. Everett Vokes, M.D. University of Chicago 5841 S. Maryland Ave. MC 2115 Chicago, IL 60637 Ph: (773) 702-9753 wstadler@medicine.bsd.uchicago.edu	**Study Registrar:** BERNIE LIBAO, CCRP 5841 S. Maryland | Room I-519, MC 2115 | Chicago, IL 60637 Direct line: 773-702-6634 | Fax: 773-702-4889 | Pager: 773-702-6800, ID# 6796 Email: blibao@medicine.bsd.uchicago.edu
	Research Nurses: Allison Dekker 773-702-2068 adekker@medicine.bsd.uchicago.edu University of Chicago Medical Center 5841 S. Maryland Ave. MC2115 Chicago, IL 60637
Contract #	
NCI Approval:	Approved
UC Protocol Approval:	Approved

NCI Supplied Agents:
Cediranib (NSC 732208), Astrazeneca
Lenalidomide (NSC 703813), Celgene

Protocol Type / Version # / Version Date:

Version Date	Description of Action
2/02/09	Initial submission
2/8/10	Consensus Review Response
2/23/10	In response to additional recommendation comments. Consent version date 2/3/10 "What are the Risks" Updated risk profile for Lenalidomide v. 2.2 1/15/10.
3/17/10	Amendment # 1. In response to RRA for Cediranib risk profile update. Face page Amendment # 1 Version date 3/17/10. Section 7.1.1 Cediranib CAEPR updated with v. 2.9 2/19/10. Consent Phase I & Phase II version date 3/17/10 "What are the Risks" Updated risk profile for Cediranib v. 2.9 2/19/10.

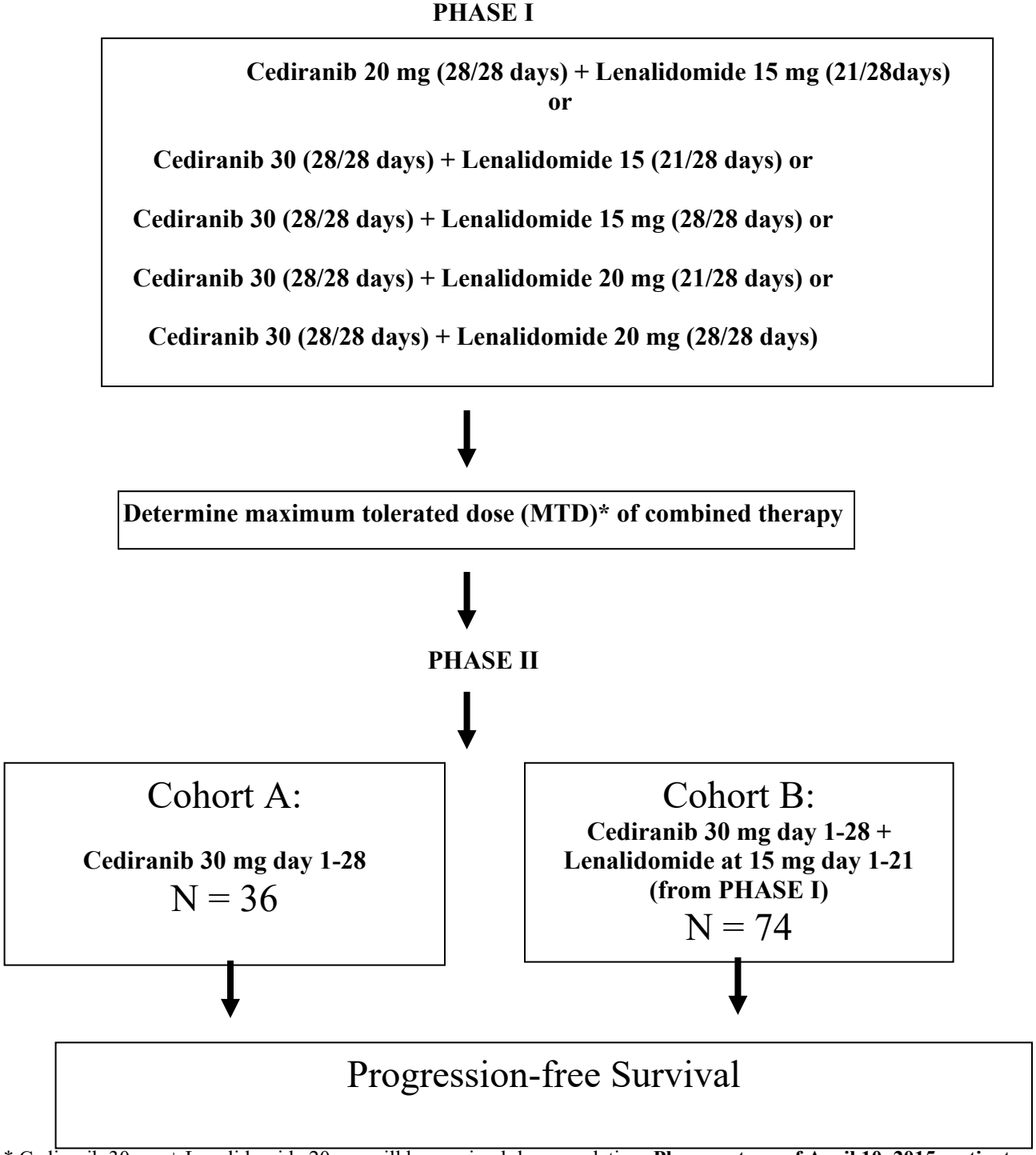
6/9/10	Administrative Amendment Changed all reference from patient to subject in appendices B, J and K per IRB request.
7/6/10	Further IRB requested administrative changes.
7/9/10	Amendment # 2 Further IRB requested administrative changes.
8/4/10	Follow up response to NCI Follow Up review. Cover Page: Amendment # 3, Version Date 8/4/10. Protocol History updated. Dr. Ginny Kamboj removed from the cover page. Consent Forms (phase I and II) Cediranib spelling has corrected under "During the study". Cetuximab has been replaced with Cediranib in the last sentence of paragraph 3 under "Tests for Research Purposes Only." The "also reported" adverse effects list for cediranib, on page 9, has been removed.
10/25/10	**Amendment #4 –** revised eligibility (prior therapies for Ph I, prior RT, change documented disease progression from 6 to 12 months), updated study calendar (add prophylactic anticoagulation and radiology assessments every 2 cycles)
12/21/10	**Amendment # 5** Face Sheet: Version Date 12/21/10. Removed Northern Indiana Cancer Research Consortium, Medical University of South Carolina and Oncology Care Associates as participating affiliates. Updated Francis Worden as PI at U Michigan. Section 7.3.1 updated with new AdEERS reporting language. All reference to paper AdEERS removed. Section 10.0 Study Calendar LDH removed as a required chemistry lab.
3/2/11	**Amendment #6** In response to RRA for Cediranib risk profile update. Face page Amendment #6 Version Date 3/2/2011. Section 7.1.1 updated with Cediranib CAEPR version 2.10, January 13, 2011.
4/19/11	Protocol updated to include Secondary Malignancy reporting in section 7.6.
5/16/11	Amendment #8 In response to request for change in reproductive risk language and lenalidomide bottle counts. Face page Amendment #8 Version 5/16/2011. Section 3.1.11 eligibility criterion for contraception and pregnancy monitoring updated. Section 4.2 updated with requirement for two trained counselors through LCP. Sections 7.4.1 and 7.4.2 updated with expedited reporting guidelines for pregnancy occurrence. Sections 8.1.2 and 8.1.4 pharmaceutical information for lenalidomide updated. Appendices H, I, and J updated. Appendix K Registration for Lenalidomide Counseling Program inserted.
8/8/2011	**Amendment #9** Face Sheet: Version 8/8/11. Updated Regulatory Affairs Manager. Schema updated with Phase II Cediranib and Lenalidomide dosing. Section 2.1 updated with Phase II Cediranib and Lenalidomide dosing. Section 3.2.8 updated to state that Cediranib can be administered via nasogastric or gastostomy tube. Section 4 updated to remove references to Jeffrey Bozeman as study registrar and update study registrar email address, Section 5.1 updated with information for patients who are unable to swallow cediranib. Section 5.1.1 third row updated to ≤ 1 out of 6. Section 5.1.2 first bullet point updated with Phase II dosing for Cediranib and Lenalidomide. Section 6 dose modification for Phase II Lenalidomide 5 mg days 1-21 added and "<" updated to "≤" and ">" updated to "≥." Section 7.6 updated to state that all malignant tumors must be reported through AdEERs whether or not they are thought to be related to either previous or current treatment. Section 10 footnote m added to TSH and Thyroglobulin to state that evaluations will be repeated every 2 cycles.
9/15/11	**Amendment #10** In response to RRA for Lenalidomide risk profile update. Face Sheet: Version 9/15/11. Section 7.1.3 updated with Lenalidomide CAEPR v. 2.3, June 27, 2011.
12/21/11 Disapproved	**Amendment #11** Face Sheet: Version 12/21/11, PI contact info removed for Central Illinois Hem/Onc, Loyola, Medical College of Wisconsin, PI contact info added for Northwestern, Indiana University, St. Joseph Medical Center, Fox Chase Cancer Center, Tom Baker Cancer Centre, Nurse contact info updated. Schema updated with 30 patients in Cohort A and 60 patients in Cohort B. Section 1.2.1 Primary Objectives changed to maximal change in target lesion size from baseline. Section 2.1 updated to state Phase II will compare maximal change in target lesion size of cediranib to cediranib plus lenalidomide. Section 3.1.4 updated to state cytotoxic or targeted prior chemotherapy. Section 5.1 updated to state lenalidomide may be administered via gastrostomy feeding tube. Section 5.1.1 information regarding phase I toxicity added. Section 5.1.2 updated to state 30 patients in Cohort A and 60 patients in Cohort B, only one cycle of therapy will be dispensed each month. Section 6 updated based on Phase II dose. Section 7.1.1

	in response to RA for Cediranib, updated with Cediranib CAEPR v 2.11, November 10, 2011. Section 9.1 Removed references to blood and shipping address for archival tumour samples was updated. Section 11.1 updated to state that primary outcome of the Phase II study will be maximal change in tumor size. Section 11.1.4.1 updated to state maximal change in target lesion size from baseline. Maximal change in target lesion size compared to baseline. Section 13.1.2 updated to state that data will be analyzed after 45 patients have been evaluated and if the combination arm is doing no better the trial will be terminated. Section 13.2 updated to state that Phase II will have sample size of 90 patients, Section 13.4.1 6 months updated to 12 months in this section. References updated. Appendix B lenalidomide drug diary updated. Appendix M Procedure for Dosing Lenalidomide Via Gastrostomy Feeding Tube added.I
1/24/12	**Amendment #12** Face Sheet: Version 1/24/12. PI contact info removed for Central Illinois Hem/Onc, Loyola, Medical College of Wisconsin, PI contact info added for Northwestern, Indiana University, St. Joseph Medical Center, Fox Chase Cancer Center, Tom Baker Cancer Centre, Nurse and CRA contact info updated. Section 3.1.4 updated to state cytotoxic or targeted prior chemotherapy. Section 5.1 updated to state lenalidomide may be administered via gastrostomy feeding tube. Section 7.1.1 in response to RA for Cediranib, updated with Cediranib CAEPR v 2.11, November 10, 2011. Section 9.1 Shipping information for tumor samples updated. Appendix B lenalidomide drug diary updated. Appendix M Procedure for Dosing Lenalidomide Via Gastrostomy Feeding Tube added.
3/12/12 - Disapproved	**Amendment #13** Face Sheet: Version 3/12/12. PI contact info for Northwestern updated. Schema updated to 36 participants in cohort A and 74 in Cohort B, primary objective updated to Progression-free survival. Section 1.2 Phase II primary objectives updated to progression-free survival. Section 1.3 secondary objectives to determine response rates and duration of response and early tumor size changes. Section 2.1 grammatical corrections. Section 2.1 updated to accurately state starting dose of cediranib will be 20 mg. Section 2.1 updated to state that primary endpoint will be progression-free survival and that after 18 cycles, radiologic disease re-evaluation will occur every 16 weeks. Section 3.1 updated to state that patients with hyperbilirubinemia due to Gilbert's syndrome may enroll in the trial. Amended to state that patients who have been on trial for greater than 12 months may be counseled every two cycles. Section 3.2.8 updated with procedures for patients who are unable to swallow cediranib and lenalidomide. Section 3.2 added prior therapy with a VEGF-pathway inhibitor and ECOG performance status added to the required documents to be sent the data manager. Section 5.1 added criteria for subjects to receive two cycles of drug after being on study 12 or more months. Section 5.1.1added that after 18 cycles, radiologic disease re-evaluation will occur every 16 weeks. Section 5.1.2 updated subject number in each cohort, added that after 18 cycles, disease re-evaluation will occur every 16 weeks, stated that FCBP must still have pregnancy testing at least every 28 days. Added that subjects who have been on protocol for 18 months or more will have radiographic-tumor response assessed every 4 cycles. Section 8.1.2 updated to indicate that after 12 months, patients may be able to receive two cycles of drug at a time. A reference to section 5.1 and appendix m was added for patients who cannot swallow lenalidomide. Section 10 reference to section 5.1 added to footnote b, footnote l updated to state that subjects on protocol 18 months or more will have radiology evaluation every 4 cycles. Section 11.1 added that subjects who have been on treatment for 18 months or more will have radiological evaluation every 4 cycles. Section 13.1 updated with new phase II study endpoints. Section 13.2 updated phase II sample size. Section 13.4 updated analysis of Phase II secondary endpoints, Section 13.5.2 updated made to evaluation of response. References updated. Appendix B updated to state that 2 cycles of lenalidomide may be dispensed if subject on study 12 or more months. Appendix C Grade updated to CTCAE v. 4.0 and grady systolic and diastolic values updated. Appendix D updated references to CTCAE v4.0. Appendix H updated to state that counseling may occur every two cycles but pregnancy tests must be done at least every 4 weeks. Added that after 12 months on study two cycles of drug therapy may be dispensed. Appendix J updated to state that after 12 months, you may be eligible to receive a 56 day supply of study drug.
4/9/12	**Amendment #14** Face Sheet: Version 4/9/12. PI contact info for Northwestern updated. Schema updated to 36 participants in cohort A and 74 in Cohort B, primary objective updated to Progression-free survival. Section 1.2 Phase II primary objectives updated to

	progression-free survival. Section 1.3 secondary objectives to determine response rates and duration of response and early tumor size changes. Section 2.1 grammatical corrections. Section 2.1 updated to accurately state starting dose of cediranib will be 20 mg. Section 2.1 updated to state that primary endpoint will be progression-free survival and that after 18 cycles, radiologic disease re-evaluation will occur every 16 weeks. Section 3.1 updated to state that patients with hyperbilirubinemia due to Gilbert's syndrome may enroll in the trial. Section 3.2.8 updated with procedures for patients who are unable to swallow cediranib and lenalidomide. Section 3.2 added prior therapy with a VEGF-pathway inhibitor and ECOG performance status added to the required documents to be sent the data manager. Section 5.1.1added that after 18 cycles, radiologic disease re-evaluation will occur every 16 weeks. Section 5.1.2 updated subject number in each cohort, added that after 18 cycles, disease re-evaluation will occur every 16 weeks. Added that subjects who have been on protocol for 18 months or more will have radiographic-tumor response assessed every 4 cycles. A reference to section 5.1 and appendix m was added for patients who cannot swallow lenalidomide. Section 10 reference to section 5.1 added to footnote b, footnote l updated to state that subjects on protocol 18 months or more will have radiology evaluation every 4 cycles. Section 11.1 added that subjects who have been on treatment for 18 months or more will have radiological evaluation every 4 cycles. Section 13.1 updated with new phase II study endpoints. Section 13.2 updated phase II sample size. Section 13.4 updated analysis of Phase II secondary endpoints, Section 13.5.2 updated made to evaluation of response. References updated. Appendix B Lenalidomide drug diary updated with information about administration via gastrostomy tube. Appendix C Grade updated to CTCAE v. 4.0 and grade systolic and diastolic values updated. Appendix D updated references to CTCAE v4.0.
11/15/12	**Amendment #15** Face Sheet: Version 11/15/12. Added new investigators under additional sites, Drs, Lim, Belani, Sukari, Semrad, Gitlitz and Koehler. Also updated other research personnel (Regulatory Affairs Manager and Research Nurse) on the Face page. Section 3.1.8. Changed the inclusion criteria for creatinine to be "below or equal to upper limit of institutional limits." The rationale here is be inclusive of subjects whose creatinine may be below the normal reference range. Section 6.1. Management of Hypertension. Updated the language for dose adjustment for hypertension to be more consistent with Appendix C and to allow for less ambiguity for treating physicians when adjusting study medication for high blood pressure. Section 6.2. Other Hematologic and Non-Hematologic Adverse Events. Adjusted the recommendations for the management for fatigue to give the treating physician more guidance for dose adjustment. Section 10. Study Calendar. Added footnotes "n" and "o"; n: After 12 months, subjects can be evaluated every 2 cycles; o: In select patients. See section 3. 1.10 for further details. Appendix C. Management of cediranib-induced hypertension. Deleted the figure in Appendix C. This figure referred to CTCAEv3.0 guidelines for hypertension management and was inconsistent with the management of hypertension as discussed in Section 6.1.
12/12/12	**Amendment #16** Face Sheet: Version 12/12/12. Added a new site, The Cancer Institute of New Jersey. Site PI is Joseph Aisner, MD. John Godwin, MD was removed from Decatur Memorial Hospital site. St. Joseph Medical Center Cancer Institute also was deleted from the face page. Section 3.1.8. Changed the inclusion criteria for bilirubin as: X total serum bilirubin: below or equal to upper limit of institutional normal**. Similarly, for creatinine it should read "OR" instead of "AND" X creatinine clearance >50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.The rationale here is be inclusive of subjects whose bilirubin or creatinine may be below the normal reference range.
03-28-13	**Amendment #17** Face Sheet: Version 3/28/13. UC lead PI, Rebecca Brown is replaced by Jonas De Souza, M.D. Indiana University site PI, Noah Hahn is replaced by Romnee Clark-Seaberg, M.D. Section 6.2 - Other Hematologic and Non-Hematologic Adverse Events: clarifications in the instruction for dose modification for proteinuria. Section 10.0 -Study calendar: is updated to show Day 113 for clarification.
04-03-13	**Amendment #18** Face Sheet: Version 4/3/13. Section 7.1.2 : Deleted the lenalidomide CAPER and replaced with the new version in its entirety. Section 7.1.2 : Under how supplied, removed "Bottles contain either 21 or 28 capsules per container" with "Bottles each

	contain 100 capsules". Deleted the italicized paragraph directly below the how supplied section. Section 8.1.3 : Removed 2nd paragraph and replaced with updated information.
07-09-13	**Amendment #19** Face Sheet: Version 7/09/13. Updated the site PI at the University of Maryland.
07-31-13	**Amendment #20** Face Sheet: Version 7/31/13. Removed Virginia Commonwealth University (VCU)/Massey Cancer Center. Added 4 new Mayo consortium sites. Section 7.1.1: Deleted the Cediranib CAPER and replaced with the new version in its entirety. Section 8.1 updated lenalidomide dispensing language and ordering information for PMB supplied agents.
1-14-14	**Amendment #21** Updated language in title page, updated site PI at Indiana University and University of Colorado and added new sites. Section 7.0 changed AdEERS to CTEP-AERS. Under Section 8.1, corrected Lenalidomide availability section per CTEP recommendations. Section 10.0 study calendar edited minor typographical errors. Updated contact/shipping information for the bio specimen facility throughout the protocol.
5-20-14	**Amendment #22** Updated site PI at Illinois Cancer Care, updated Fort Wayne address and added a new sub-site/PI.
10-9-14	**Amendment #23** Section 7.1.2: Deleted the lenalidomide CAPER and replaced with the new version in its entirety.
4-10-15	**Amendment #24** Corrected local PI at University of Coloardo to Byan Haugen and made changes to the version date (footer) throughout the protocol.
5-26-16	**Amendment #25** Updated CAPER for lenalidomide version with version 2.6, December 24, 2015.
07-07-16	**Amendment #26** Updated section 8.1- cediranib monograph; IB access; PMB contacts
12-22-16	**Amendment #27** Updated section 5.1.2 to indicate that as of April 10, 2015, lenalidomide is discontinued on Arm B.
1-11-17	**Amendment #28** Updated section 7.1.1 updated Cediranib CAPER to ver 2.13; section 8.1.3 and study schema re discontinuation of lenalidomide
5-10-17	**Amendment #29** Protocol face page updated to reflect the lead PI change from DeSoza to Seiwert
8-18-17	**Amendment #30** Protocol face page updated to reflect the change local PI at UNC from Hayes to Weiss
10-13-17	**Amendment #31** Protocol face page updated to reflect the change in IND from 72740 to 132089
03.05.18	**Amendment #32** Updated site personnel. Per CTEP request updated CTAE v4.0 to v5.0 throughout the document.
05.14.18	**Amendment #33** Per CTEP request updated Cediranib CAEPR (Version 2.14, November 14, 2017). In addition, as part of the implementation of version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE), the (CAEPR) list for cediranib, which was previously in CTCAE 4.0 language, has been migrated to CTCAE 5.0 language.
01.09.19	**Amendment #34** Per CTEP request updated Cediranib CAEPR (Version 2.15, November 7, 2018)
03.14.2019	**Amendment #35** Local Principal Investigator contact information updated on face page
09.25.2019	**Amendment #36** Per CTEP request updated Lenalidomide CAEPR (Version 2.8, June 27, 2019). Revision of the ICD to provide further clarification. Updated Study Team information, changing the Regulatory Affairs Manager to Mary Harris.

SCHEMA



* Cediranib 30 mg + Lenalidomide 20 mg will be maximal dose escalation. **Please note as of April 10, 2015, patients on Arm B are no longer receiving lenalidomide. For further details refer to section 5.1.2.**

TABLE OF CONTENTS

OBJECTIVES

1.1. Phase I

1.1.1. Primary Objective

- Determine the MTD of cediranib plus lenalidomide.

1.1.2. Secondary Objectives

- Determine the response rate of cediranib in combination with lenalidomide in patients with iodine refractory, unresectable DTC who have evidence of disease progression within 12 months of study enrollment.

- Determine the toxicity, duration of response, progression free survival, and overall survival in patients with DTC treated with cediranib plus lenalidomide.

1.2. Phase II

1.2.1 Primary Objectives

- Determine the progression-free survival rates of single agent cediranib in patients with iodine refractory, unresectable differentiated thyroid cancer (DTC) who have evidence of disease progression within 12 months of study enrollment.

- Determine the progression-free survival rates of cediranib in combination with lenalidomide in patients with iodine refractory, unresectable DTC who have evidence of disease progression within 12 months of study enrollment.

- Compare the progression-free survival curves of single agent cediranib to combination therapy with cediranib with lenalidomide.

1.3. Secondary Objectives

- Determine response rates and duration of response, early tumor size changes, the toxicity, and overall survival in patients with DTC treated with cediranib or cediranib plus lenalidomide.

- Determine whether the presence of *B-RAF* or *K-RAS* mutations in patients with DTC predict response to cediranib or cediranib plus lenalidomide.

2. BACKGROUND

2.1. Differentiated Thyroid Cancer

The annual incidence of thyroid cancer is between 14.2 cases per 100,000 in women and 4.9 per 100,000 in men.[1] There will be an estimated 37,200 new cases of thyroid cancer (27,200 in women, and 10,000 in men) in the United States alone in 2009.[2] In 2008, thyroid cancer became the 6th most diagnosed cancer in women.[2] Although several types of cancer are derived from the thyroid gland, differentiated thyroid cancer (DTC) accounts for up to 90% of cases. DTC arises from thyroid follicular cells and comprises both papillary and follicular histologies. Papillary thyroid cancer is by far the most common subtype, accounted for 70-80% of thyroid cancer overall. The prognosis for DTC is extremely good, with overall 10-year survival rates of greater than 90%.

Total thyroidectomy is the recommended initial treatment for thyroid carcinoma. Several retrospective studies have suggested that near-total or total thyroidectomy improves disease-free survival and reduces recurrence rates.[3-5] Following surgery, radioactive iodine (^{131}I) treatment has been shown to decrease recurrence and mortality in high risk patients.[6-8] Radioactive iodine is effective because well-differentiated DTCs are able to concentrate iodine. ^{131}I emits short path-length (1-2 mm) β-radiation that is cytotoxic to thyroid cells. The success of ^{131}I ablation is dependent on the amount of residual thyroid tissue that is present after surgery (^{131}I is more effective with less tissue) and its ability to concentrate iodine in the setting of TSH stimulation.

Patients who develop recurrent disease are offered surgery if possible. For locoregional recurrences that are not surgically resectable, repeat radioactive iodine and/or external beam radiation can be considered. For metastatic disease, palliative surgery can be performed especially if the tumor involves weight-bearing bones. Other options include ^{131}I if the radioiodine scan is positive and/or external beam radiation.[6]

Post surgical radioactive iodine is not effective in patients whose tumors do not concentrate iodine. These tumors have become less differentiated and have lost the ability to express thyroid-specific markers, specifically, the sodium iodine symporter, which allows iodine into the thyroid follicle. Tumors that are not amenable to surgical resection that have lost the ability to concentrate iodine currently have no effective therapeutic options.

VEGF and thyroid cancer:
Thyroid carcinomas are characteristically vascular. Therefore, anti-angiogenic strategies have been postulated to be effective in DTCs. Preclinical and anecdotal clinical evidence has accumulated suggesting that anti-angiogenic strategies indeed have efficacy.[7, 8] Vascular endothelial growth factor (VEGF) is a key component in angiogenesis and is important in the pathogenesis of thyroid carcinomas. Viglietto *et al.* have shown that elevated VEGF expression was associated with a high tumorigenic potential in human

thyroid tumor cell lines.[12] Viglietto *et al.* also showed that the VEGF receptors, FLT-1 and flk/KDR, were expressed in endothelial cells that lined tumor-embedded microvascular vessels, suggesting that VEGF, contributes to thyroid tumor development. There is now mounting clinical evidence from Phase II trials that the inhibition of VEGF signaling has activity in thyroid cancers. Phase II studies of axitinib and motesanib diphosphate, two tyrosine kinase inhibitors with specific activity against VEGFR, showed 30% and 14% partial tumor response, respectively.[13, 14] A large number of patients also had stable disease (42% and 67%, respectively). Cediranib is a potent and selective tyrosine kinase inhibitor with activity against VEGFR1, VEGFR2, and VEGFR3. Although it has not been studied in thyroid cancer, the efficacy of axitinib and motesanib diphosphate in thyroid cancer suggests that cediranib may have anti-thyroid cancer activity.

Thalidomides and thyroid cancer:
Thalidomide was originally developed as a sedative in the 1950s, but its teratogenic effects led to its discontinued usage in that setting. Thalidomide, however, was noted to have anti-angiogenic effects. It has been shown to be an effective therapy for multiple myeloma; in addition, it is currently under evaluation for treatment of a variety of other cancers although its exact mechanism remains uncertain. Because thalidomide is not activated in rodent models, preclinical efficacy studies have not been useful. Ain and colleagues assessed thalidomide's effectiveness in patients with progressive thyroid cancer in a Phase II trial.[9] A total of 36 patients (11 PTC, 2 tall cell PTC, 4 FTC, 8 HCC, 4 insular, 7 MTC) with radioiodine-unresponsive progressive disease were recruited. Daily oral thalidomide was administered at a starting dose of 200 mg and increased over 6 weeks to 800 mg or to the maximum tolerated dose. Of 28 patients available for evaluation, 5 had partial responses with a median duration of 4 months and 9 had stable disease for a median duration of 6 months. Fatigue was the most commonly reported side effect. Serious adverse events included infection, pericardial effusion, and pulmonary embolus. A Phase II study with lenalidomide, a derivative of thalidomide with less toxicity, also showed anti-cancer activity. Data from a Phase II study of lenalidomide in patients with progressive iodine-refractory thyroid cancer has been presented.[10] A total of 25 patients were initiated on 25 mg of oral lenalidomide daily. Of 18 evaluable patients, 67% were responders (22% with partial response and 44% with stable disease.) Grade 3 toxicities, neutropenia and thrombocytopenia responded to dose reduction. The mean daily dose was 20 mg.

Patient Population:
Patients with iodine refractory DTC have few therapeutic options. Cytotoxic chemotherapy is often ineffective and the most studied agent, doxorubicin, is associated with significant toxicity.

Study Design:
This is a phase I study followed by a phase II, 2 arm, open-label, randomized trial of cediranib alone or in combination with lenalidomide.

Patients should have measurable disease (papillary, follicular, Hürthle cell type, or other

papillary/follicular variants) and evidence of disease progression (objective growth of existing tumors within the last 12 months).

Prior to the randomized phase II portion of this study, we will evaluate cediranib plus lenalidomide in a phase I trial at three dose levels of lenalidomide (10, 15, and 20 mg). Cediranib will be administered at a starting dose of 20 mg daily. Dose escalation will not exceed 30 mg cediranib with 20 mg of lenalidomide. The MTD from the Phase I was determined at cediranib 30 mg day 1-28 and lenalidomide 15 mg on day 1-21 of the 28 day cycle.
After determining the MTD, we will initiate recruitment for a Phase II trial comparing cedirinib alone to cedirinib plus lenalidomide. Subjects will be randomized in a 1:2 ratio to one of two arms. Randomized stratification will employ prior therapy with a VEGF-pathway inhibitor (yes vs. no) and performance status (0 and 1 vs. 2). Subjects in Arm A will receive cediranib alone at 30 mg daily. Subjects on Arm B will receive cediranib 30 mg daily and lenalidomide 15 mg on day 1-21 of the 28 day cycle (as determined above in the Phase I trial).

Each cycle will be 4 weeks in length. Disease re-evaluation will occur every 8 weeks using RECIST guidelines.* The primary endpoint will be progression-free survival. Patients without evidence of anti-thyroglobulin antibodies will continue to have thyroglobulin levels measured at each response assessment (usually every 8 weeks). All patients are expected to be on thyroxine suppression therapy and thyroid stimulating hormone (TSH) levels will be monitored pre-therapy and every 8 weeks.

*After 18 cycles, radiologic disease re-evaluation will occur every 16 weeks.

2.2. CTEP-Supplied Investigational Agent(s)

2.2.1. Cediranib

Cediranib is a potent inhibitor of all three vascular endothelial growth factor (VEGF) receptors (VEGFR-1, -2 and -3) at nanomolar concentrations. Inhibition of VEGF signaling leads to the inhibition of angiogenesis, lymphangiogenesis, neovascular survival and vascular permeability. Cediranib also inhibits c-Kit tyrosine kinase, which could be relevant in c-Kit-dependent tumors. Cediranib inhibited the growth of tumors in preclinical models in a dose-dependent manner. A reduction in micro-vessel density and metastasis was also observed in these preclinical models. Collectively, these changes indicate that cediranib inhibits tumor growth, metastases and vascular permeability.[11] Cediranib is in Phase III clinical development in colorectal cancer (CRC) and recurrent glioblastoma (GBM) and is being evaluated in a Phase II program against a broad range of tumors.

Mechanism of Action
Angiogenesis, the process of new blood vessel formation, is an essential step in tumor growth and metastasis. The inhibition of angiogenesis has therefore emerged as a key

strategy for the treatment of cancer. Although it is possible to disrupt blood vessel formation at several stages in the angiogenic process, VEGF and its receptor (VEGFR) provide a promising target since VEGF is known to be the most important proangiogenic factor.[12, 13] Two high-affinity receptors for VEGF with associated tyrosine kinase activity have been identified on human vascular endothelium: VEGFR-1 and VEGFR-2. VEGFR-3, a third member of the VEGFR gene family, is thought to be important for lymphangiogenesis and activated by the ligands, VEGF-C and VEGF-D. Although their relative contributions in mediating tumor progression have not been resolved, a number of studies suggest VEGFR-2 performs a predominant role.[13]

Cediranib is a potent inhibitor of all three vascular endothelial growth factor (VEGF) receptors (VEGFR-1, -2 and -3) at nanomolar concentrations. Inhibition of VEGF signaling leads to the inhibition of angiogenesis, lymphangiogenesis, neovascular survival and vascular permeability. Cediranib also inhibits c-Kit tyrosine kinase, which could be relevant in c-Kit dependent tumors.

Cediranib inhibited the growth of tumors in preclinical models in a dose-dependent manner. A reduction in micro-vessel density and metastasis was also observed in these preclinical models. Collectively, these changes indicate that cediranib inhibits tumor growth, metastases and vascular permeability.[11]

Nonclinical Specificity and Efficacy Studies

Using enzyme-linked immunoabsorbent assays or scintillation proximity based assays,[11] cediranib potently inhibited the tyrosine kinase activity associated with the VEGF receptors, VEGFR-2 (IC50 <0.001 μM), VEGFR-1 (IC50=0.005 μM) and VEGFR-3 (IC50 ≤0.003). Cediranib was also found to have activity versus additional structurally-related Class III RTKs (c-Kit, PDGFR)□□ at nanomolar concentrations, but demonstrated selectivity versus other tyrosine and serine/threonine kinases examined. The ability of cediranib to directly inhibit tumor cell growth *in vitro* was examined using a variety of histologically distinct tumor cell types. The IC50 values (mean ±SE) for the inhibition of tumor cell growth were 3.0 ±0.4 μM(SKOV-3), 3.8 ±0.5 μM (MDA-MB-231),5.8 ±0.2 μM (PC-3), 6.4±0.6 μM (Calu-6) and 7.4 ±0.7 μM (SW620).[11] These concentrations are between 7500- and 18500-fold greater than those required to inhibit VEGF-stimulated human umbilical vein endothelial cell proliferation . The data are consistent with cediranib anti-tumor activity *in vivo* being attributable to inhibition of VEGF signaling in endothelial cells, rather than a direct anti-proliferative effect on tumor cells.

Nonclinical Toxicology Studies

Single- and multiple-dose toxicology studies were conducted in rats, dogs, and monkeys (Investigator's Brochure, Cediranib (AZD2171), 2009). Cediranib has not shown mutagenic or clastogenic potential.

Hypertension after dosing with cediranib has been observed in rats, dogs, and primates. These changes were thought to be mechanistically related to VEGF. Histopathologic changes seen in rats treated with cediranib included choroid plexus vasculitis, ventricular myocarditis and coronary arteritis; these findings were consistent with systemic hypertension. Other changes were seen in the adrenal glands, pancreas, thyroid, liver and biliary system.

In primates, doses of 0.5, 1.5 and 2.5 mg/kg/day were not tolerated. Pathologic changes were observed in the choroid plexus and kidney; these changes were consistent with hypertension although a direct effect on these tissues could not be excluded. In addition, mucosal hypertrophy of the gall bladder and bile duct hyperplasia in the liver were seen. A dose of 0.2 mg/kg/day given to primates for 6 months produced minimal changes in the choroid plexus and kidney; the majority of changes showed reversibility after a 3-month off-treatment. A dose of 0.025 mg/kg/day was considered to be the no adverse effect level.

As anticipated, cediranib showed reversible effects on female fertility and significant findings on embryo-fetal development, consistent with its pharmacological activity.

Nonclinical Pharmacokinetics and Pharmacology
Bioavailability of cediranib after oral administration was high: 70% to 75% in rat and 24% to 74% in dog. Absorption was relatively slow with peak concentrations occurring 4 to 6 h after dosing. Cediranib pharmacokinetics indicate high clearance and very high volume of distribution.

Over the dose ranges examined in rat, plasma concentrations and exposure generally increased in proportion to dose; however, in monkey, plasma cediranib concentration-time profiles obtained following a single oral dose indicated that systemic exposure increased in a greater than dose-proportional manner over the dose range 0.05 to 2.5 mg/kg. On multiple dosing, there was limited accumulation (<2-fold) and no evidence of auto-induction in rat, but a slightly greater degree of accumulation (2- to 3-fold) was observed in monkey at higher dose levels.

Protein binding of cediranib (90% to 95%) was relatively high across all species examined. In the rat and monkey, cediranib was extensively metabolized and considerable amounts of metabolites plus unchanged cediranib were present in the feces (the major route of elimination) and urine.

Cediranib did not induce rat hepatic microsomal P450 activities, but caused a 40% to 60% reduction in CYP1A activity at the 5 mg/kg dose level. Cediranib showed minimal inhibitory effects on the activity of human P450 CYP2D6 and CYP3A4 *in vitro*; the IC_{50} values were far in excess of clinically relevant concentrations.

Clinical Experience
Cediranib has been in evaluated in a number of clinic trials. Phase I studies with cediranib were designed primarily to identify the safety, tolerability, and PK profiles of the drug rather

than to determine efficacy; however, encouraging evidence of biological and anti-tumour activity has also been seen in these studies. In Phase I studies, cediranib has shown single agent activity in a wide variety of tumors including prostate, renal, colorectal, lung, liver, breast, skin/soft tissue, stomach, head and neck, ovarian, biliary duct, thyroid, thymus, pancreatic tumors, acute myeloid leukemia.[16-20] A number of Phase II/III studies have been completed or are underway.

Phase I experience. Several dose escalation and pharmacokinetic studies have assessed the MTD for cedirinib. The MTD is reported between 20 mg and 45 mg daily, depending on the study.

In one study, 83 patients with advanced solid tumors received cedirinib.[18] After a single dose, maximum plasma (peak) drug concentration after a single-dose administration (Cmax) was achieved 1 to 8 hours postdosing with a mean half-life of 22 hours. Cedirinib doses of less than 45 mg/d were generally well-tolerated. The most frequently dose related adverse events were fatigue, diarrhea, dysphonia and hypertension. Preliminary results showed two confirmed partial responses and 22 patients with stable disease.

In a second study in Japanese patients with advanced solid tumors, cediranib 30 mg/day was considered the MTD since 50% of evaluable patients received 45 mg/day experienced dose limiting toxicities (proteinuria, diarrhea, thrombocytopenia).[14] Of 32 evaluable patients, two had partial responses and 24 had stable disease greater than 8 weeks.

Cediranib has been evaluated in Phase I studies of particular tumors. In a study of patients with hormone refractory prostate cancer, the MTD was found to be 20 mg/day.[15] One objective response and several PSA declines were noted after the discontinuation of therapy. A Phase I study of cediranib in patients with acute myeloid leukemia reported that cediranib was generally well-tolerated at doses less than 30 mg/day.[16] Six of 35 patients had an objective response. Cediranib at two doses (30 mg and 45 mg) was evaluated in combination with cisplatin and gemcitabine in a Phase I study of patients with advanced non-small cell lung cancer.[23] At 45 mg/day, toxicity was increased compared to the 30 mg/day dose. Confirmed responses were observed in four of 12 evaluable patients.

Cediranib is being evaluated in a number of other Phase I studies. Cedinanib in combination with gefitinib is under evaluation in patients with advanced solid tumors to determine the MTD of combination therapy. It is also being evaluated in patients with advanced solid tumors in combination with different standard chemotherapy regimens. Another study is looking at cediranib in combination with AZD0530.

Phase II and III Experience

To determine the optimal timing of cediranib administration, 34 patients with advanced solid tumors were randomized to receive cediranib 45 mg in a fed or fasted

state.[17] Both the AUC and C_{max} of cediranib were lower in the presence of food by a mean of 24% and 33% respectively. Therefore, it is recommended that cediranib be administered at least 1 hour before or 2 hours after food.

Because hypertension is a main adverse effect of cediranib, a Phase II study investigated hypertension management strategies in 125 patients. Cediranib 30 mg or 45 mg daily was administered with or without anti-hypertension prophylaxis. The overall response rate was similar across the treatment groups with evidence of anti-tumor activity apparent at both 30 mg and 45 mg dose levels, and irrespective of whether the patient was receiving prophylaxis.

A Phase II randomized, double-blind, parallel-group study comparing the efficacy of cediranib to placebo in patients with renal cell cancer showed promising anticancer activity.[18] At 12 weeks, 20.8% of the 53 patients randomized to cediranib had a partial response compared with none on placebo. The disease control rate (responders + SD) at this stage was 81% in the cediranib arm versus 22% in the placebo arm. Overall, for patients originally randomized to cediranib: 34% had partial response, 47.2% had stable disease, 17% had disease progression, and 1 was not evaluable. Some 78% of the 18 patients with partial response had responses lasting ≥10 months, and 61% had responses lasting for ≥1 year.

A total of 36 patients were enrolled in a Phase II, open-labeled study of cediranib 45 mg in patients with metastatic gastrointestinal stromal tumors (GIST) or soft tissue sarcomas (STS). Some 62.5% of GIST patients had stable disease. In the 6 alveolar soft part sarcoma patients, 3 had partial response and 3 had stable disease.

Efficacy of cediranib has also been evaluated in 8 Phase II NCI-sponsored monotherapy studies. Anti-cancer activity has been observed in some patients with a wide range of cancer types including recurrent glioblastoma, recurrent epithelial ovarian cancer, recurrent or persistent ovarian, peritoneal or fallopian tube cancer, docetaxel-resistant, castrate-resistant prostate cancer, malignant pleural mesothelioma, and progressive stage IV breast cancer. In some trials, the initial dose of cediranib 45 mg daily was decreased to 30 mg daily due to toxicity.

Cediranib is under evaluation in both Phase II/III studies and Phase III studies. The efficacy of cediranib in combination with FOLFOX versus bevacizumab in combination with FOLFOX in patients with metastatic colorectal cancer is under evaluation (HORIZON III). Following the Phase II portion, patients in the Phase III portion received the selected dose of cediranib 20 mg. In another Phase III study (HORIZON II), patients with previously untreated metastatic colorectal cancer are being randomized to receive cediranib + FOLFOX or XELOX with placebo + FOLFOX or XELOX. Cediranib 20 mg was the dose selected for the Phase III portion in this study as well.

Another Phase III study is looking at the efficacy of cediranib monotherapy, cediranib in combination with lomustine, or lomustine with placebo in patients with recurrent glioblastoma. A Phase II/III study of cediranib in combination with standard paclitaxel/carboplatin chemotherapy in patients with Stage IIIB or IV NSCLC was halted following a recommendation by the Data Safety Monitoring Committee prior to the Phase III portion as discussed below.

Safety Profile

Commonly reported adverse events (AEs) include fatigue, hypertension, diarrhea, nausea, vomiting, and anorexia. (Investigator's Brochure, Cediranib (AZD2171), 2009) Although cediranib 45 mg daily was determined as the MTD in early studies, later studies have found that 30 mg or 20 mg daily are better tolerated.[17, 19, 20]

Hypertension has emerged as an important AE and serious adverse event (SAE) with cediranib therapy. It is the major cardiovascular adverse event associated with cediranib therapy. Hypertension is an expected AE with agents that inhibit VEGF signaling. In cediranib studies, increases in blood pressure have been observed, including CTC Grade 4 hypertension and end-organ damage related to hypertension, such as cerebrovascular events. A Phase II study with looked at cediranib 30 mg or 45 mg +/- hypertension prophylaxis found that no single treatment strategy emerged as clearly better managing high blood pressure. Overall, treatment of hypertension in a stepwise fashion with rigorous monitoring of blood pressure appears to be effective in managing cediranib-induced hypertension.

Left ventricular dysfunction, in some cases leading to cardiac failure, has been observed in patients receiving cediranib with risk factors for left ventricular dysfunction (including previous or concomitant anthracycline treatment). To investigate left ventricular dysfunction, two Phase II studies of cediranib included serial echocardiogram/MUGA studies. (Investigator's Brochure, Cediranib (AZD2171), 2009) The changes in LVEF observed in these two studies appeared to be mild and occurred more frequently in patients who had received prior anthracyclines. Based on these findings, it was not considered necessary to implement additional monitoring of LVEF dysfunction in studies with cediranib.

A number of events of bleeding and hemorrhage have occurred. Some events of hemorrhage were fatal but causality could not be unequivocally assigned to cediranib. Gastrointestinal perforation, sometimes associated with fistula formation, has been observed in patients receiving cediranib. Some events of gastrointestinal perforation have been fatal but causality could not be unequivocally assigned to cediranib.

Fatigue, hand and foot syndrome, diarrhea, headache, nausea, vomiting, anorexia and weight loss are commonly occurring AEs in cediranib studies. Dehydration has been observed in clinical studies as a consequence of cediranib-related or chemotherapy-related diarrhea, vomiting, anorexia, or reduced oral intake.

Hoarseness (dysphonia) has been reported as common and dose-related.

Muscle weakness, proteinuria, dry mouth and oral mucosal inflammation have been observed in cediranib studies.

Reversible posterior leukoencephalopathy syndrome (RPLS) has been observed in patients receiving cediranib in clinical studies. RPLS is a rare syndrome affecting vascular endothelial cells in the brain that may lead to capillary leak and edema. It has been associated with a number of conditions, including renal failure, hypertension, fluid retention, and the use of cytotoxic or immunosuppressive drugs. RPLS also been reported in association with the use of VEGF inhibitors including bevacizumab, sunitinib, and sorafenib.

Increases in transaminases, which are sometimes associated with increases in total bilirubin, have been seen. Thrombocytopenia, of CTC Grade 1 or 2 in the majority of cases, has been seen with monotherapy and combination cediranib treatment. In addition, cediranib has been associated with increases in TSH which may be associated with clinical hypothyroidism.

A Phase II/II study of cediranib in combination with standard paclitaxel/carboplatin chemotherapy in patients with Stage IIIB or IV NSCLC was halted following a recommendation by the Data Safety Monitoring Committee prior to the Phase III portion. There was a significantly higher response rate seen in cediranib patients.[19] However, although the overall number of deaths in each arm was similar, there appeared to be an imbalance in the number of fatal SAEs that were reported, with more patients on cediranib having been reported as experiencing fatal SAEs than on placebo (11 patients vs 1 patient). While some of these reported fatal SAEs appeared to be drug-related, others appeared to be a consequence of disease progression.

Clinical Pharmacokinetics, Pharmacology, and Pharmacodynamics
Cediranib has a PK profile that supports once-daily oral dosing. Although absolute bioavailability has not been determined, cediranib appears well absorbed with apparently linear PK for single and multiple doses ranging from 0.5 to 60 mg. After multiple once-daily oral doses, steady-state plasma concentrations are attained after approximately 7 days. There is limited accumulation, consistent with the $t_{½\lambda z}$ observed following single doses, and steady-state plasma concentrations are predicted by the single dose PK, indicating no time-dependent changes in PK.

In vitro protein binding studies showed that cediranib binds to human plasma proteins (95.4%), including serum albumin and α1-acid glycoprotein, and was independent of concentration over the range 0.06 to 22 μM (30 to 1000 ng/mL)

Cediranib showed minimal inhibitory effects on the activity of human P450 CYP2D6 and CYP3A4 (testosterone and midazolam) *in vitro*; the IC_{50} values were far in excess of clinically relevant concentrations. Cediranib had no inhibitory effect on the activity

of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1. Co-administration of known inhibitors or inducers of hepatic CYP enzymes would not be expected to have significant effects on the clearance of cediranib. However, since potent inhibitors or inducers of CYP enzymes can also affect drug disposition by interaction with transporter proteins and phase II metabolism, two clinical studies are currently ongoing to investigate the PK of cediranib when co-administered with a potent inhibitor ketoconazole and the potent inducer rifampin.

Clearance of cediranib is moderate, approximating 64% of nominal hepatic plasma flow. Following a single dose of ^{14}C-labelled cediranib, the ratios of whole blood to plasma radioactivity suggest that the radioactive components in whole blood are confined to plasma. Concentrations of total radioactive material in plasma were also higher than those measured for cediranib itself, particularly at later times, demonstrating the presence of circulating metabolites. In patients able to provide samples during the entire collection period, the majority of the radioactivity was eliminated in feces. The large number of metabolites detected in the feces and urine show that cediranib is cleared extensively by metabolism. Less than 1% of the administered dose of cediranib was excreted unchanged in the urine.

Cediranib has been administered in combination with a number of chemotherapy regimens. There was little or no apparent effect (<1.5-fold change) on exposure to paclitaxel, carboplatin, oxaliplatin, 5-FU (given as mFOLFOX6), docetaxel, pemetrexed, irinotecan +SN38, gefitinib, gemcitabine or fulvestrant, when given in the presence of cediranib steady state plasma concentrations. Steady-state PK parameters of cediranib in combination with the chemotherapy agents are comparable with those seen previously with cediranib monotherapy.

Data obtained following a single 45-mg cediranib dose in the presence and absence of a standard high-fat meal, showed that food decreases the C_{max} by 33% and AUC by 24%. Cediranib should be administered at least 1 h before or 2 h after food.

Initial pharmacodynamic assessments indicated potential biological activity of cediranib in clinical studies. Reductions in blood flow in hepatic metastases have been detected by DCE-MRI in patients with solid tumors and metastatic liver disease, and initial biomarker assessments have shown increases in serum VEGF, bFGF, and PLGF and reductions in sVEGFR-2 levels. Decreases in sVEGFR-2 levels may be a surrogate for decreased angiogenesis and changes in VEGF could potentially indicate acute vascular effects. The general trends for soluble biomarkers of angiogenesis (increases in serum VEGF and decreases in sVEGFR-2) were also observed in a Phase II study in patients with renal cell carcinoma.

<u>Proposed Dose and Schedule for Phase 2 Clinical Trials</u>
Based on the totality of the safety, tolerability, efficacy, PK, and pharmacodynamic data that are currently available from both AZ-sponsored and collaborative group studies with cediranib, at daily dose of cediranib 30 mg is the recommended dose for

monotherapy. Cediranib 20 mg is the recommended dose in combination with chemotherapy agents.

2.2.2. Lenalidomide

Lenalidomide is the lead compound in a new class of immunomodulatory drugs known as the IMiDs®. The IMiDs are characterized by a wide range of effects, including the enhancement of T cells and natural killer (NK) cell activity, the inhibition of angiogenesis, the inhibition of tumor cell proliferation, the modulation of stem cell differentiation, and inhibition of inflammation and hyperalgesia. On the basis of this varied pharmacological profile, lenalidomide is under investigation as a treatment for a range of oncologic and non-oncologic indications.

On 27 December 2005, the United States (US) Food and Drug Administration (FDA) approved lenalidomide for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Lenalidomide also received approval for MDS from Argentina (on 15 February 2008) and conditional approval from Canada (on 17 January 2008). Subsequently, the FDA (on 29 June 2006) and the European Commission (on 14 June 2007) approved lenalidomide in combination with dexamethasone for the treatment of patients with multiple myeloma (MM) who received at least 1 prior therapy.

Mechanism of Action
Although lenalidomide shows immunomodulatory activity both *in vitro* and *in vivo*, its exact mechanism is uncertain.

Nonclinical Specificity and Efficacy Studies
The pharmacologic activity of lenalidomide has been characterized in an extensive series of nonclinical studies. In several *in vitro* assays, lenalidomide was shown to inhibit monocyte production of various proinflammatory cytokines; inhibit expression of cyclooxygenase-2 (COX-2) and release of prostaglandin E_2 (PGE_2); and elevate interleukin (IL)-10 production. Both *in vitro* and *in vivo*, lenalidomide increased the proliferation and production of IL-2 and interferon gamma (IFN-γ) by T cells and enhanced T cell and natural killer (NK) cell-mediated killing of tumors. The proliferation of various hematopoietic tumor cell lines was also inhibited by lenalidomide *in vitro*. *In vivo* tumor growth models have demonstrated that lenalidomide inhibits growth of MM cells. In a model of hematopoietic progenitor differentiation, lenalidomide increased expression of fetal hemoglobin in CD34+ stem cells. Lenalidomide also suppressed edema and mechanical and thermal hyperalgesia in a model of inflammatory pain.

The antiangiogenic activity of lenalidomide, demonstrated using human endothelial cells and arterial explant models *in vitro*, has also been shown to result in reduced growth of solid tumors. As a single agent, lenalidomide has demonstrated some activity toward a prostate tumor xenograft and had an additive effect in combination with docetaxel (Investigator's

Brochure, Lenalidomide, 2008). Lenalidomide, in combination with sorafenib, inhibited angiogenesis *in vitro* and reduced tumor growth in an ocular melanoma xenograft model.[20] Lenalidomide, in combination with sunitinib and cyclophosphamide, also inhibited angiogenesis *in vitro* and effectively blocked tumor growth in ocular melanoma, colon cancer, pancreatic cancer, and cutaneous melanoma models.[21]

Nonclinical Toxicology Studies

Lenalidomide has been evaluated in rats, rabbits and monkeys (Investigator's Brochure, Lenalidomide, 2008). Lenalidomide has a low potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg in rodents. Chronic administration of lenalidomide to rats resulted in kidney pelvis mineralization, most notably in females. The no observed adverse effect level (NOAEL) in rats is considered to be < 75 mg/kg.

In monkeys, repeated oral administration resulted in a dose-dependent decrease in neutrophil count, an effect that is related to the pharmacodynamic effects of the drug. Repeated oral administration of 4 and 6 mg/kg to monkeys for up to 52 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ hemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Monkeys dosed with 1 and 2 mg/kg/day exhibited changes in bone marrow cellularity, a slight decrease in the myeloid: erythroid cell ratio, and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day. The NOAEL in monkeys was identified as 1 mg/kg/day.

Studies in rats administered up to 500 mg/kg/day of lenalidomide indicate it has no effects on male or female reproductive performance or fertility or prenatal and postnatal reproductive toxicity. Lenalidomide is not genotoxic.

An embryofetal development study was conducted in monkeys administered lenalidomide at doses up to 4 mg/kg/day. Findings from this ongoing study indicate that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy.

In rats, lenalidomide was not teratogenic at doses up to 500 mg/kg/day. In rabbits administered 3, 10, and 20 mg/kg/day orally, developmental toxicity at the 10 and 20 mg/kg/day dose levels was characterized by slightly reduced fetal body weights, increased incidences of postimplantation loss (early and late resorptions and intrauterine deaths), and gross external findings in the fetuses associated with morbidity and pharmacotoxic effects of lenalidomide (purple discoloration of the skin on the entire body). In rabbits, the maternal and developmental NOAELs for lenalidomide were 3 mg/kg/day.

Nonclinical Pharmacokinetics and Pharmacology

Pharmacokinetics of lenalidomide was evaluated in male beagle dogs, male cynomolgus monkeys, and male Sprague-Dawley rats (Investigator's Brochure, Lenalidomide, 2008). Following oral administration, lenalidomide was absorbed rapidly, with t_{max} achieved at 0.5, 1.3, and 1.5 hours postdose in rats, dogs, and monkeys, respectively. High plasma

concentrations were achieved, with good oral bioavailability in all the species examined (≥ 50%).

Protein binding was low in all species, including humans (19% to 29%). Lenalidomide is not a substrate of human cytochrome P450 enzymes. Lenalidomide was excreted largely as unchanged drug (approximately 55% of the dose) in both rats and monkeys. Hydrolysis of the glutarimide ring of lenalidomide was another important clearance mechanism in animal models. In both rats and monkeys, the major route of elimination of radioactivity following intravenous (IV) administration was renal. Excretion of radioactivity following oral administration to rats and monkeys was also similar; radioactivity was eliminated in almost equal proportions in the urine and feces for both species.

Clinical Experience

Phase I Experience.

Several Phase I studies in healthy volunteers have investigated the single-dose safety, tolerability, and pharmacokinetics of lenalidomide. Lenalidomide had an acceptable safety profile in healthy male subjects at doses of 5 to 400 mg. The most frequently reported adverse events were rhinitis, headache, pruritus, rash, and cough. Analysis of CD4 blood counts showed a significant decrease from baseline CD4 levels at 24 hours postdose for the 5-, 200-, and 400-mg lenalidomide dose levels, each administered in the fasted state, with the greatest decrease being observed at the 200-mg dose level.

Two phase I/II, single-center, open-label, and dose-escalation studies were performed to determine the MTD and to evaluate the safety and efficacy of lenalidomide in subjects with relapsed or refractory multiple myeloma (MM). In the Phase I portion, subjects received lenalidomide at a dose of 5, 10, 25, or 50 mg/day for the first 28 days under fasting conditions. Subjects who tolerated the therapy were allowed to continue on treatment after Day 28 until disease progression occurred. The MTD of lenalidomide was determined to be 25 mg/day.

The safety of lenalidomide in patients with solid tumors refractory to conventional treatment has been evaluated in several Phase I studies. Tumor types have included metastatic melanoma, pancreatic cancer, NSCLC, lymphoma, and high grade gliomas. The majority (85.6%) of subjects in the pooled Phase I studies received doses between 25 -150 mg. The most frequently reported adverse events in patients who received these doses were fatigue, nausea, and constipation. Other clinically relevant events occurring in fewer than 20% of subjects who received lenalidomide at any dose included anemia, thrombocytopenia, DVT, thrombosis and thrombophlebitis.

Lenalidomide has also been evaluated in a Phase I study in combination with docetaxel in patients with advanced solid tumors. Diarrhea, fatigue, and nausea were the most frequently reported adverse events. Other clinically relevant events occurring in fewer than 20% of subjects included DVT, febrile neutropenia, and jugular vein thrombosis. The recommended Phase II dosing was doxetaxel 75 mg/m2 on Day 1, lenalidomide 25 mg on days 1-14, and pegfilgrastim 6 mg on day 2, given every three weeks.[22]

Phase II and III Experience

The safety and efficacy of lenalidomide has been explored in a number of oncologic indications.

Thirteen studies of lenalidomide in the treatment of MM have been undertaken to evaluate lenalidomide as monotherapy, in combination with high-dose dexamethasone therapy, and as part of a lenalidomide, doxorubicin, vincristine, and dexamethasone (DVd) regimen. As a result, lenalidomide has been shown to be an effective treatment for MM with a favorable safety profile, and has been approved by a number of regulatory agencies for use in combination with dexamethasone for the treatment of MM in patients who have had at least 1 prior therapy. Cytopenias are the primary adverse events associated with the administration of lenalidomide, particularly in subjects with compromised bone marrow. These, however, are manageable with dose interruptions and reductions.

Three multicenter, single-arm, open-label studies of lenalidomide in subjects with red blood cell transfusion-dependent anemia and Low- or Intermediate-1-risk MDS are ongoing: one phase I/II study in subjects with or without a del 5 (q31-33) cytogenic abnormality, one phase 2 study in subjects without a del 5 (q31-33), and one phase 2 study in subjects with a del 5 (q31-33). In the del 5 (q31-33) population, hematological improvement, manifested clinically as transfusion independence, is supported objectively by sustained elevations and improvements in hemoglobin values, cytogenetic responses, and bone marrow. More recently, a phase III, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of lenalidomide versus placebo has been initiated in red blood cell (RBC) transfusion—dependent subjects with Low- or Intermediate-1-risk MDS associated with a del 5 (q31-33).

Several studies of lenalidomide in the treatment of solid tumors have been completed, and data for others are currently being analyzed.

Lenalidomide has been evaluated in a Phase II study of patients with progressive, iodine-resistant thyroid cancer.[10] Some 25 patients received lenalidomide 25 mg daily. Of 18 evaluable patients, 22% had a partial response and 44% had stable disease. Main toxicities were hematological and responded to dose reduction. The mean daily dosage was 20 mg.

A phase II open-label study to evaluated the safety and efficacy of lenalidomide in subjects with androgen independent prostate cancer. These subjects had increasing serum prostate-specific antigen (PSA) levels but did not have detectable metastatic disease. The study was terminated for lack of efficacy. Two Phase I/II studies of lenalidomide in patients with advanced ovarian and primary peritoneal carcinoma were terminated prematurely. The first was to evaluate lenalidomide in combination with liposomal doxorubicin. A Grade 1 adverse event of left ventricular systolic dysfunction was reported in Subject 1. The event was suspected as study drug related and resulted in study discontinuation prior to establishing the MTD. A second study intended to determine the MTD of oral lenalidomide given on Days 1 to 14 and topotecan given on Days 1 to 5 every 21 days as combination therapy for subjects

with advanced ovarian or primary peritoneal carcinoma. The study was prematurely terminated due to toxicity. Neutropenia, thrombocytopenia and anemia were the most commonly experienced treatment –related adverse events. One subject experienced a pulmonary embolism considered to be related to study drug.

Lenalidomide has been evaluated in a Phase II/III and Phase III trial in patients with refractory metastatic melanoma. A phase II/III, controlled, randomized, parallel-group study compared the efficacy and safety of 2 dose regimens (5 mg daily for 28 days or 25 mg daily for 21 days, followed by a 7-day rest). No significant differences in response rates were observed between the two doses. A phase III, multicenter, controlled, randomized, placebo-controlled, parallel group study evaluated the efficacy and safety of lenalidomide in subjects with previously treated metastatic malignant melanoma. Subjects were randomized to receive either 25 mg/day of lenalidomide or placebo for 21 days of a 28-day cycle. There were no significant differences between lenalidomide and placebo in overall survival, time to progression, or RECIST criteria. In contrast with those seen in the MDS studies, the incidences of neutropenia and thrombocytopenia were low ($\leq 8\%$ and $\leq 3\%$, respectively) among subjects treated with lenalidomide in these melanoma studies.

Safety Profile

Data on the safety of lenalidomide had developed from over 6000 subjects from clinical trials (Investigator's Brochure, Lenalidomide, 2008).

Lenalidomide is associated with anemia, neutropenia, febrile neutropenia, thrombocytopenia, and pancytopenia. Grade 3/4 neutropenia and thrombocytopenia are the most common, dose limiting adverse events associated with the administration of lenalidomide. The adverse event profile of lenalidomide, particularly with regard to cytopenias, is milder in patients with MM, malignant melanoma, solid tumors or gliomas, CRPS, or Crohn's disease than that in patients with MDS, likely reflecting the underlying bone marrow disease of the MDS patients.

Lenalidomide, in combination with dexamethasone, has been associated with an increased incidence in thrombotic or thromboembolic events, including deep vein thrombosis (DVT), pulmonary embolism, thrombosis, and thromboembolism, particularly among MM patients receiving concomitant therapy with an erythropoietic agent. DVT has been reported with both indications but is more frequent in MM than in MDS.

Constipation, diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal adverse events during treatment with lenalidomide. Occasional treatment-emergent adverse events like atrial fibrillation, myocardial infarction, and congestive heart failure have been reported with the use of lenalidomide from clinical studies. Treatment-emergent adverse events of infections specifically pneumonia are commonly seen with lenalidomide. The rare treatment-emergent adverse event of rhabdomyolysis has been observed with lenalidomide.

Rare treatment-emergent adverse events of angioedema and serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with lenalidomide during commercial use. These events have the potential to be fatal. Permanent discontinuation of lenalidomide should be considered if skin rash ≥Grade 2 is exfoliative or bullous or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected.

Considering an unclear, temporal relationship of angioedema to lenalidomide, clinicians should exercise caution when prescribing lenalidomide for patients who have had a history of hypersensitivity adverse reactions, specifically to thalidomide. Clearly, once angioedema has been identified, the risks and benefits of lenalidomide therapy should be considered. Review of current postmarketing data, which consists of thousands of patient exposure, did not identify any additional significant safety signal.

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.

Clinical Pharmacokinetics, Pharmacology, and Pharmacodynamics

The clinical pharmacology experience with lenalidomide includes 9 completed studies (8 in healthy subjects and 1 in subjects with renal impairment); 2 ongoing studies in healthy subjects; and 3 completed pharmacokinetic reports (2 in subjects with MM and 1 in subject with MDS).

Single doses of lenalidomide over the dose range of 5 to 400 mg and multiple doses of 200 mg/day (administered as 100 mg twice daily) had a favorable safety profile in healthy subjects. No clinically significant changes in ECGs, blood pressure, or pulse rate were observed.

In healthy subjects, lenalidomide was rapidly absorbed following single- and multiple-dose oral administration, with the maximum concentration (C_{max}) occurring between 0.5 and 1.5 hours postdose. The C_{max} and area under the concentration-time curve (AUC) values increased proportionally from 5 to 400 mg/day in single-dose studies. Steady-state levels were observed within 4 days of multiple dosing. There was no accumulation of drug with multiple dosing. Coadministration with food delayed absorption somewhat, but did not alter the extent of absorption.

Approximately, 65% to 85% of lenalidomide was eliminated unchanged through urinary excretion. The mean renal clearance of lenalidomide was approximately 180 to 220 mL/min across all doses, which exceeded the glomerular filtration rate, and therefore is at least partially active. The mean total clearance of lenalidomide was approximately 300 mL/min, and it was independent of time and dose. The mean half-life of elimination ($t_{1/2}$) was approximately 3 to 4 hours on all study days at the clinically relevant doses (5 to 50 mg/day).

Following a single 25-mg dose of of [^{14}C]-lenalidomide as an oral suspension, total recovery of urinary radioactivity indicated that approximately 90% of the administered dose was absorbed systemically. The mean AUC_{∞} ratio of unchanged lenalidomide to the radioactivity in plasma was about 92%, suggesting that the parent compound was the primary radioactive component circulating in plasma. The total recovery of the radioactivity over 10 days averaged approximately 94% of the administered dose, with approximately 90% in urine, 4% in feces, and 0.006% in semen. Two identified metabolites are hydroxy-lenalidomide (pharmacological activity unknown) and N-acetyl-lenalidomide (CC-15656; pharmacologically inactive), with either being less than 5% of the parent in plasma and urine.

No pharmacokinetic or pharmacodynamic interactions were observed between lenalidomide and warfarin; therefore, lenalidomide and warfarin may be co-administered. The effects of lenalidomide on digoxin pharmacokinetics (if any) are small, but a drug interaction cannot be excluded based on the available data.

Proposed Dose and Schedule for Phase 2 Clinical Trials

Lenalidomide doses between 5 mg and 25 mg per day have commonly been used in clinical trials. Because the optimal dose of lenalidomide when given in combination with cediranib is unknown, we will perform a Phase I escalation study. Because lenalidomide 20 mg daily was the mean tolerated dose in the Phase II study of single agent lenalidomide in thyroid cancer,[10] we will start our dose escalation of lenalidomide at 15 mg on 21 days of a 28 day cycle and designate 20 mg daily as the maximal possible dose.

2.3. Rationale

Patients with DTC have few therapeutic options once surgery and RAI have proven ineffective. There are currently no widely accepted standards of care for patients in this setting. Doxorubicin is approved for patients with iodine-refractory thyroid cancer, but response rates are poor and short-lived. There is now mounting clinical data that inhibition of VEGF stimulated angiogenesis has anti-cancer activity. Although cediranib has not been evaluated in thyroid cancer, clinical trials with other VEGFR inhibitors have shown promising results. Likewise, clinical trials with thalidomide and its derivative lenalidomide also show anti-cancer activity. The rationale for combination therapy is to simultaneously target different aberrant pathways implicated in thyroid cancer. We hypothesize that this will limit resistance as seen in single agent therapy and improve response rates.

2.4. Correlative Studies Background

2.4.1. MAPK pathway

RET/PTC rearrangements and *B-RAF* mutations are the most commonly reported molecular aberrations reported in papillary thyroid cancer. *B-RAF* mutations have

been associated with more aggressive iodine-resistant cancers. Additionally, *RAS* mutations have commonly been document in follicular thyroid cancers. When available, patients enrolled in the phase II study will have archival tumor tissue analyzed for *B-RAF* and *K-RAS* mutations. Testing for these mutations will be done at the University of Chicago.

2.4.2. Plasma

TSH and thyroglobulin measurements will be performed at the respective institution of the enrollee. TSH can stimulate thyroid cancer growth. Participants will have TSH measured pretherapy and every 8 weeks to assess for adequate TSH suppression. Thyroglobulin serves as a tumor marker in thyroid cancer. It is not always reliable because some patients have anti-thyroglobulin antibodies that falsely alter the thyroglobulin measurement and because some advance cancers lose the ability to make thyroglobulin effectively. However, in patients with cancers that make thyroglobulin, this protein can serve as a useful surrogate of targeted agent activity. Patients who do not have anti-thyroglobulin antibodies will have thyroglobulin measurements pretherapy and at 8 week intervals.

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Patients must have histologically or cytologically confirmed papillary, follicular, papillary/follicular variant or Hürthle cell carcinoma. Patients must be felt to be poor candidates for or refractory to further surgery or radioactive I-131 therapy. I-131 therapy must have been completed at least 4 weeks prior to enrollment. All patients are expected to be on thyroxine suppression therapy.

3.1.2. Patients must have radiographically measurable disease. Radiographically measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan. Lesions in previously irradiated anatomic areas (external beam radiation) cannot be considered target lesions unless there has been documented growth of those lesions after radiotherapy.

3.1.3. Patients must have evidence of disease progression (20% objective growth of existing tumors by RECIST criteria) within the last 12 months.

3.1.4. In the Phase I portion, there is no limit on prior systemic therapies (cytotoxic or targeted therapies). However, patients who have discontinued previous VEGF inhibitors secondary to adverse events are not eligible. In the Phase 2 portion,

patients cannot have received more than 1 prior chemotherapy (cytotoxic or targeted) regimen. Prior VEGF-pathway inhibitors or B-RAF inhibitors are permissible.

3.1.5. Although there are data for lenalidomide in pediatric populations,23 no dosing or adverse event data is currently available on the use of cediranib or cediranib with lenalidomide in patients <18 years of age. Therefore, children are excluded from this study but will be eligible for future pediatric phase II combination trials.

3.1.6. Life expectancy of greater than 12 weeks.

3.1.7. ECOG performance status 0-2 (Karnofsky >60%; see Appendix A).

3.1.8. Patients must have normal organ and marrow function as defined below:

X	leukocytes	>3,000/mcL
X	absolute neutrophil count	>1,500/mcL
X	platelets	>100,000/mcL
X	hemoglobin	>9 g/dL
X	serum calcium	<12.0 mg/dL
X	total serum bilirubin	below or equal to upper limit of institutional normal**
X	AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
X	creatinine	below or equal to upper limits of institutional limits
	OR	
X	creatinine clearance	>50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

** Patients with hyperbilirubinemia due to Gilbert's syndrome may enroll in the trial.

3.1.9. <u>Patients must have QTc < 480 msec.</u>

3.1.10. The following groups of patients are eligible provided they have New York Heart Association Class II (NYHA; see Appendix G) cardiac function on baseline ECHO/MUGA:

* those with a history of Class II heart failure who are asymptomatic on treatment
* those with prior anthracycline exposure
* those who have received central thoracic radiation that included the heart in the radiotherapy port.

3.1.11. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix H: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix I: Education and Counseling Guidance Document.

† A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

3.1.12. Females of childbearing potential (FCBP)† who receive cediranib alone must also have a negative initial and ongoing pregnancy tests as described above in 3.1.11. FCBP who receive cediranib alone must also commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking cediranib. Men on cediranib alone must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients receiving cediranib alone must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

3.1.13. Ability to understand and the willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. At least 4 weeks must have elapsed since any major surgery. Patients with prior use of thalidomide or lenalidomide are excluded.

3.2.2. Patients may not be receiving any other investigational agents.

3.2.3. Patients with known brain metastases should be excluded because of their poor prognosis and because they often develop progressive neurologic

dysfunction that would confound the evaluation of neurologic and other adverse events. N.B.: Patients with brain metastases with stable neurologic status following local therapy (surgery or radiation) for at least 8 weeks from definitive therapy and without neurologic dysfunction that would confound the evaluation of neurologic and other adverse events are eligible for participation.

3.2.4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to cediranib or lenalidomide or other agents used in the study.

3.2.5. Patients with poorly controlled hypertension (systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher) are ineligible.

3.2.6. Patients with 1+ proteinuria or greater on urinalysis should collect a 24 hour urine collection. Patients with greater then 1.5 gram protein/ 24 hours are excluded.

3.2.7. Because lenalidomide may increase the risk of DVT or PE, patients must stop Epogen at least 4 weeks prior to enrollment.

3.2.8. Patients with any condition (e.g., gastrointestinal tract disease resulting in malabsorption, prior surgical procedures affecting absorption, or active peptic ulcer disease) that impairs their ability to absorb cediranib tablets or lenalidomide capsules are excluded. However, for patients who are unable to swallow cediranib tablets, cediranib tablets may be administered as a dispersion in water (ie, either drinking water, sterile water [for injection] or purified water). Cediranib can be administered via nasogastric tube or gastostomy tube. See section 5.1 for recommended procedure. For patients unable to swallow lenalidomide whole, lenalidomide can be administered via gastrostomy feeding tube following the instructions in Appendix M.

3.2.9. Patients with any of the following conditions are excluded:

- Serious or non-healing wound, ulcer, or bone fracture.
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment.
- Any history of cerebrovascular accident (CVA) or transient ischemic attack within 12 months prior to study entry.
- History of myocardial infarction, cardiac arrhythmia, stable/unstable angina, symptomatic congestive heart failure, or coronary/peripheral artery bypass graft or stenting within 12 months prior to study entry.
- History of pulmonary embolism within the past 12 months.
- Class III or IV heart failure as defined by the NYHA functional classification system (see Appendix G).

3.2.10. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infections or psychiatric illness/social situations that would limit compliance with study requirements are ineligible.

3.2.11. Pregnant women are excluded from this study because cediranib and lenalidomide are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cediranib or lenalidomide, breastfeeding should be discontinued if the mother is treated with cediranib with or without lenalidomide.

3.2.12. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cediranib or cediranib with lenalidomide. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3. Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial. Below is an estimate of expected accrual targets for this trial.

3.4. Accrual Targets

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	8	+	8	=	16
Not Hispanic or Latino	47	+	47	=	94
Ethnic Category: Total of all subjects	55	+	55	=	110
Racial Category					
American Indian or Alaskan Native	2	+	2	=	4
Asian	2	+	2	=	4
Black or African American	7	+	7	=	14
Native Hawaiian or other Pacific Islander	2	+	2	=	4
White	42	+	42	=	84
Racial Category: Total of all subjects	55	+	55	=	110

4. REGISTRATION PROCEDURES

4.1. General Guidelines

Eligible patients will be entered on study centrally at the University of Chicago by the Study Registrar. All sites should call the Study Registrar at **773-834-3095** or **PhaseIICRA@medicine.bsd.uchicago.edu**, to verify agent availability. The UC

Phase II Consortium Affiliate Forms are available on the University of Chicago Cancer Research Center website.

- http://uccrc.uchicago.edu/current/home.html
- Click on the **Staff Resources** link and scroll down to "UC Phase II Consortium Forms" section.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies. Eligible patients will be entered on study centrally at the University of Chicago by the Registrar. All sites should call the Registrar at (773) 834-3095 to verify agent availability.

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Registrar should be notified of cancellations as soon as possible.

4.2. Registration Process

All patients must be registered with the University of Chicago Registrar at least 48 hours prior to the commencement of treatment. The following documents should be completed by the research nurse or data manager and faxed **(773) 702-4889** or emailed **PhaseIICRA@medicine.bsd.uchicago.edu** to the Registrar:

- Provider of information
- Treating Physician
- Patient name and hospital ID number
- Patient's zip code of residence
- Date & copy of signed informed consent
- Race, gender, date of birth of patient
- Diagnosis and date of initial diagnosis
- Prior therapy with a VEGF-pathway inhibitor (yes/no)
- ECOG performance status
- Complete **Phase II Consortium Affiliate Clinical Trial Patient Registration Form**
- Source documentation for eligibility and pre-study procedures

The research nurse or data manager at the participating site will then call **(773-834-3095)** or e-mail **PhaseIICRA@medicine.bsd.uchicago.edu** to confirm all selection criteria listed in Section 4.0. To complete the registration process, the Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number and dose to the participating site

Call the research nurse or data manager at the participating site and verbally confirm registration.

Each site must have two trained counselors available for counseling all patients receiving lenalidomide supplied by the Division of Cancer Treatment and Diagnosis. Trained counselors must complete training using the online program provided free by Celgene, the Lenalidomide Counseling Program (LCP). Registration for LCP is done by completing the form found in Appendix K and following the directions provided in the email notification. After the training is complete, the counselors must generate a training certificate and provide it to the PMB for documentation. Sites may not order lenalidomide until documentation for two trained counselors is provided to the appropriate office.

5. TREATMENT PLAN

5.1. Agent Administration

Treatment will be administered on an outpatient basis. Cediranib tablets should be taken either 1 hour before or 2 hours after meals. Cediranib will be taken daily on a continuous basis for each 28 day cycle. If a dose of cediranib is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Lenalidomide will either be taken for 21 days of the 28 day cycle or daily, depending on the level of dose escalation. Lenalidomide can be taken with or without food. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Lenalidomide capsules should be swallowed whole. For patients who are unable to swallow lenalidomide whole, lenalidomide can be administered via gastrostomy feeding tube following the instructions in Appendix M.

For patients who are unable to swallow cediranib tablets, cediranib tablets may be administered as a dispersion in water (ie, either drinking water, sterile water [for injection] or purified water). The following procedure is recommended:

Cediranib tablets may be dispersed in half a glass (2 fluid ounces or 50 ml) of non-carbonated drinking water. No other liquids should be used. The tablet is dropped in water, without crushing, stirred until dispersed (approximately 10 minutes) and the resultant dispersion swallowed immediately. Any residues in the glass are mixed with half a glass of

water and swallowed. The liquid can also be administered through nasogastric or gastrostomy tubes. Where patients require the dose to be administered by nasogastric or gastrostomy tubes, cediranib tablet(s) dispersed in water can be dosed with: Polyurethane (PUR) or Poly vinylchloride (PVC) naso-gastric, naso-intestinal or percutaneous endoscopic gastrostomy (PEG) feeding systems in conjunction with PUR syringes. PVC syringes are not recommended for use. Two system washes are conducted through the giving set to ensure the correct dose is obtained.

Only one cycle of therapy may be dispensed to the patient each month.

Reported adverse events and potential risks for cediranib and lenalidomide are described in Section 7. Appropriate dose modifications for cediranib and lenalidomide are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

All patients on lenalidomide should receive prophylactic anti-coagulation. See 5.1.3 **Anticoagulation Consideration.**

5.1.1. Phase I

To determine the MTD, a 3+3 design will be used (see below). Dose modifications are listed below. Three patients will be enrolled with a starting dose of cediranib 20 mg daily (28 days of 28 day cycle) with lenalidomide 15 mg on day 1-21 of the 28 day cycle. If cediranib 20 mg daily is not tolerated with lenalidomide 15 mg on day 1-21 of a 28 day cycle, a new cohort will be added with cediranib 20 mg daily (28 days of 28 day cycle) and lenalidomide 10 mg on day 1-21 of 28 day cycle. After 4 weeks of therapy, if no DLTs are observed, 3 patients will be enrolled at the next dose, cediranib 30 mg daily (28 days of 28 day cycle) with lenalidomide 15 mg on day 1-21 of 28 day cycle. If no DLTs are observed after 4 weeks, 3 addition patients will be enrolled with cediranib 30 mg daily (28 days of 28 day cycle) and lenalidomide 15 mg daily (28 days of 28 day cycle). After 4 weeks of therapy, if no DLTs are observed, 3 patients will be enrolled at the next dose, cediranib 30 mg daily (28 days of 28 day cycle) with lenalidomide 20 mg on day 1-21 of the 28 days cycle. After 4 weeks, if no DLTs are observed, 3 patients will be enrolled at the next dose, cediranib 30 mg daily (28 days of 28 day cycle) with lenalidomide 20 mg daily (28 days of 28 day cycle). Dose escalation beyond cediranib 30 mg daily and lenalidomide 20 mg daily will not be performed. At any level, if more than 2 patients experience a DLT, this dose will declared the maximally administered dose. Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. If 1 out of 3 patients develop a DLT at a certain dose, 3 additional subjects will be entered at this dose. If 0 of 3 patients develop a DLT, an additional 3 patients will proceed to the next dose. If 1 of 3 patients develops a DLT, dose escalation will stop. Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

Dose modification for Phase I study	**Cediranib + Lenalidomide**
-1	Cediranib 20 mg (28/28 days) + Lenalidomide 10 mg (21/28 days)
0	Cediranib 20 mg (28/28 days) + Lenalidomide 15 mg (21/28 days)
+1	Cediranib 30 mg (28/28 days) + Lenalidomide 15 mg (21/28 days)
+2	Cediranib 30 mg (28/28 days) + Lenalidomide 15 mg (28/28 days)
+3	Cediranib 30 mg (28/28 days) + Lenalidomide 20 mg (21/28 days)
+4	Cediranib 30 mg (28/28 days) + Lenalidomide 20 mg (28/28 days)

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level
> 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Dose Limiting Toxicity (DLT) will be determined during the first cycle for dose escalation. Toxicity occurring in subsequent cycles will not be considered dose limiting but will require dose modification. (See Section 6.0 for Dose Modification)

DLT will be defined as follows:

- Hematological toxicities:
  - Any grade 4 neutropenia (ANC < 500) lasting more than 5 days
  - Any grade 4 neutropenia with concomitant fever (temperature > 38.5)
  - Any grade 4 neutropenia and sepsis or other severe infection
  - Any grade 4 thrombocytopenia

- Any other grade 3-4 non-hematological adverse drug reactions, except untreated nausea/vomiting, or hypersensitivity reactions.

- Grade 4 hypertension

- Grade 4 proteinuria

- Delay in the administration of a subsequent dose of cediranib and lenalidomide exceeding 2 weeks, due to an adverse drug reaction.

For patients in the Phase I trial, disease re-evaluation will occur every 8 weeks using

RECIST guidelines.* Patients without evidence of anti-thyroglobulin antibodies will continue to have thyroglobulin levels measured at each response assessment (usually every 8 weeks). All patients are expected to be on thyroxine suppression therapy and thyroid stimulation hormone (TSH) levels will be monitored pre-therapy and every 8 weeks during therapy.

*After 18 cycles, radiologic disease re-evaluation will occur every 16 weeks.

Phase I toxicity: In the Phase I study, of 15 evaluable patients, 4 were enrolled at the starting dose (cediranib 20 mg daily with lenalidomide 15 mg on days1- 21 of 28 days), 6 were enrolled in the +1 dose modification, 5 in the + 2 dose modification. DLTs in the +2 dose modification were Grade 3 fatigue and Grade 3 mucocitis. The DLT in the +1 modification was Grade 3 fatigue. Since 1 of 6 patients in the +1 group (cediranib 30 mg daily and lenalidomide 15 mg on day 1-21,) this was determined to be the starting dose for the Phase II trial.

5.1.2. Cediranib and lenalidomide administration

Please note, as of **April 10, 2015**, patients assigned to Arm B (Combination of cediranib and lenalidomide) are to discontinue lenalidomide and may continue on cediranib alone.

After determining the MTD or reaching the maximum dose specified above of cediranib with lenalidomide in the Phase I portion of this study, the Phase II study will be initiated.

Subjects will be randomized in a 1:2 ratio to one of two arms. Randomized stratification will employ prior therapy with a VEGF-pathway inhibitor (yes vs. no) and performance status (0 and 1 vs. 2). In Cohort A, subjects (n = 36) will receive cediranib alone at 30 mg daily. In Cohort B, subjects (n = 74) will receive cediranib and lenalidomide at the dose determined in the Phase I study. Each cycle will be 4 weeks in length. Disease re-evaluation will occur every 8 weeks using RECIST guidelines. After 18 cycles, disease re-evaluation will occur every 16 weeks. Patients without evidence of anti-thyroglobulin antibodies will continue to have thyroglobulin levels measured at each response assessment (usually every 8 weeks). All patients are expected to be on thyroxine suppression therapy and thyroid stimulation hormone (TSH) levels will be monitored pre-therapy and every 8 weeks during therapy.

- Patients will take cediranib or cediranib and lenalidomide. Cediranib will be taken daily at 30 mg. Lenalidomide will be taken on day 1-21 of the 28 day cycle at 15 mg. Proper administration of cediranib and lenalidomide is described in Section 5.1. A 4-week period constitutes one cycle of treatment.

- Patients will be provided with a Medication Diary for cediranib and lenalidomide (Appendix B), instructed in its use, and asked to bring the diary with them to each

appointment. A new copy of the Medication Diary will be given to patients each cycle and for those whose dose is reduced due to adverse events.

- Because hypertension is a known and potentially serious but rare adverse event associated with cediranib treatment, patients will have their blood pressure monitored and recorded at least weekly during the first cycle of therapy and then at least every two weeks for the duration of the study, either at the doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). The health care team may request for more frequent blood pressure checks as clinically indicated. Patients will be provided a Blood Pressure Diary (Appendix L) to record blood pressure. Patients should be asked to bring the diary with them to each appointment. (See Section 6.1 for hypertension management and dose reduction guidelines.)

- Routine monitoring for cardiac function (ECHO/MUGA) should be performed at baseline and every other cycle of treatment in the following groups of patients: (1) those entering the trial with NYHA Class II cardiac dysfunction (see Appendix G), (2) those with a history of Class II heart failure who are asymptomatic on treatment, and (3) in those previously exposed to anthracyclines or thoracic irradiation if the heart was included in the radiotherapy port. Routine cardiac monitoring is not required in patients with no known cardiac dysfunction at entry or in the absence of clinically observed adverse cardiac events.

- Patients with bulky solid tumors should be monitored closely for pneumothorax, intestinal fistulae, or intestinal perforation in the event of rapid tumor destruction.

- Subjects who have been on protocol for 12 months or more can be evaluated every 2 cycles (8 weeks). (However, only one cycle of therapy may be dispensed to the patient each month)

- Subjects who have been on protocol for 18 months or more will have radiographic tumor response assessed every 4 cycles (16 weeks).

5.1.3. Anticoagulation Consideration

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased.

- All patients receiving lenalidomide should receive prophylactic anti-coagulation. Aspirin (81 or 325 mg) is the recommended agent for anti-coagulation prophylaxis.

Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

- Prophylactic anti-coagulation should be held for platelet counts < 50,000/mm³and then restarted when platelet counts are above this level.

- Full therapeutic anti-coagulation should be considered for patients who have a history of venous thromboembolism. Whether therapeutic anti-coagulation is used or not, patients with a history of venous thromboembolism should be closely monitored throughout the study, especially during periods of fluctuating platelet counts.

5.2. General Concomitant Medication and Supportive Care Guidelines

The case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies including herbal supplements, specifically, St. John's wort.

5.2.1. Concomitant Medications

The use of coumarin-derivative **anticoagulants** such as warfarin (Coumadin®) is not recommended. It may be used for both thrombosis prophylaxis and treatment. However, coumadin should be used with caution and close monitoring of INR. When possible, low molecular weight heparin should be used instead of coumadin.

5.2.2. Supportive Care

- **Nausea/vomiting** Patients with treatment-related nausea should be treated initially with a phenothiazine (prochlorperazine – 10 mg every 8 hours orally as needed or promethazine – 12.5-25 mg IV every 6 hours as needed). If this is inadequate, a benzodiazepine should be added until acute nausea is controlled or toxicity is limiting. Should this prove inadequate acutely, a steroid may be added (*e.g.*, dexamethasone 4 mg every 6 hours as needed). (Steriod use must be limited to 5 consecutive days within a 4 week cycle.)

  After acute nausea has resolved, consideration should be given to initiation of prophylactic antiemetic therapy. If nausea recurs despite reasonable medical intervention (as outlined above), dose reduction will be needed as described in Section 6.

- **Diarrhea** should be managed with loperamide: 4 mg at first onset, then 2 mg every 2-4 hours until diarrhea is controlled (maximum = 16 mg loperamide per day).

- **Hand-foot syndrome** may be treated with topical emollients (such as Aquaphor), topical/systemic steroids, and/or antihistamine agents. Vitamin B6 (pyridoxine; 50-150 mg orally each day) may also be used.

- Patients with **neutropenic fever** or infection should be evaluated promptly and treated with IV antibiotic therapy plus/minus therapeutic colony-stimulating factors as appropriate following the ASCO guidelines.[24] Packed red blood cell and platelet transfusion should be administered as clinically indicated. GCSF may be used at the discretion of the treating physician.

5.3. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,

- Intercurrent illness that prevents further administration of treatment,

- Unacceptable adverse events(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4. Duration of Follow Up

Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Unless the patient withdraws from the study, the subject will be followed until disease progression or death, whichever comes first.

5.5. Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

The dose levels and the general approach to dose modification of cediranib and lenalidomide on this trial are shown below. Managing patients on combination therapy will be discussed below. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the case report form (CRF).

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

CTCAE v5.0 documents, including a mapping document, are available on the CTEP website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Dose Level for Phase II study	Cediranib
-2	15 mg cediranib daily
-1	20 mg cediranib daily
0	30 mg cediranib daily

Dose Level for Phase II study	Lenalidomide
-2	Lenalidomide 5 mg on day 1-21 of 28 day cycle
-1	Lenalidomide 10 mg on day 1-21 of 28 day cycle
0	Lenalidomide 15 mg on day 1-21 of 28 day cycle

6.1. Management of Treatment-Emergent Hypertension

Hypertension is more frequently associated with cediranib than lenalidomide. Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Specific guidelines for management of this adverse event and a table of various antihypertensive medications are provided in Appendix C. In addition, guidance on the collection and recording of BP information is provided in Appendix D.

6.1.1 Management of Hypertension

Adverse event	NCI CTCAE v.5 grade	Management	Cediranib administration
Hypertension	Grade 1 Systolic 120-139 mmHg or diastolic 80-89 mmHg	Consider increased BP monitoring	No change
	Grade 2-Mild Stage 1 hypertension: (140-159 mmHg Systolic or 90-99 mmHg Diasolic)	Start/ add long acting DHP CCB (See Appendix C). Gradually increase dose to control BP up to maximum dose. If partial or no control and still moderate hypertension, see Persistent Moderate Hypertension.	First occurrence: Continue cediranib at full dose or decrease dose by one level Second occurrence: Decrease cediranib dose by one level
	Grade 2-Persistent Moderate Hypertension Stage 1 hypertension: (140-159 mmHg Systolic or 90-99 mmHg Diasolic) Recurrent or persistent ≥ 24-48 hrs);	Start/ add long acting DHP CCB (See Appendix C). Gradually increase dose to control BP up to maximum dose. If partial or no control and still moderate hypertension, add an additional drug and increase dose until BP control up to maximum dose.	Hold cediranib and add additional drugs. Restart cediranib at one lower dose level (when controlled).
	Grade 3 Stage 2 hypertension (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg);	If asymptomatic: Hold cediranib and start immediate antihypertensive therapy with 2 drug combination including at least a DHP CCB. Increase dose until BP control up to maximum dose of both agents. If partial or no BP control, add another drug up to 4; increase to optimal or maximal doses on all drugs.	First occurrence: Hold cediranib until blood pressure within Stage 1 hypertension range (systolic 140-159 mmHg or diastolic 90-99 mmHg); and decrease cediranib dose by one level Second occurrence: Hold cediranib until blood pressure within Stage 1

		If symptomatic: stop cediranib, hospitalize with aggressive IV therapy as per hypertensive crisis management	hypertension range (systolic 140-159 mmHg or diastolic 90-99 mmHg); and either decrease cediranib by one dose level or stop cediranib permanently
	Grade 4 Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurological deficit, hypertensive crisis); urgent intervention indicated	Stop cediranib, hospitalize with aggressive IV therapy as per hypertensive crisis management.	Stop cediranib permanently

- While patients are receiving treatment with cediranib, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.

- Decisions to hold or decrease the cediranib dose during treatment must be based on BP readings taken in the clinic by a medical professional.

6.2. Other Hematologic and Non-Hematologic Adverse Events

In the setting of combination therapy, it may be difficult to identify the agent causing the adverse event. When the adverse event could be due to either agent, the dose of lenalidomide should be decreased. When an adverse event is more commonly associated with a particular agent, that drug will be decreased.

Event	AE Grade or Observation	Dose modification (single agent cediranib)	Dose modification (cediranib + lenalidomide)
Neutropenia	Grades 1 and 2	Maintain dose	Maintain dose
	Grade 3	• Hold cediranib dose • Follow CBC weekly • Hold cediranib until ≤ grade 2, then resume treatment at same dose cediranib or reduce 1 dose level G-CSF may be used for treatment. • Dose reduction should be considered for recurrent episodes.	• Hold cediranib and lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to the scheduled end of the cycle, restart lenalidomide at next lower dose level and cediranib at the same dose and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and

			reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Maintain cediranib dose. Omitted doses are not made up. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF (or other white blood cell growth factor) may be used for treatment and the lenalidomide dose maintained • Dose reduction should be considered for recurrent episodes.
	Grade 4	• Hold cediranib dose • Follow CBC weekly • Hold cediranib until ≤ grade 2, then resume treatment at same dose cediranib or reduce 1 dose level • G-CSF may be used for treatment. • Dose reduction should be considered for recurrent episodes.	• Hold cediranib and lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to the scheduled end of the cycle, restart lenalidomide at next lower dose level and cediranib at the same dose and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Cediranib dose will be maintained. Omitted doses are not made up. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF (or other white blood cell growth factor) may be used for treatment and the lenalidomide dose maintained. Dose reduction should be considered for recurrent episodes.
Thrombocytopenia	Grades 1 and 2	Maintain Dose	Maintain Dose
	Grade 3	• Hold cediranib dose	• Hold cediranib and

		• Follow CBC weekly • Hold cediranib until ≤ grade 2, then resume treatment at same dose cediranib or reduce 1 dose level • Repeated episodes require dose reduction	lenalidomide dose. • Follow CBC weekly. • Hold prophylactic anti-coagulation for platelet counts ≤ 50,000/mm3. Prophylactic anti-coagulation should be resumed when lenalidomide is restarted. • If thrombocytopenia resolves to ≤ grade 2 prior to the scheduled end of the cycle, restart lenalidomide at next lower dose level and cediranib at same dose and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Cediranib dose will remain the same. Omitted doses are not made up.
	Grade 4	• Hold cediranib dose. • Follow weekly CBC • Hold cediranib until ≤ grade 2, then resume treatment at same dose cediranib or reduce 1 dose level • Repeated episodes require dose reduction	• Hold cediranib and lenalidomide dose. • Follow CBC weekly. • Hold prophylactic anti-coagulation for platelet counts ≤ 50,000/mm3. Prophylactic anti-coagulation should be resumed when lenalidomide is restarted. • If thrombocytopenia resolves to ≤ grade 2 prior to the scheduled end of the cycle, restart lenalidomide at next lower dose level and cediranib at same dose and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Cediranib dose will remain the same. Omitted doses are not made up.

Fever, chills, flu-like symptoms	Grades 1-4	Maintain dose	Maintain dose
Fatigue (lethargy, malaise, asthenia)	Grades 1 and 2	Maintain dose. For sustained Grade 2 fatigue, cediranib may be held until ≤ grade 1. Then resume same dose.	Maintain dose. For sustained Grade 2 fatigue, cediranib and lenalidomide may be held until ≤ grade 1. Then resume same dose or reduce 1 dose level of lenalidomide. If fatigue recurs, cediranib may be reduced 1 dose level. If no further dose reductions are available, the lowest doses of cediranib and lenalidomide may be continued at the discretion of the treating physician.
	Grade 3	Hold cediranib until ≤ grade 2, then resume treatment at same dose cediranib or reduce 1 dose level	Hold cediranib and lenalidomide until ≤ grade 2, then resume treatment at same dose or reduce 1 dose level of lenalidomide. If fatigue recurs, cediranib may be reduced 1 dose level .
	Grade 4	Hold cediranib until ≤ grade 2, then resume treatment at same dose or reduce 1 dose level of cediranib	Hold cediranib and lenalidomide until ≤ grade 2, then resume treatment at same dose or reduce 1 dose level of lenalidomide. If fatigue recurs, reduce 1 dose level of cediranib.
Hand-foot syndrome	Grades 1 and 2	Maintain dose	Maintain dose
	Grade 3	Hold cediranib until ≤ grade 1, then resume treatment at same dose or reduce 1 dose level of cediranib	Hold cediranib and lenalidomide until ≤ grade 1, then resume treatment at same dose or reduce 1 dose level of cediranib
	Grade 4	Hold cediranib until ≤ grade 1, then reduce 1 dose level or discontinue treatment	Hold cediranib and lenalidomide until ≤ grade 1, then reduce 1 dose level of cediranib or discontinue treatment
AST and/or ALT elevation (SGOT, SGPT)	Grades 1 and 2	Maintain dose	Maintain dose
	Grade 3	Maintain dose. If recurrent, reduce cediranib 1 dose level	Maintain dose. If recurrent, reduce lenalidomide 1 dose level

	Grade 4	Reduce cediranib 1 dose level	Reduce lenalidomide 1 dose level
Proteinuria**	Grade 1	Maintain dose	Maintain dose
	Grade 2	Hold cediranib. Collect 24 hour urine. If 24 hour urine results with ≤ Grade 2, continue at same dose.	Hold cediranib and lenalidomide. Collect 24 hour urine. If 24 hour urine results with ≤ Grade 2, continue at same dose.
	Grade 3	Hold cediranib. Collect 24 hour urine. If 24 hour urine = Grade 3, hold cediranib until urinalysis ≤ grade 2, then reduce 1 dose level of cediranib	Hold cediranib and lenalidomide. Collect 24 hour urine. If 24 hour urine = Grade 3, hold cediranib and lenalidomide until urinalysis ≤ grade 2, then reduce 1 dose level of cediranib
	Grade 4 (Nephrotic syndrome)	Discontinue treatment	Discontinue treatment
DVT/ Pulmonary Embolism		Hold cediranib until therapeutic on anti-coagulation. Then resume cediranib at same dose* Discontinue treatment if recurrent DVT/PE when fully anticoagulated.	Hold cediranib and lenalidomide until therapeutic on anti-coagulation. Then resume cediranib and lenalidomide at same dose* Discontinue treatment if recurrent DVT/PE when fully anticoagulated.
Anaphylaxis, Stevens Johnson syndrome, TEN		Discontinue treatment	Discontinue treatment
Bowel perforation		Discontinue treatment	Discontinue treatment
Suspected pregnancy, positive HCG, missed menses		Hold cediranib. If pregnancy ruled out, continue treatment at same dose cediranib.	Hold cediranib and lenalidomide. If pregnancy ruled out, continue treatment at same dose cediranib and lenalidomide
Confirmed pregnancy (endocrine, other fetal exposure to drug)	Grade 4	Discontinue treatment. Appropriate follow-up, see Section 7.3.3.	Discontinue treatment. Appropriate follow-up, see Section 7.3.3.

***Low Molecular Weight Heparin (LMWH) should be first choice for anticoagulation. Coumadin can be used but requires close monitoring of INR. Aspirin can be discontinued in patients who are on therapeutic anticoagulation.**

**** For proteinuria +2 or greater on urinalysis, study drugs should be held and 24 hour urine should be collected to confirm degree of proteinuria. Dose modification based on 24 hour urine protein assessment as above.**

6.3. Management of Other Clinically Significant AEs (not specifically addressed above)

General Management Guidelines

Observation	Action: Cediranib alone	Action: Cediranib and lenalidomide
AE resolves promptly with supportive care	Maintain dose level	Maintain dose level
1. Grade 3 or higher (non-hematologic or grade 4 (hematologic) AE related to cediranib or lenalidomide and lasting >5 days that does not resolve to grade 2 or below despite maximum supportive care for ≤ 48 hours. 2. Lower grade but related AEs (*e.g.*, creatinine)	Hold cediranib until ≤ grade 2. Resume same dose cediranib. If recurs, reduce one dose level of cediranib	Hold cediranib and lenalidomide until ≤ grade 2. Resume same dose of cediranib and lenalidomide. If recurs, reduce 1 dose level of lenalidomide. If recurs again, reduce cediranib 1 dose level.
AE does not resolve to grade 2 or below after treating patient at the lowest reduced dose level.	In general, remove patient from study *	In general, remove patient from study *
* After consultation with study sponsor (DCTD, NCI), a lower dose of single or combination therapy may be considered for patients on study ≥ 3 months who are benefiting from the agent.		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via CTEP-AERS) reporting **in addition** to routine (via CDUS) reporting.

7.1. Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

7.1.1. CAEPR for Cediranib (AZD2171, NSC 732208)

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 1608 patients.* Below is the CAEPR for Cediranib (AZD2171).

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 2.15, November 7, 2018[1]

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis		***Anal mucositis (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dysphagia		***Dysphagia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
		Pancreatitis	
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lymphocyte count decreased		

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Neutrophil count decreased		
	Platelet count decreased		
	Thyroid stimulating hormone increased		***Thyroid stimulating hormone increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 4)***
	Vascular disorders - Other (hemorrhage)[5]		

[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]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

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

[5]Hemorrhage is a known consequence of VEGF/VEGFR signaling inhibition. The majority of hemorrhage events reported were mild; however, serious events, defined as symptomatic bleeding in a critical area or organ system (e.g., eye, gastrointestinal tract, genitourinary [GU] tract, respiratory tract, and nervous system) have been reported.

Adverse events reported on cediranib (AZD2171) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that cediranib (AZD2171) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (polycythemia); Bone marrow hypocellular; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ears feel full/plugged); Ear and labyrinth disorders - Other (viral labyrinthitis); Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Bloating; Colitis; Colonic obstruction; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileus; Oral pain; Periodontal disease; Peritoneal necrosis; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Fever; Gait disturbance; Hypothermia; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder obstruction; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Hemoglobin increased; INR increased; Investigations - Other (elevated ammonia level); Investigations - Other (increased blood erythropoietin); Lipase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Avascular necrosis; Back

pain; Bone pain; Chest wall pain; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Myalgia; Myositis; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Memory impairment; Muscle weakness left-sided; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Hallucinations; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Menorrhagia; Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Sinus pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Skin ulceration; Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hypotension; Vasculitis

Note: Cediranib (AZD2171) 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.

7.1.2. CAEPR for Lenalidomide (CC-5013, NSC 703813)

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 2.8, June 27, 2019[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		
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)***

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%)**	
	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		
	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		

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%)**	
	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)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
		Rhabdomyolysis[5]	
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		
	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			

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%)**	
		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 (pyoderma 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 (SPM) including ALL, AML, and MDS, and certain other types of cancers of the skin and other organs in multiple myeloma (MM) patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant. The use of lenalidomide in cancers other than MM, shows that invasive SPMs occurred in a small number of patients. Patients treated with lenalidomide should be closely followed for the occurance of SPMs.

[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.

NOTE: In a trial of first line treatment of patients with chronic lymphocytic leukemia (CLL), single agent lenalidomide (CC-5013) increased the risk of death as compared to control arm (chlorambucil).

NOTE: In two randomized trials of patients with multiple myeloma (MM), the addition of MK-3475 (pembrolizumab) to a thalidomide analog plus dexamethasone, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody, such as MK-3475 (pembrolizumab), in combination with a thalidomide analog, such as lenalidomide, is not recommended outside of controlled clinical trials.

NOTE: In a clinical trial in patients with Mantle cell lymphoma (MCL), there was an increase in early deaths (within 20 weeks); 12.9% in the lenalidomide (CC-5013) arm vs. 7.1% in the control arm.

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.

7.2. Adverse Event Characteristics

CTCAE term (AE description) and grade: 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.

- CTCAE v5.0 documents, including a mapping document, are available on the CTEP website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1.1).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3. Expedited Adverse Event Reporting

7.3.1. Expedited AE reporting for this study must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.3).

In the rare occurrence when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon reestablishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website.

7.3.2. CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.4. Expedited Reporting Guidelines

7.4.1. CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 1 Trials

Phase 1 Trials								
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2,3]
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

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

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

1. Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

[3] Pregnancy is Grade 4/5 unexpected event.

December 15, 2004

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

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

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

- Pregnancy (Grade 4/5 unexpected event) must be reported within 24 hour of learning of the event. This applies to patients on cediranib alone or cediranib and lenalidomide.

  For patients who become pregnant while on cediranib alone. Discontinue cediranib immediately. The Investigator will follow the subject until completion of the pregnancy, and must notify CTEP-AERS reporting system of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to cediranib should also be reported.

  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 is to 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.

7.4.2. CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2,3]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.
[3] Pregnancy is Grade 4/5 unexpected event.

December 15, 2004

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

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

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

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

- Pregnancy (Grade 4/5 unexpected event) must be reported within 24 hour of learning of the event. This includes pregnancies while on cediranib or lenalidomide or within 4 weeks after a subjects last dose of cediranib or lenalidomide.

  For patients who become pregnant while on cediranib alone. Discontinue cediranib immediately. The Investigator will follow the subject until completion of the pregnancy, and must notify CTEP-AERS reporting system of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to cediranib should also be reported.

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 is to 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.

7.5. Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

7.6. Secondary Malignancies (including AML and MDS)

Investigators are required to report cases of secondary malignancies, including AML/MDS, occurring on or following treatment on NCI-sponsored chemotherapy protocols via CTEP-AERS with CTCAE 5.0. Refer to the CTEP web site (http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

- In addition to all routine AE reporting mechanisms and any Cooperative Group-specific second/secondary malignancy reporting requirements, all new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and *in situ* tumors.
- Using CTCAE v5.0, the event(s) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy; (2) Myelodysplastic syndrome; (3) Treatment-related secondary malignancy; or (4) Neoplasm other, malignant (grade 3 or 4).
- These events should be reported for the duration of the study treatment and during any protocol-specified follow-up periods. Refer to the "CTEP website http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or

commercial agents administered in this study can be found in Section 7.1.

8.1. CTEP-Supplied Investigational Agents

8.1.1. Cediranib (AZD2171, NSC 732208)

Chemical Name: 4-[(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1- yl)propoxy] quinazoline maleate

Other Names: cediranib, AZD2171 maleate

CAS Registry Number: 288383-20-0 (for the free base)

Molecular Formula: $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$ **M W:** 566.59 (maleate salt), 450.52 (free base)

Approximate Solubility: The aqueous solubility of AZD2171 (cediranib) is 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.76 mg/mL for the maleate salt (distilled water, at 25°C).

Mode of Action: AZD2171 (cediranib) is a highly potent tyrosine kinase inhibitor of all three vascular endothelial growth factor receptors (VEGFR-1, -2 and -3). Inhibition of VEGF signaling leads to inhibition of angiogenesis, neovascular survival and vascular permeability. Pre-clinical tumor models show that AZD2171 (cediranib) reduces micro-vessel density and metastasis, indicating that it limits tumor growth.

How Supplied: Astra-Zeneca supplies and CTEP, NCI, DCTD distributes AZD2171 (cediranib). The agent is available as beige, round, biconvex, film-coated tablets containing 15 mg, and 20 mg of AZD2171 (cediranib) free base. The 15 mg and 20 mg tablets are 7 mm and 8 mm in diameter, respectively. Each high-density polyethylene bottle contains 35 tablets.

Tablet excipients include mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate, microcrystalline cellulose, and magnesium stearate with a film coat containing hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

Storage: Store intact bottles at controlled room temperature 20°C to 25°C (68 to 77°F) and protect from light and moisture.

Stability: Stability studies are ongoing. Dispense AZD2171 (cediranib) tablets in their original containers. Alternatively, if exact quantity is dispensed in a pharmacy bottle, the supply should be assigned a 30-day expiration.

If a storage temperature excursion is identified, promptly return AZD2171 (cediranib) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Route and Method of Administration: Oral. AZD2171 (cediranib) tablets should be taken either one hour before or two hours after meals.

If the study sponsor determines appropriate, cediranib tablets may be administered as a dispersion in plain water. Liquids other than non-carbonated water should not be used and the tablets should not be crushed or ground. The following procedure is recommended by the manufacturer for patients who can swallow liquids:

> Drop the appropriate dose of cediranib tablet/s into a glass containing 50-60 mL non-carbonated water. Stir the tablet/s until dispersed in the water, about 10 minutes (no crushing). Swallow the liquid immediately after dispersion is completed. Any residue in the glass is mixed with a half glass of water and swallowed.

The manufacturer recommends the following for naso-gastric or gastrostomy tube administration:

> Follow the dispersion instructions above. Administer the dispersion using polyurethane or PVC naso-gastric, naso-intestinal or percutaneous endoscopic gastrostomy feeding systems in conjunction with polyurethane syringes. PVC syringes are not recommended. Conduct two system washes to ensure the patient receives the full dose.

Potential Drug Interactions: AZD2171 (cediranib) is primarily metabolized by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that AZD2171 (cediranib) is a substrate for P-glycoprotein (Pgp), but not breast cancer resistance protein (BCRP). Since clinically relevant induction or inhibition of FMO enzymes is uncommon**,** use caution in patients taking concomitant medications that are strong inhibitors (e.g. ketoconazole) or strong inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's Wort) of UGT1A4 or Pgp in particular. If chronic concomitant administration of strong inducers or inhibitors is unavoidable, consult the protocol document and/or the principal investigator before making any dose adjustments.
In vitro studies show that AZD2171 (cediranib) did not inhibit CYP 1A2, 2A6, 2C8, 2C9, 2C19 and 2E1 and showed no induction of CYP 1A2, 2B6 and 3A4/5. It did weakly inhibit CYP 2D6 and 3A4/5, but this inhibition not expected to cause any clinically relevant drug interactions.

In vitro studies show that AZD2171 (cediranib) is a weak inhibitor of BCRP, but not Pgp. Use caution in patients who are taking concomitant medications that are sensitive substrates of BCRP transporters since there is a potential for drug-drug interactions.

AZD2171 (cediranib) is approximately 95% bound to human plasma proteins, with human serum albumin and α1-acid glycoprotein accounting for most of this binding. Use caution in patients taking concomitant medications with narrow therapeutic ranges that are also highly protein-bound.

Oral anticoagulants are not absolutely contraindicated during treatment with AZD2171 (cediranib); however, use AZD2171 (cediranib) with caution and increase monitoring in patients while on study. Patients who receive VEGF inhibitors are at increased risk of bleeding and hemorrhage.

Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing. For patients already enrolled onto the protocol, the manufacturer recommends holding AZD2171 (cediranib) for 2 weeks prior to elective surgery and restarting when the surgical wound is healed. Protocol exclusion criteria should include patients who have had major thoracic or abdominal surgery within 2 weeks prior to start of study or patients with any surgical incision that is not fully healed.

8.1.2. Lenalidomide (CC-5013, NSC 703813)

NOTE:
Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification Form in the protocol). The counseling requirements for investigational-use lenalidomide are separate from the RevAssist program. Only a 28-day supply may be dispensed to a patient at one time.

Chemical Name:	3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione; α-(3-aminothalamido) glucaride.
Other Names:	Lenalidomide, Revlimid™ (formerly known as Revimid™), CDC-501
Classification:	Immunomodulatory Agent
CAS Registry Number:	191732-72-6
Molecular Formula:	$C_{13}H_{13}N_3O_3$ **M.W.:** 259.26
Mode of Action:	CC-5013, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is not fully characterized. In vitro, it inhibits secretion of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 and increases secretion of the anti-inflammatory cytokine IL-10. It also induces T-cell proliferation, IL-2 and IFN-γ production in vitro.
How Supplied:	Celgene supplies and CTEP, NCI, DCTD distributes lenalidomide 5 mg (size 2) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps. Bottles contain 100 capsules per container. The 21-count and 28-count bottles are no longer available. The capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.
Storage:	The capsules should be stored at room temperature (15-30°C) away from moisture and direct sunlight.
Stability:	Refer to the package labeling for expiration date. Lenalidomide stability is adequate for at least 28 days after transferring to a pharmacy vial."
Route of Administration:	Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules. See Section 5.1 and Appendix M for patients who cannot swallow lenalidomide.
Dispensing:	Only a 28-day supply may be dispensed at one time. Sites may not mail lenalidomide to patients.

Patient Care Implications and Counseling:

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryo fetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Definition of female of childbearing potential (FCBP)
This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Before starting study drug:
Female Subjects:

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

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

All Subjects:

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

- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Counseling

- In investigational studies where lenalidomide is supplied by the NCI, patients will be counseled by a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). Two healthcare professionals at each site will be trained by Celgene in requirements specific to counseling of subjects (investigators cannot counsel patients as part of this requirement). Refer to specific protocol sections for more information about training requirements.

- Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Lenalidomide Education and Counseling Guidance Document (Appendix I) and no drug will be dispensed until this step occurs. Counseling includes verification with the female patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix J) will be supplied with each medication dispense."

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Potential Drug Interactions:
Periodic monitoring of digoxin levels is recommended during coadministration with CC-5013. Digoxin levels were slightly higher when digoxin was administered with CC-5013 in a clinical study. There was no effect on CC-5013 pharmacokinetics.

Warfarin and CC-5013 may be co-administered without additional monitoring. No pharmacokinetic or pharmacodynamic interactions were observed between CC-5013 and warfarin.

Nonclinical in vitro metabolism studies suggest that CC-5013 is not likely to result in metabolic drug interactions in humans. In vitro, CC-5013 did not significantly inhibit marker enzyme activities for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. In rats, no induction of any CYP450 enzymes was observed. Administration of CC-5013 in monkeys showed no effects on the activities of CYP1A, CYP2B, CYP2C, CYP2E, CYP3A, or CYP4A.

Availability
Lenalidomide is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Lenalidomide is provided to the NCI under a Collaborative Agreement between Celgene and the DCTD, NCI (see Section 12.3).

8.1.3. Agent Ordering

Please note, as of April 10, 2015, patients on Arm B are no longer receiving

lenalidomide. For further details refer to section 5.1.2

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the 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.

Note that mailed and faxed Clinical Drug Requests (CDRs) are no longer accepted. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can 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.

8.1.4. 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 for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.).

8.1.5. IB access

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.6. PMB contacts

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. CORRELATIVE/SPECIAL STUDIES

All subjects will be asked to provide archival tumor tissue.

9.1. Rationale

Archival tumor tissue:
B-RAF gene
K-RAS gene

Pharmacogenomics:
Advanced thyroid carcinoma is a heterogenous group of diseases likely caused by a variety of molecular defects. Variable responses in previous clinical trials are likely due in part to differences in the underlying disease processes. Data from studies with other targeted agents suggest that different molecular aberrations may affect clinical response. For example, in the Phase II clinical trial with motesanib diphosphate with advanced DTC, DNA from 33 tumors of trial patients was screened for mutations often observed in DTC. Six of the 10 patients (60%) whose tumor contained the *B-RAF*^{V600E} mutation had either a partial response or durable stable disease. In contrast 5 of 15 patients without the mutation (33%) had a partial response or durable stable disease.[25] While the number of tumor samples was too small to show significance, the findings do suggest that *B-RAF* mutations may affect response. In addition, in a Phase II study of the multi-target tyrosine kinase inhibitor sorafenib, of sixteen DTC patients who had genotype testing, those with *B-RAF*^{V600E} mutations had significantly longer PFS compared to those who did not (84+ weeks versus weeks).[26] *B-RAF* mutations have been reported in 29-83% of PTCs and *K-RAS* mutations have been found in 21-50% of FTCs.[27] We plan to evaluate *B-RAF* mutations and *K-RAS* mutations in available tumor samples to assess whether these mutations predict response. This study will provide an excellent opportunity to further clarify the role of the previously described polymorphisms in thyroid carcinoma.

Shipping Instructions:
The shipment of all human samples (tissue) must comply with appropriate regulations as specified by the carrier. Paraffin archival tissue can be shipped at room temperature. The outer container must be puncture resistant (e.g., cardboard mail tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.
All shipments must contain a completed Sample Identification form (Appendix F).

Archival Tumour Samples can be shipped to the address below Monday through Thursday.
Shipping address:
University of Chicago
HTRC, Room P-616
5835 S. Cottage Grove
Chicago, IL 60637
Phone: 773-834-8391
E-mail: tissuebank@bsd.uchicago.edu

On arrival, each sample will be assigned a **Study Number**. All subsequent handling of the tissue samples will be blinded to the investigators performing various tests, except for the clinical pathologists. Only biopsy samples determined by the pathologist to contain tumor will be subjected to immunohistochemical analysis. For all immunohistochemical studies, samples will only be marked with an assigned study number. Patient name, diagnosis and other information will be unknown to the laboratory/clinical investigators involved and will be revealed only after studies are completed for further data analysis and statistics.

9.2 Laboratory Correlative Studies

B-RAF and *K-RAS* mutations
Formalin-fixed paraffin-embedded (FFPE) tissue blocks and H&E stained slides will be collected at the site of the enrollee when available and packed and shipped by FedEX to the University of Chicago as described above. H&E stained slides will be reviewed and the optimal block will be picked for molecular analysis. It should have a contiguous convex area at least 3 mm in minimum dimension with at least 50% involvement by tumor. DNA will be prepared from the FFPE tissue blocks. Ten unstained 5 micron sections are then cut, the 5th slide in the set is stained (H&E) to confirm pathology and guide macrodissection (if necessary) of the other slides. Following deparaffinization DNA is extracted and quantified using either the Nanodrop(TM-superscript) or a Picogreen dye binding assay.

DNA is analysed for any *K-RAS* mutation in codons 12 or 13 following the procedure described by Nikiforova *et a.l*[28] This is a real-time hybridization probe polymerase chain reaction assay run on a LightCycler™ 2.0. To increase sensitivity (when tumor involves less than 20% of section) a modified form of this assay *LightMix® Kit k-ras Mutations Codons*

12/1 3 ™ from TIB-MolBiol may be used. This uses a 'blocking' probe modified with locked nucleic acids to block amplification of the normal sequence at codons 12 and 13. At present this modification is for research use only.

Detection of *B-RAF^{V600E}* mutation will be performed using real-time PCR and fluorescence melting curve analysis (FMCA) from DNA as previously reported by our group. Briefly, a pair of oligonucleotide primers flanking the mutation site have been designed, together with two fluorescent probes, with the sensor probe spanning the nucleotide position 1799. Amplification will be performed in a glass capillary using 50 ng of DNA in a 20 microliter volume. The reaction mixture is then to 45 cycles of rapid PCR consisting of denaturation at 94 degrees C for 1 sec, annealing at 55 degrees C for 20 sec, and extension at 72 degrees C for 10 sec. Post-amplification FMCA is performed by gradual heating of samples at a rate of 0.2degreesC/sec from 45 degrees C to 95 degrees C. All PCR products that showed deviation from the wild-type (placental DNA) melting peak are sequenced to verify the presence of mutation.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 week prior to start of protocol therapy. Scans and x-rays must be done 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study [k]	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 64	Day 71	Day 78	Day 85	Day 113	Off Study [k]
Cediranib[a]																
Lenalidomide[b]																
Anticoagulation[c]																
Informed consent	X															
Demographics	X															
Medical history	X															
ECHO/MUGA[o]	x															
Physical exam[n]	X	X		X		X		X		X				X	X	X
Vital signs[n]	X	X		X		X		X		X				X	X	X
Height	X															
Weight[n]	X	X		X		X		X		X				X	X	X
Performance status[n]	X	X		X		X		X		X				X	X	X
CBC w/diff, plts[n]	X	X		X		X		X		X		X		X	X	X
Serum chemistry[d, n]	X	X		X		X		X		X		X		X	X	X
Blood pressure measurement[e]	X	X	X	X	X	X		X		X		X		X	X	X

EKG	X															
Urinalysis[i, n]	X	X				X				X				X	X	X
B-HCG	X[f,g]	X[f,g]	X[f,g]	X[f,g]	X[f,g]	X[f,g]		X[f,g]		X[f,g]		X[f,g]		X[f,g]	X[f,g]	X[f,g]
Patient Education and counseling[h]	X[h]	X[h]				X[h]				X[h]				X[h]	X[h]	X[h]
TSH	X									X[m]						X
Throglobulin	X									X[m]						X
Radiology studies [l]	X									X						X
Archival tissue for correlative studies [j]	X															

a: **Cediranib**: Dose as assigned; *administration schedule*
b: **Lenalidomide:** Dose as assigned, only enough lenalidomide for 28 days or one cycle of study treatment (whichever is shorter) may be provided to the patient each cycle*; administration schedule*
c: Anticoagulation: All patients receiving lenalidomide should receive prophylactic anti-coagulation. Aspirin (81 or 325 mg) is the recommended agent for anti-coagulation prophylaxis. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
e: Blood pressure measurement may be performed more frequently as dictated by clinical observations. See Appendix D for blood pressure measurement guidelines.
f: Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
g: Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix H: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
h: The Lenalidomide Education and Counseling Guidance Document (Appendix I) must be completed and signed by a trained counselor at the participating site prior to each dispensing of lenalidomide treatment. A copy of this document must be maintained in the patient records. The Lenalidomide Information Sheet (Appendix J) will be given to each patient receiving lenalidomide treatment. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.
i: Pre-study, all patients with 1+ protein reading or greater on urinalysis should collect a 24 hour urine collection to measure protein. During the study, patients with 2 + or greater proteinuria should collect a 24 hour urine collection to measure protein. Study medication should be held until 24 hour urine collected and evaluated. See Section 6.2 for dose modification.
j: Archival tissue should be requested pre-study but should not delay the start of therapy.
k: Study calendar can vary +/- 3 days without a study violation.
l: Radiology evaluation repeated every 2 cycles. Subjects on protocol 18 months or more will have radiology evaluation every 4 cycles.
k: Off-study evaluation.
m: TSH and thyroglobulin evaluation repeated every 2 cycles.
n: After 12 months on study, subjects can be evaluated every 2 cycles.
m: O: In select patients see section 3.1.10 for further detail

11. MEASUREMENT OF EFFECT

11.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every *8* weeks. In addition to a baseline scan, confirmatory scans should also be obtained *8* weeks following initial documentation of objective response. Subjects who have been on treatment for 18 months or more will have radiological evaluation every 4 cycles.

Response and progression will be evaluated in this study using the new international criteria

proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1. Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with cediranib or cediranib in combination with lenalidomide.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2. Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should

not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

11.1.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

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

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body
scans should be performed with breath-hold scanning techniques, if possible.

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

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In

addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.4. Response Criteria

11.1.4.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2. Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3. Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5. Duration of Response

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

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

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

11.1.6. Progression-Free Survival

Progression free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death of any cause.

11.1.7. Response Review

All responses will be reviewed by an expert(s) independent of the study at the study's completion.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1. Data Reporting

12.1.1. Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov). **Note**: **All** adverse events that have occurred on the study, including those reported throughCTEP-AERS, must be reported via CDUS.

12.1.2. Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center quarterly by January 31, April 30, July 31, and October 31 to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.1.1.). For trials monitored by CTMS, the monthly data submission to CTEP from Theradex should be copied to the Coordinating Center

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2. CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix E.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (*PIO@ctep.nci.nih.gov*) except for Group studies.

12.3. Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

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/industry) 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 investigational 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 investigational 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 NIH, 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 investigational 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 investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. 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:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: anshers@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 Collaborators confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1. Study Design/Endpoints

13.1.1. Phase I.

The phase I trial will use a 3+3 design with the MTD defined as the highest dose level such that <2 of 6 patients experience dose-limiting toxicity.

13.1.2. Phase II.

There is no standard therapy for differentiated thyroid cancer that is refractory to radioactive iodine. The best studied agent in this disease, doxorubicin, has an estimated response rate of 10%. Although cediranib has not been studied in thyroid cancer, a phase II study of the VEGF inhibitor motesanib diphospate showed a median progression-free survival (PFS) of 40 weeks. Because we hypothesis that combination therapy will be more effective than single agent treatment, we will randomize in a 1:2 ratio, which should enhance recruitment. The randomization will be stratified by prior therapy with a VEGF-pathway inhibitor (yes vs. no) and performance status (0-1 vs. 2)

The primary endpoint will be PFS, which will be compared between the two treatment arms using a stratified logrank test. To determine the sample size, we noted that the median PFS in 93 patients with radioiodine-resistant thyroid cancer treated with motesanib diphosphate[25] was 40 weeks. We therefore assume a median of 40 weeks for the cediranib alone arm. In order to have 85% power to detect a 75% improvement in the median to 70 weeks with combination therapy (hazard ratio [HR]=1.75), 110 patients will be required (36 randomized to cediranib and 74 to cediranib plus lenalidomide), based on a one-sided test at the alpha=0.10 significance level. This calculation assumes 1 year of accrual (9 patients per month) and 1.5 years of additional follow-up for a total study duration of 2.5 years. Kaplan-Meier[30] curves will be generated for each treatment arm and the median PFS times estimated using the Brookmeyer and Crowley method[31]. In addition to the logrank test, PFS in the two groups will be analyzed by fitting a Cox[32] proportional hazards regression model, adjusting for prior VEGF inhibitor use, performance status, and other baseline risk factors. The goodness of fit of the Cox model and the appropriate functional form for continuous covariates will be assessed using graphical techniques, including inspection of martingale residual plots.

An interim futility analysis will be performed after half of the total number of projected events (40 of 80 projected events). The trial will stopped for futility if the conditional power at this time point is 15% or less, reducing the power by 2-3%.

13.2. Sample Size/Accrual Rate

Phase I1: 9-18 patients. Accrual 3 patient/mo
Phase II: Sample size 110 patients. Accrual 9-10 patients/mo.

13.3. Stratification Factors

Phase II. Patients will be stratified on prior use of VEGF-pathway inhibitors (yes vs no) and performance status (0 and 1 vs 2).

13.4. Analysis of Secondary Endpoints

13.4.1. Phase I.

The objective response rate of cediranib in combination with lenalidomide in patients with iodine refractory, unresectable DTC who have evidence of disease progression within 6 months of study enrollment will be estimated. In addition, the toxicity, duration of response, progression free survival, and overall survival in patients with DTC treated with cediranib plus lenalidomide will be evaluated.

13.4.2. Phase II.

Overall survival (OS) rates will be estimated and compared between groups using methods similar to that described above for PFS Response rates will be compared using a chisquare test followed by logistic regression analysis to adjust for covariates.

The percent change in tumor size from baseline to the end of cycle 2 (two months) will be compared between the two groups using a two-sample t test[33]. The post-treatment total sum of lengths for a patient with a new lesion will be scored as 1.2*max(pre-sum, post-sum) to ensure that the appearance of new lesions corresponds to a disease progression per RECIST criteria. In the event of any early deaths prior to two months, a nonparametric rank sum test will be used in place of the t test, with deaths ranked at the extreme end of the distribution.

Adverse events will be summarized by type and grade. Adverse event rates will be compared between the two treatment groups using a chisquare test for common toxicities and Fisher's exact test for less frequent events.

Repeated measures analysis of variance (RM ANOVA) will be performed to determine the effect of the treatments on serial measurements of TSH and thyroglobulin. It is hypothesized that these levels will decrease over time. Baseline tissue biomarker expression, scored as present or absent, of *B-RAF* and *RAS* mutations will be correlated with response rates using Fisher's exact test, and with PFS and OS by fitting a Cox proportional hazards regression model.

13.5. Reporting and Exclusions

13.5.1. **Evaluation of toxicity.** All patients (Phase I and II) will be evaluable for toxicity from the time of their first treatment with cediranib or cediranib plus lenalidomide.

13.5.2. **Evaluation of response.** All patients included in the study (Phase I and II) will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early

death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of the response rate.

All conclusions will be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. Data will be reported to CTEP using CDUS -Complete.

REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. http://seer.cancer.gov/ Accessed 2009.
2. American Cancer Society. www.cancer.org/docroot/home//. Accessed 2009.
3. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114(6):1050-7; discussion 7-8.
4. DeGroot LJ, Kaplan EL, Straus FH, Shukla MS. Does the method of management of papillary thyroid carcinoma make a difference in outcome? World J Surg 1994;18(1):123-30.
5. Mazzaferri EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 1981;70(3):511-8.
6. Bernier MO, Leenhardt L, Hoang C, et al. Survival and therapeutic modalities in patients with bone metastases of differentiated thyroid carcinomas. J Clin Endocrinol Metab 2001;86(4):1568-73.
7. Schoenberger J, Grimm D, Kossmehl P, et al. Effects of PTK787/ZK222584, a tyrosine kinase inhibitor, on the growth of a poorly differentiated thyroid carcinoma: an animal study. Endocrinology 2004;145(3):1031-8.
8. Bauer AJ, Patel A, Terrell R, et al. Systemic administration of vascular endothelial growth factor monoclonal antibody reduces the growth of papillary thyroid carcinoma in a nude mouse model. Annals of clinical and laboratory science 2003;33(2):192-9.
9. Ain KB, Lee C, Williams KD. Phase II trial of thalidomide for therapy of radioiodine-unresponsive and rapidly progressive thyroid carcinomas. Thyroid 2007;17(7):663-70.
10. Ain K LC, Holbrook KM, Dziba JM, Williams KD. Phase II study of lenalidomide in distantly metastatic, rapidly progressive, and radioiodine-unresponsive thyroid carcinomas: preliminary results. J Clin Oncol 26: 2008 (May 20 suppl; abstr 6027) 2008.
11. Wedge SR, Kendrew J, Hennequin LF, et al. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer research 2005;65(10):4389-400.
12. Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer 2002;2(10):795-803.
13. Ferrara N. Role of vascular endothelial growth factor in the regulation of angiogenesis. Kidney international 1999;56(3):794-814.
14. Yamamoto N, Tamura T, Yamamoto N, et al. Phase I, dose escalation and pharmacokinetic study of cediranib (RECENTIN), a highly potent and selective VEGFR signaling inhibitor, in Japanese patients with advanced solid tumors. Cancer chemotherapy and pharmacology 2009;64(6):1165-72.
15. Ryan CJ, Stadler WM, Roth B, et al. Phase I dose escalation and pharmacokinetic study of AZD2171, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinase, in patients with hormone refractory prostate cancer (HRPC). Investigational new drugs 2007;25(5):445-51.

16. Fiedler W, Mesters R, Heuser M, et al. An open-label, Phase I study of cediranib (RECENTIN) in patients with acute myeloid leukemia. Leukemia research 2009.
17. Jayson GC ET, Harris A, Mitchell CL, Kelly C, Middleton M, Fielding A, Laud P, Robertson J, Puchalski TA. J Clin Oncol 26: 2008 (May 20 suppl; abstr 14533)
18. Mulders P HR, Nathan P, de Jong I, Mookerjee B, Osanto S, et al. Cediranib (RECENTINTM) in patients with advanced renal cell carcinoma: results of a randomized Phase II study. 7th International Kidney Cancer Symposium 2008: abstract 21.
19. Laurie SA AA, Shepherd FA, Dediu M, Ciuleanu T, Fenton D, et al. Randomized, double-blind phase II trial of carboplatin + paclitaxel [C+P] with either daily oral cediranib,an inhibitor of vascular endothelial growth factor receptor [VEGFR] tyrosine kinases, or placebo, in advanced non-small cell lung cancer [NSCLC]: a study of the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 2008:19(Suppl 8):viii90, abstract231PD.
20. Mangiameli DP, Blansfield JA, Kachala S, et al. Combination therapy targeting the tumor microenvironment is effective in a model of human ocular melanoma. Journal of translational medicine 2007;5:38.
21. Blansfield JA, Caragacianu D, Alexander HR, 3rd, et al. Combining agents that target the tumor microenvironment improves the efficacy of anticancer therapy. Clin Cancer Res 2008;14(1):270-80.
22. Sanborn SL, Gibbons J, Krishnamurthi S, et al. Phase I trial of docetaxel given every 3 weeks and daily lenalidomide in patients with advanced solid tumors. Investigational new drugs 2009;27(5):453-60.
23. Berg S. Phase I and pharmacokinetic (PK) study of lenalidomide (LEN) in pediatric patients with relapsed/refractory solid tumors or myelodysplastic syndrome (MDS): A Children's Oncology Group Phase I Consortium study. J Clin Oncol 27:15s, 2009 (suppl; abstr 10023)
24. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24(19):3187-205.
25. Sherman SI, Wirth LJ, Droz JP, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. N Engl J Med 2008;359(1):31-42.
26. Brose MS TA, Redlinger M, Harlacker K, Redlinger C, Chalian AA, Flaherty KT, Loevner LA, Mandel SJ, O'Dwyer PJ Effect of BRAFV600E on response to sorafenib in advanced thyroid cancer patients. J Clin Oncol 2009;27:15s, 2009 (suppl; abst 6002).
27. Trovisco V, Soares P, Sobrinho-Simoes M. B-RAF mutations in the etiopathogenesis, diagnosis, and prognosis of thyroid carcinomas. Hum Pathol 2006;37(7):781-6.
28. Nikiforova MN, Lynch RA, Biddinger PW, et al. RAS point mutations and PAX8-PPAR gamma rearrangement in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. J Clin Endocrinol Metab 2003;88(5):2318-26.
29. Sherman SI SM, Droz J, M. Hoffmann, L. Wirth, L. Bastholt, R. G. Martins, L. Licitra, Y. Shi, D. E. Stepan. Initial results from a phase II trial of motesanib diphosphate (AMG 706) in patients with differentiated thyroid cancer (DTC). Journal

of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I Vol 25, No 18S (June 20 Supplement), 2007: 6017;25(18S):6017.
30. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Assoc, 1958; 53:457-81.
31. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics, 1982; 38:29-41.
32. Cox DR. Regression models and life tables (with discussion). Journal of the Royal Statistical Soc B, 1972; 34:187-220.
33 Karrison TG, Maitland ML, Stadler WM, Ratan MJ. Design of phase II cancer trials using a continuous endpoint of change in tumor size: Application to a study of sorafenib and erlotinib in non-small-cell lung cancer. Journal Natl Cancer Inst, 2007; 99:1455-61.

APPENDIX A
Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B
Subject's Study Drug Diary

CTEP-assigned Protocol #_____
Local Protocol # _____

SUBJECT'S STUDY DRUG DIARY – CEDIRANIB

Today's date_____ Subject Name_____ (*initials acceptable)* **Subject Study ID_____**

INSTRUCTIONS TO THE SUBJECT:

1. Complete one form for each 4 week-period while you take **cediranib**.
2. You will take your dose of **cediranib** each day in the morning. You will take ____15 mg tablets, and ____ 20 mg tablets every morning. You can take cediranib at least 1 hour before you eat or 2 hours after you eat. If a dose of **cediranib** is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return this form to your physician when you go for your next appointment.

Day	**Date**	**Time of daily dose**	**# of tablets taken**		**Comments**
			15 mg	**20 mg**	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Physician's Office will complete this section:

1. Date subject started protocol _____2.Date subject was removed from study_____
3. Subject planned total daily dose_____ 4.Total number of capsules taken this month (each size)_____5.Physician/Nurse/Data Manager's Signature _____

Subject's signature _____

UC IRB # 10-182-B
NCI # 8317
Version Date: 09/25/2019

CTEP-assigned Protocol #_____

Local Protocol # _____

SUBJECT'S STUDY DRUG DIARY – LENALIDOMIDE

Today's date _____ Subject's Name_____ Subject's Study ID _____

INSTRUCTIONS TO THE SUBJECT:

1. Complete one form for each 4 week-period while you take **lenalidomide**. Only one cycle of study drug may be dispensed each month.
2. You will take your dose of **lenalidomide** each day in the morning. You will take ____5 mg capsules. You may take the capsules with or without food as you wish.
3. **Lenalidomide** capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of **lenalidomide** is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. If you cannot swallow lenalidomide, you may be able to take it via gastrostomy tube. Your doctor will explain the procedure.
4. If you take more than the prescribed dose of **lenalidomide, you** should seek emergency medical care if needed and contact study staff immediately.
5. Record the date, the number of capsules you took, and when you took them.
6. If you have any comments or notice any side effects, please record them in the Comments column.
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken 5 mg	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

Physician's Office will complete this section:

1. Date subject started protocol _____2.Date subject was removed from study_____
3. Subject's planned total daily dose_____4.Total number of capsules taken this month (each size)_____ 5.Physician/Nurse/Data Manager's Signature _____

Subject's signature _____

UC IRB # 10-182-B
NCI # 8317
Version Date: 09/25/2019

APPENDIX C
Hypertension Monitoring and Management*

Grade (CTCAEv5.0)	**Antihypertensive Therapy**	**Blood Pressure Monitoring**	**Cediranib Dose Modification**
Grade 1 120-139 mmHg Systolic 80-89 mmHg Diastolic	None Baseline	Standard monitoring Consider diuretics	No Change
Grade 2- Mild 140-159 mmHg Systolic 90-99 mmHg Diastolic	Initiate BB **or** Initiate DHP CCB **&/or** Increase doses of existing medications until BP controlled or at maximum dose	Increased frequency of monitoring until stabilized	No Change
Persistent Moderate Hypertension 140-159 mmHg Systolic 90-99 mmHg Diastolic	Initiate BB **or** Initiate DHP CCB **or** ACEI **or** Vasodilator **&/or** Increase doses or number of medications until BP controlled or at maximum dose	Increased frequency of monitoring until stabilized (*e.g.*, every 48 hours) Supervised by healthcare professional	If partial or no control and BP still in a moderate range for 24-48 hours, hold *cediranib* and add additional drugs, increasing to a maximum dose until hypertension controlled; monitor for hypotension. Decrease *cediranib* by 1 dose level
Grade 3- Severe ≥ 160 mmHg Systolic ≥ 100 mmHg Diastolic	Start immediate therapy with 2 drug combination including at least a DHP CCB Escalate doses to achieve optimal control of BP, up to the maximum dose If partial or no BP control, add additional drugs up to 4; increase to optimal or maximum doses of all drugs	Increased frequency of monitoring until stabilized (*e.g.*, every 48 hours) Supervised by healthcare professional	Hold *cediranib*; if control of BP in the Mild range, restart *cediranib* at the next lower dose level If partial or no control, decrease *cediranib* by another dose level or discontinue therapy per investigator Stop *cediranib* if hypertension is symptomatic, and hospitalize patient for management of BP
Grade 4 Hypertensive Crisis	Optimal management with intensive IV support in ICU	Hospitalize patient for management	Off protocol therapy, discontinue *cediranib*, and monitor closely for **hypo**tension

Abbreviations: Dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB)

*See table below for suggested antihypertensive medications by class
If patients require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
If patients require >2 dose reductions, discontinue protocol therapy
Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in *cediranib*
24-48 hours should elapse between modifications of antihypertensive therapy
Hypertension should be graded using the NCI CTCAEv5.0

Oral Antihypertensive Medications: *Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with cediranib through CYP450.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

APPENDIX D
Collection/Recording of Blood Pressure Information

1.0 General Guidelines

1.1 Frequency of monitoring. Blood pressure (BP) should be monitored weekly during the first cycle of cediranib therapy, then at least every 2 weeks for the duration of treatment. More frequent monitoring may be considered on a study by study basis, particularly during the first two cycles of cediranib therapy.

1.2 Data recording. All required data should be recorded in the appropriate CRF or on the patient's blood pressure monitoring diary, as appropriate. **The following data are required at baseline and at each subsequent assessment**:

- Assessment date and time
- Pulse
- Systolic and diastolic BP (2 readings/assessment taken 5 minutes apart while patient sitting)

1.3 Risk factors for hypertension (assess and record data in baseline history/physical CRF)

- Diabetes (type 1 or type 2)
- Renal disease (specify on CRF)
- Endocrine condition associated with HTN (specify on CRF)
- Use of steroids or NSAIDs (specify all concomitant meds)
- Underlying cardiovascular condition – specify (*i.e.*, ischemic heart disease)

2.0 Baseline data collection (at study entry)

2.1 All patients

- Current BP
- Proteinuria, if present

2.2 Patients with preexisting hypertension (*i.e.*, those for whom "hypertension" is entered as a concomitant condition at study entry, or those who are currently receiving therapy with antihypertensive medication) – also record:

- Date of HTN diagnosis (original)
- Type HTN (essential or secondary)
- CTCAE v5.0 grade of HTN (at time of study entry)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of the following:
  - Antihypertensive agents taken at study entry
  - Antihypertensive agents taken in past (e.g., discontinued for toxicity, lack of efficacy)

3.0 Follow up BP data collection (during study)

3.1 All patients (at each clinic visit)

- Current BP
- Proteinuria, if present

3.2 Patients with treatment-emergent hypertension [defined as BP increase of >20 mmHg (diastolic) OR BP >150/100 (if previously within normal limits)] – record at time of hypertension diagnosis and at all subsequent clinic visits:
- BP changes from baseline (or from previous assessment) (specify CTCAE v5.0 grade changes)
- Hypertension-related symptoms as reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Trade name, drug class*, dose, dose frequency, start/stop dates/ongoing of currently prescribed antihypertensive agents

3.3 Patients with preexisting hypertension at study entry – record at each clinic visit
- BP changes from previous clinic visit (specify CTCAE v5.0 grade changes)
- Hypertension-related symptoms reported by patient (*e.g.*, headache)
- Other relevant changes associated with development of hypertension (*e.g.*, ECG abnormalities)
- Changes in antihypertensive medications since last assessment (*e.g.*, dose change, add/discontinue drug)

Classes of antihypertensive drugs include ACE inhibitors, calcium channel blockers, alpha blockers, beta blockers, diuretics, angiotension II receptor antagonists.

APPENDIX E
CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.

- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX F

Protocol 8317

The University of Chicago

Tissue Collection Form

Clinician: Please Fill Out

Tissue Samples

Patient Name: _____

Patient Protocol ID #:_____ Date Tissue Obtained: _____

Date of Birth: _____ Attending Physician: _____

Site of Biopsy: _____ Institution: _____

Date consent was signed: _____ Diagnosis:_____

Pre/Post Therapy (Please circle) Day started on clinical protocol:_____

Did Surgical Pathology receive tissue for diagnosis? **Yes No**

Contact Person's Phone Number and email Address at Affiliate:

Researcher: Please Fill Out

Date Samples received: _____

Questions regarding tissue/blood specimens: Contact HTRC
Phone: 773-834-8391

APPENDIX G
New York Heart Association Classifications

Clinical Evaluation of Functional Capacity of Patients
with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to work**
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

Reference:

Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953.

APPENDIX H

Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females 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 for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should 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 understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., 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.

<u>Contraception</u>

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) during 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. FCBP must be referred to a qualified provider of contraceptive methods if needed. 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.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

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

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 28 days following study drug discontinuation

Female Patients:

- FCBP 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. If menstrual cycles are irregular, the pregnancy testing must

occur 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 FCBP 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.

- If pregnancy or a positive pregnancy test does occur in a study patient, study drug 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 treatment must be discontinued during this evaluation.

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

Male Patients:

Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.

- 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 this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.

- Female patients should not donate blood during treatment and for at least 28 days following discontinuation of lenalidomide.

- Male patients should not donate blood, semen or sperm during treatment or for at least 28 days following discontinuation of lenalidomide.

- Only enough study drug for 28 days or one cycle of therapy (whichever is shorter) may be dispensed with each cycle of therapy.

Appendix I:
Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

□ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

□ NOT FCBP

Male: □

<u>Do Not Dispense study drug if:</u>

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to treatment, during treatment and during dose interruption].**

<u>FCBP:</u>

1. I verified that the required pregnancy tests performed are negative.

2. I counseled FCBP regarding the following:

   - Potential risk of fetal exposure to lenalidomide: 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. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.

   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to treatment, during treatment, during dose interruption and 28 days after discontinuation of lenalidomide].

   - That even if she has amenorrhea she must comply with advice on contraception

   - Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

     – Highly effective methods:

       o Intrauterine device (IUD)

       o Hormonal (birth control pills, injections, implants)

       o Tubal ligation

       o Partner's vasectomy

     – Additional effective methods:

       o Male condom

       o Diaphragm

       o Cervical Cap

   - Pregnancy tests before, during, and after treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.

   - Frequency of pregnancy tests to be done:

     – Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.

- If the patient missed a period or has unusual menstrual bleeding.

- When the patient is discontinued from the study and at day 28 after study drug discontinuation 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 study drug discontinuation.

– Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.

– NEVER share study drug with anyone else.

– Do not donate blood while taking study drug and for 28 days after stopping study drug.

– Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.

– Do not break, chew, or open study drug capsules.

– Return unused study drug to the study doctor.

3. Provide Lenalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

4. I counseled the female NOT of child bearing potential regarding the following:

   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)

   - NEVER share study drug with anyone else.

   - Do not donate blood while taking study drug and for 28 days after stopping study drug.

   - Do not break, chew, or open study drug capsules

   - Return unused study drug capsules to the study doctor.

5. Provide Lenalidomide Information Sheet to the patient.

MALE:

6. I counseled the Male patient regarding the following:

- Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
- To engage in complete abstinence or use 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 study drug, during dose interruptions and for 28 days after stopping study drug.
- Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
- NEVER share study drug with anyone else.
- Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping study drug.
- Do not break, chew, or open study drug capsules.
- Return unused study drug capsules to the study doctor.

7. Provide Lenalidomide Information Sheet to the patient.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

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

APPENDIX J
Lenalidomide Information Sheet

FOR SUBJECTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking study drug and each time you get a new supply. 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?

8. **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. Findings from a monkey study indicate that lenalidomide caused birth defects in the babies of female monkeys who received the drug during pregnancy**.**

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

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **Either do not have sexual intercourse at all 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 to 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 study drug if you become pregnant during treatment**

  – If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation**.**

- **Do not breastfeed while taking study drug**

- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

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.

If you are a man:

Lenalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

- Men (including those who have had a vasectomy) must either abstain from sexual intercourse or use a condom during sexual contact with a pregnant female or a female that can become pregnant:

  – While you are taking lenalidomide

  – During dose interruptions of lenalidomide

  – For 28 days after you stop taking lenalidomide

- **Men should not donate sperm or semen** while taking study drug and for 28 days after stopping lenalidomide.

- **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 and the pharmaceutical collaborator, Celgene Corporation. Your partner should call their healthcare provider immediately if she gets pregnant.**

9. **Restrictions in sharing lenalidomide and donating blood:**

   - **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 donate blood** while you take lenalidomide and for 28 days after stopping study drug.

- **Do not break, chew, or open study drug capsules.**

- You will get no more than a 28-day supply of lenalidomide at one time.

- Return unused study drug 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 K
REGISTRATION FOR LENALIDOMIDE COUNSELING PROGRAM

Counselor Information

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: _____

Previously approved as a _____ Counselor? □ No □ Yes If Yes, which Protocol: _____

CTEP-assigned Protocol #_____

Local Protocol # _____

Document A _Version 2.0 July 20, 2010

Lenalidomide Counseling Program
Site Counselor Identification Form
NCI Protocol#: _____
Cooperative Group Name *(if applicable, ex. SWOG, ECOG)* _____

- **Please provide at least two (2) counselors and fax back to 908.673.2779**
- **Use one form per counselor.**
- **Identified counselors must be a licensed healthcare professional (e.g. RN, PA, RPh, PhD, LPN, CNP or MD).**
- **If you have any questions, please contact tfranco@celgene.com**

General Information

Principal Investigator: _____Institution Name: _____
CTEP site ID: _____

Today's Date: _____/_____/_____ Subject Name:
_____ Subject ID _____ (*initials acceptable)*

APPENDIX L: SUBJECT'S BLOOD PRESSURE DIARY

INSTRUCTIONS TO THE SUBJECT: 1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, normal blood pressure is 120/80). 2. Record the date, then record your blood pressure using a home blood pressure monitor. You should check you blood pressure at least once a week for your first cycle but more often depending on your doctor's instructions 3. If you take your blood pressure at other times of the day, please record the numbers and time under "Other readings." 4. If your systolic pressure is greater than 150 or your diastolic blood pressure is greater than 90, repeat after several hours. If it remains elevated, please contact your doctor's office at _____ for instructions. 5. **Please bring this form to every clinic visit or appointment.**

Date	AM readings	PM readings	Other readings (include time of day)	Date	AM readings	PM readings	Other readings (include time of day)
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	

Subject's Signature: _____ Date: _____

Physician's Office will complete this section: _____/_____/_____ Date of this clinic visit
Physician/Nurse/Data Manager's Signature

APPENDIX M
Procedure for Dosing Lenalidomide Via Gastrostomy Feeding Tube

1) Obtain One (1) cup of **HOT** water.

2) Arrange the required articles for dose administration
   - One (1) clean 20cc disposable syringe with plunger rod.
   - One (1) clean 10cc disposable syringe with plunger rod.
   - One (1) 3-way Stop Cock valve
     - 3-Way Stop Cock valve – Qosina Part # 99729
     - All Plastic Disposable Syringe 20mL capacity Luer Lock Syringe – National Scientific Target Part # 03-377-24
   - One (1) adapter (for use from valve to tube)
     - Adapter – Qosina Part # 11519

3) Using the 20CC syringe, place the luer-lock end in the cup of hot water and fill the syringe completely by pulling back on the plunger rod until it stops. This syringe will be designated as the "RINSE SYRINGE." Set "RINSE SYRINGE" down and **allow water to cool**.

4) Connect the 3-way valve to the 10CC syringe via the luer-lock at the "C' position (luer-lock opposite the Fixed Male Luer leaving the second luer lock to the right @ the "B" position) (see Figure 1).

5) Position the valve handle @ the "B" position (see Figure 1).

6) Pull back on the plunger rod and remove the plunger rod from the syringe barrel. This will be the "DOSING SYRINGE."

7) Insert the required dose (capsules) into the barrel of the "DOSING SYRINGE."

8) Replace the plunger rod into the syringe barrel and slowly depress the plunger rod until it touches the capsules.

9) Place the Fixed Luer ("A") end of the valve into the cup of **HOT** water and draw the plunger rod back filling the syringe with hot water until it stops (see Figure 1).

10) **Immediately position the valve handle to the "C" position** (see Figure 1). This will prevent any leakage from the syringe as the capsules begin to dissolve. Note: a few drops may leak from the Fixed Luer end of the valve. This will only be water downstream of the closed valve.

11) Gently swirl the syringe to assist in the hot water dissolving the gelatin capsules. Verify that the capsules have dissolved and allow the solution to come to a suitable temperature for dosing. The temperature in the "RINSE SYRINGE" should be checked as well (warm to the touch on the exterior of the syringe body).

12) Once a suitable temperature (warm to the touch on the exterior of the syringe body) is reached and the capsules appear dissolved, connect the "RINSE SYRINGE" to the 2nd luer-lock fitting on the 3-way valve (Position "B") (see Figure 1).

13) Attach the adapter to the Fixed Male Luer end (position "A") of the valve (see Figure 1).

14) The daily dose is now ready to be administered (see Figure 2).

15) Insert the adapter into the port on the Feeding Tube, making sure it is a tight fit that will not allow leaking.

16) Turn the valve handle on the 3-way valve to the "B" position (see Figure 1). Depress the plunger rod on the "DOSING SYRINGE" until it stops.

17) Turn the valve handle to the "A" position (see Figure 1). Gently pull back on the plunger rod of the "DOSING SYRINGE" allowing approximately 1/3 (7cc) of rinse water to enter the "DOSING SYRINGE" from the "RINSE SYRINGE."

18) Turn the 3-way valve back to the "B" position and depress the plunger rod on the "DOSING SYRINGE" until it stops (see Figure 1).

19) Turn the valve handle to the "A" position (see Figure 1). Gently pull back on the plunger rod of the "DOSING SYRINGE" allowing approximately 1/3 (7cc) of rinse water to enter the "DOSING SYRINGE" from the "RINSE SYRINGE."

20) Turn the 3-way valve back to the "B" position and depress the plunger rod on the "DOSING SYRINGE" until it stops (see Figure 1).

21) Turn the valve handle to the "A" position (see Figure 1). Gently pull back on the plunger rod of the "DOSING SYRINGE" allowing the remaining rinse water to enter the "DOSING SYRINGE" from the "RINSE SYRINGE."

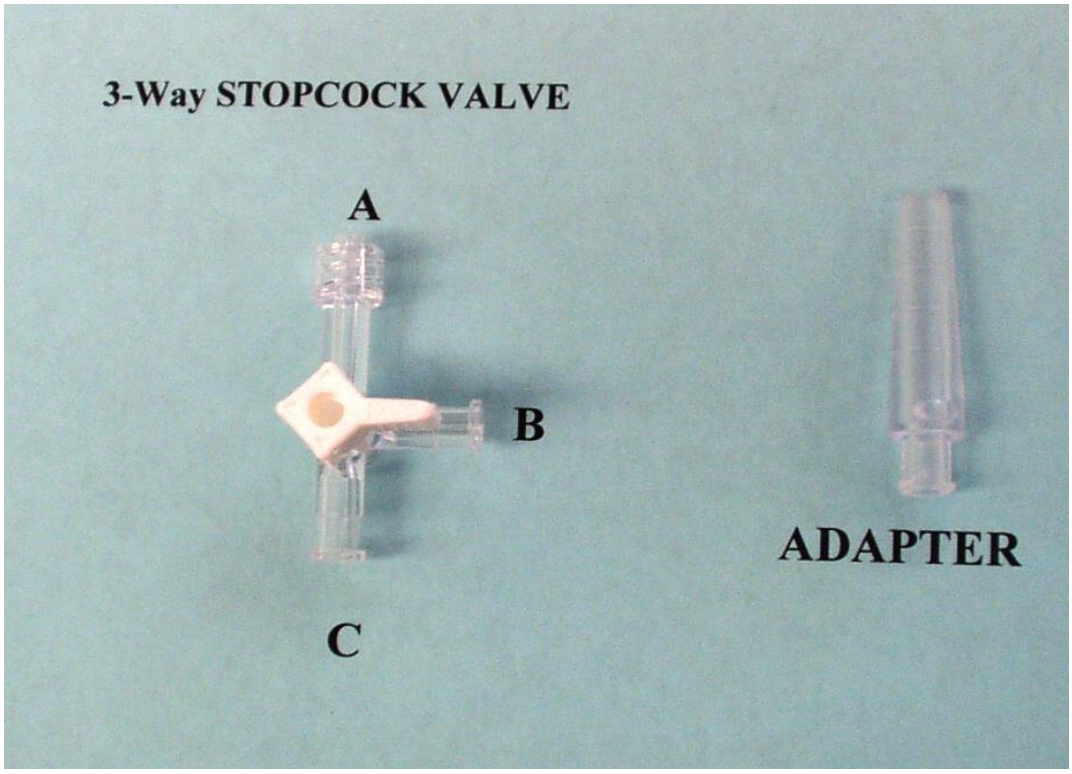
22) Turn the 3-way valve back to the "B" position and depress the plunger rod on the "DOSING SYRINGE" until it stops (see Figure 1).

23) Visually verify that the three (3) rinse steps have removed the entire dose from the "DOSING SYRINGE" and the Feeding Tube is clear. If additional rinse water is needed remove the "RINSE SYRINGE" from the 3-way valve. Draw additional **WARM** water into the syringe. Reconnect the "RINSE SYRINGE" to the 3-way valve and repeat Steps #17 through #22 or until the "DOSING SYRINGE" and Feeding Tube are clear.

24) Disconnect the adapter from the Feeding Tube, secure the port on the Feeding Tube.

25) Dissemble the adapter, 3-way Stop Cock Valve and both the “DOSING” and “RINSE SYRINGES”. Thoroughly rinse all items in clean water and allow them to air dry before returning them to the storage container.

Figure 1: 3-Way Stopcock Valve and Adapter



Syringe Part # 03-377-24 National Scientific Target All Plastic Disposable Syringe 20mL capacity Luer Lock

Adapter Part # 11519 Supplier Qosina

3-Way Stop Cock valve Part # 99729 Supplier Qosina

Figure 2: Assembled Dosing Device