ECOG-ACRIN cancer research group
Reshaping the future of patient care

Operations Office

November 7, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #15 to E2905, *Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia.*

This addendum is in response to the request for Amendment from Dr. Howard Streicher on August 13, 2019.

There are no revisions to the case report forms as a result of this amendment.

Please replace your current copy of the protocol and Informed Consent document (if ICD changed) with this (these) updated version(s). We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

Full IRB review of this addendum is **recommended**, however, ECOG-ACRIN will accept the method of review determined by the standard operating procedures for the IRB of record for this protocol. It is the decision of the local IRB whether or not subjects are to be re-consented.. This addendum must be submitted and reviewed by your IRB within 90 days of receipt of this notice, unless your local IRB has different written SOPs, which must be available at future ECOG-ACRIN audits.

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. If your local IRB has different SOPs, they must be available at future E-A audit.

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The following are ECOG-ACRIN's responses to CTEP's Review of **Amendment #21** of Protocol #**E2905**: "***Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia***" dated October 07, 2019, from the disapproval of Addendum #15 submission to CTEP. Please note that the Principal Investigator's comments appear in bold below:

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	5.4	Please add the following that was not added as part of the updated CAEPR for lenalidomide under the first NOTE: **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. **PI Response: This has been added.**
2.	8	In the first and third NOTE, please rephrase the paragraph to include that those patients who previously received Procrit from the NCI will be switched to the commercially supplied Procrit. Will all vial sizes be used for this study? Recommend moving the applicable vial sizes to 8.2.8. The second NOTE should be deleted as it is now a duplicate of the first NOTE. Under availability, please make the following deletion: Lenalidomide **(NSC# 703813)** ~~and epoetin alfa **(NSC# 628281)**~~ may be requested by the Principal Investigator (or their authorized designees) at each participating institution. The third NOTE should be rephrased to: As of the activation of Addendum#13, all patients will receive epoetin alfa (Procrit) through the commercial channels, or through the ESA Apprise Oncology program. **PI Response: These edits have been applied.**
3.	8	Under availability, please update the weblinks: 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~~ https://ctepcore.nci.nih.gov/OAOP>. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < ~~https://eapps-ctep.nci.nih.gov/iam/~~ https://ctepcore.nci.nih.gov/iam/ > and the maintenance of an "active" account status, ~~and~~ a "current" password, and active person registration status. **PI Response: This has been changed.**

#	Section	Comments
4.	8.2.4 8.2.6	Please update these sections if multiple vial sizes are available. Currently only the multidose vial information is included. **PI Response: We've updated Sections 8.2.4 and 8.2.6 to include information on the multiple vial sizes available.**
5.	8.2.8	In *Availability*, please remove "~~Epoetin alfa (Procrit) will be supplied by the National Cancer Institute as a 20,000 units/mL, multidose, preserved vials for patients registered to this study on or prior to December 31, 2012~~." Add, "Those patients who had previously received Procrit from the NCI will be switched to the commercially supplied Procrit." Please edit. As of Addendum#13, all patients will receive epoetin alfa (Procrit) through the commercial channels, or through the ESA Apprise Oncology program. **PI Response: These edits have been applied.**
6.	ICD – Page 2	In the **Note** under *During the study*, please rephrase the paragraph to say that as of April 2017, epoetin alfa (Procrit) will be supplied through commercial channels, **or** through the ESA Apprise Oncology program. **PI Response: This has been changed.**
7.	ICD – Page 13	Please change the following paragraph: "As of April 2017, epoetin alfa (Procrit) will be supplied through commercial channels, referred to as the ESA APPRISE Oncology program., for all patients. You or your insurance company will have to pay for the epoetin alfa (Procrit)" **to** "As of April 2017, all patient will receive epoetin alfa (Procrit) through commercial channels, or through the ESA Apprise Oncology program. You and/or your insurance will be responsible for the cost of epoetin alfa (Procrit)." **PI Response: This has been changed.**

The following revisions to E2905 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	5.3.3	In second paragraph, first bullet, updated the AE Team at ECOG – ACRIN telephone number.
3.	5.3.3	In sub-section, "Supporting and follow up data" updated the NCI/CTEP fax number in the last sentence.
4.	5.3.4	In second paragraph, first sentence updated ECOG –ACRIN telephone number.
5.	5.4	Updated the CAEPR for Lenalidomide (CC-5013, NSC 703813) to Version 2.8, June 27, 2019.
6.	Appendix XIV	In sub-section, "Additional Required Forms", updated NCI/CTEP fax number.

The following revisions to E2905 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	"What side effects or risks can I expect from being in the study"	Updated the risk list for Lenalidomide (CC-5013, NSC 703813) to Version 2.8, June 27, 2019.

If you have any questions regarding this addendum, please contact aagu@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to E2905 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director, Protocol Development

Enclosure

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ECOG-ACRIN cancer research group
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E2905

Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

STUDY CHAIR: Alan List, M.D.
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CALGB CO-CHAIR: Andrew Artz, M.D.
SWOG CO-CHAIR: Charles A. Schiffer, M.D.

Version Date: November 7, 2019
NCI Update Date: August 18, 2010

	STUDY PARTICIPANTS	***ACTIVATION DATE***
Rev. 6/14	**NRG** / NRG Oncology Foundation, Inc	January 29, 2009
	SWOG / SWOG	
	ALLIANCE / Alliance for Clinical Trials in Oncology	Update #1 – 1/09 – Incorporated Prior to Activation
Rev. 10/14		Addendum #1 – 10/09
		Addendum #2 – 1/10
		Addendum #3 – 3/10
Rev. 6/11		Update #2 – 8/10
		Addendum #4 – 6/11
		Addendum #5 – 7/11
		Addendum #6 – 10/11
		Addendum #7 – 6/13
		Addendum #8 –11/13
		Addendum #9 – 6/14
		Addendum #10 – 10/14
		Addendum #11 – 4/15
		Addendum #12 – 7/16
		Addendum #13 – 5/17
		Addendum #14
		Addendum #15

Lenalidomide (Revlimid®) (NSC #703813) IND #70116
Epoetin Alfa (Procrit®) (NSC #628281)

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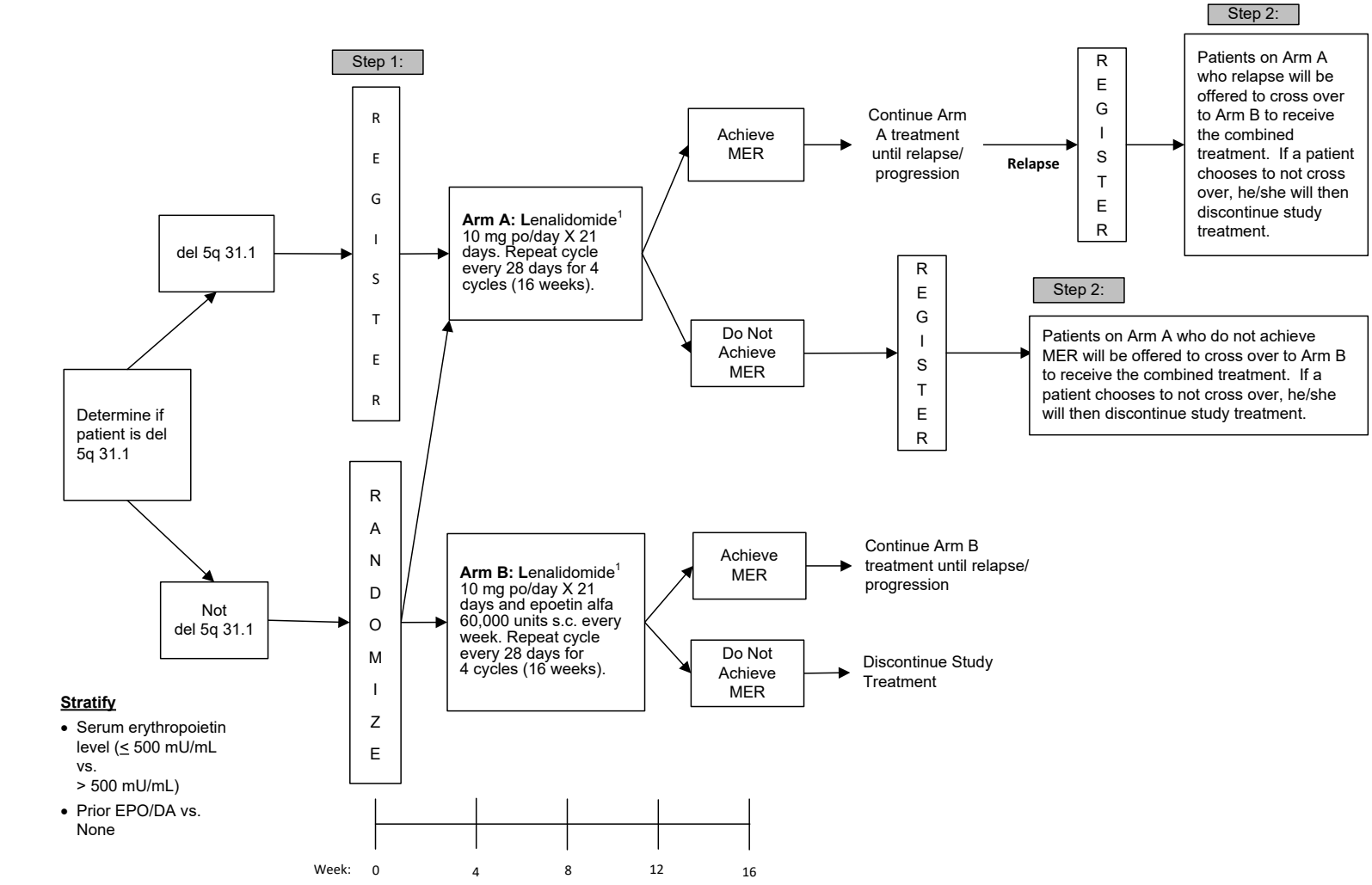
Rev. 6/11, 6/14

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	ECOG-ACRIN Operations Office - Boston, FSTRF 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990 Data should be sent via postal mail. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Rev. 6/11 **Accrual Goal = 252 patients**
MER = Major Erythroid Response
NOTE: 1 cycle = 28 days

1. Patients with a pretreatment platelet count of 50,000-99,000/mcL or an ANC of 500-999/mcL will receive a lenalidomide dose of 5 mg/day x 21 days.

1. Introduction

1.1 Hypothesis

Combined treatment with epoetin alfa and lenalidomide potentiates erythroid response in patients that have failed prior treatment with rhu-erythropoietin or epoetin alfa or have low probability of response to erythropoietic growth factors.

1.2 Rationale

Ineffective erythropoiesis remains the hallmark of myelodysplastic syndromes (MDS) for which few treatments offer sustained erythropoietic improvement (1). Treatment with rhu-erythropoietin either alone or in combination with myeloid growth factors ameliorates anemia in some patients. However, for those patients with frequent red blood cell (RBC) transfusion needs (> 2 units/month) or elevated endogenous erythropoietin levels (erythropoietin > 500 mU/mL), cytokine therapy is generally ineffective (2-4). Lenalidomide (REVLIMID®) is an oral 4-amino glutarimide derivative of thalidomide that lacks the neurological toxicities of the parent compound. (5-8). Lenalidomide is a potent modulator of ligand-induced cellular response with biological effects that range from potentiation of antigen-initiated immune response, to modulation of integrin affinity and suppression of trophic response to angiogenic molecules. In AML cell lines, lenalidomide suppresses VEGF transcription, whereas in normal and malignant erythroid progenitors, lenalidomide potentiates clonogenic response to rhu-erythropoietin. In the UT7 erythroid progenitor cell line and in MDS erythroid progenitors, lenalidomide potentiates clonogenic response to rhu-erythropoietin by augmenting ligand-induced activation of STAT5 (9), indicating that erythropoietic response to lenalidomide is erythropoietin-dependent.

In a safety and efficacy study (MDS-001) investigating erythroid response to lenalidomide monotherapy in 43 patients with MDS, lenalidomide yielded a high frequency of major erythroid response (MER) in patients that had either failed prior treatment with erythropoietin or had high endogenous levels and high transfusion burden (6). Patients received treatment with one of three lenalidomide dose schedules, 25 or 10 mg daily, or 10 mg/day x 21 days every 4 weeks. Neutropenia (67%) and thrombocytopenia (57%) > grade 3 NCI-CTC version 2.0 were dose limiting, necessitating treatment interruption and dose-reduction in 25 (61%) patients. Other adverse effects were infrequent and of mild to moderate severity including pruritus, fatigue, diarrhea, edema, thyroid dysfunction and joint discomfort. Among the 36 patients completing more than one cycle of treatment, 24 (67%) experienced an erythroid response according to International Working Group (IWG) criteria (10). MER defined by sustained transfusion-independence (> 8 weeks) or a rise in hemoglobin >2 g/dl was achieved in 21 patients and 3 patients experienced a >50% reduction in red blood cell (RBC) transfusions. Response rate was highest among evaluable patients with a chromosome 5q31.1 deletion (91%) compared to those with a normal karyotype (68%) or other chromosome abnormality (17%) [P=0.009], and response rate was higher in patients with lower (Low-/Intermediate-1) International Prognostic Scoring System (IPSS) risk categories (72% vs. 25%) [P=0.098] (11). Eleven of 17 (65%) patients with karyotypic abnormalities had a 50% or greater reduction in abnormal metaphases, including ten (57%) complete cytogenetic remissions. After a median follow-up of 109 weeks in November

2004, median duration of transfusion-independence had not been reached (81+; range, 19 to > 128 weeks) with a median sustained hemoglobin (Hgb) of 13.4 g/dL (range, 11.5-15.8 g/dL) and median Hgb rise of 5.6 g/dL. The results of this study indicate that lenalidomide has significant and sustained erythropoietic and cytogenetic remitting activity in patients with Low/Intermediate-1 IPSS risk MDS that have failed or are unlikely to benefit from conventional cytokine therapy.

Two phase II multicenter trials were completed in the past year, evaluating the frequency of MER to lenalidomide in patients with transfusion-dependent Low/Int-1 risk MDS with (MDS-003; N=148) or without a chromosome 5q31.1 deletion (MDS-002; N=215). Intent-to-treat analysis of the data confirm the high response rate in patients with del 5q31.1 (MER 66%, MER + Minor erythroid response 75%, cytogenetic response 70%) compared to a MER rate of 27% and Minor + MER rate of 44% in the MDS-002 results (7,8). Grade 3 or greater neutropenia or thrombocytopenia was more frequent in the 5q- study (approximately 50% vs. 25%) and was the principal reason for treatment interruption and dose-reduction.

A pilot study tested the potential benefit of combination treatment (CT) with epoetin alfa and lenalidomide in 40 Low/INT-1 MDS patients who had failed primary rhu-erythropoietin treatment (12). Patients received 16 weeks of treatment with lenalidomide monotherapy (MT), followed by the addition of subcutaneous epoetin alfa at a dose of 40,000 units/week for 8 weeks in those patients who failed to achieve a MER or suboptimal response to MT. Overall, 36% of patients achieved an erythroid response to lenalidomide MT, whereas among 18 MT failures who proceeded to CT, 5 (28%) achieved an erythroid response. CT was well tolerated with no thromboembolic events reported after up to 18 months of CT. This pilot study indicates that lenalidomide may restore rhu-erythropoietin responsiveness in patients who failed primary cytokine therapy. Moreover, the addition of epoetin alfa to lenalidomide may increase the rate of erythroid response compared to lenalidomide MT alone.

1.3 Toxicity Profile

Clinical trials performed to date indicate that lenalidomide has encouraging erythropoietic activity in lower risk MDS with poor rhu-erythropoietin response profile. Although response rate is moderate in patients with non-del 5q31 karyotypes, erythropoietic activity may be improved by the addition of epoetin alfa, given the erythropoietin-dependence of lenalidomide action. Erythropoietic growth factors and immunomodulatory drugs are recognized to variably increase thrombotic potential. Indeed, when combined with dexamethasone or other antineoplastics, thrombo-embolic complications have been reported in up to 10-15% of non-prophylaxed patients with multiple myeloma (13,14). The thrombotic potential of lenalidomide appears much lower than thalidomide despite greater pharmacologic activity. In two recently completed phase III trials involving 692 patients with relapsed multiple myeloma, [MM-009, and MM-010] thrombotic events were reported in 2.9% of patients assigned to treatment with dexamethasone and placebo, compared to 11.9 and 4.7% of patients in the lenalidomide and dexamethasone arms (15,16). Thrombo-embolic complications were not observed in patients receiving aspirin prophylaxis. Thrombo-embolic events were reported in 15 (3.4%) of the 408 MDS patients treated on the MDS-001, -002, and –003 trials. Among 873 patients with non-myeloid malignancy enrolled in 7 darbepoetin alfa (DA) registrational trials, thrombo-embolic events were reported in 7% of patients treated with DA, compared to 5.2% of patients

receiving epoetin alfa and 4.1% of placebo (17-20). A multivariate analysis identified DA treatment, prior TE history and poor ECOG performance status to be significant predictors of thrombo-embolic (ref. Data on File, Amgen 003). For this reason, candidates with a history of thrombo-embolic events within 3 years of registration will be excluded from study participation. Although epoetin alfa appeared less thrombogenic, thrombo-embolic events will be monitored in this study with an interim safety analysis of event frequency planned after 30 patients have completed 16 weeks of combined therapy on both arms of the study. Since platelet dysfunction is common in MDS and thrombocytopenia is a frequent adverse effect of CC-5013, aspirin prophylaxis will not be applied to this study.

1.4 Pharmacologic Effects of Lenalidomide in MDS

The precise target of lenalidomide that is responsible for its erythroid and cytogenetic remitting activity is under investigation. Blinded morphologic review of the bone marrow (BM) aspirates and biopsies from study participants suggests that in select patient populations such as those harboring a chromosome 5q31.1 deletion, lenalidomide may extinguish the dominant MDS clone and possibly influence autologous immune response within the BM microenvironment. Megakaryocytic dysplasia resolved after lenalidomide treatment in 64% of evaluable patients in the MDS-001 study and corresponded to hematologic response (10), and complete pathologic responses were reported in blinded central review in 36% of patients treated in the MDS-003 trial. Lymphoid aggregates composed of an admixture of B- and T-lymphocytes, emerged in 36% of patients in the MDS-001 trial, suggesting potentiation of autologous immunity.

Lenalidomide has broad pharmacologic properties that may contribute to its hematologic activity. Lenalidomide suppresses tumor necrosis factor-alpha (TNFα) generation (14), however, investigations involving selective TNFα antagonists have shown only modest activity both *in vitro* and in clinical trials. Similarly, BM plasma concentrations of TNFα were not significantly changed after study treatment in responding patients in the lenalidomide trial. Lenalidomide enhances cell-mediated immune response by potentiating interleukin-2 and interferon-γ production and expanding cytolytic T- and NK-cell populations in experimental models. The appearance of mixed lineage lymphoid aggregates in the trephine biopsies of responders in the MDS-001 study raises consideration that lenalidomide potentiates autologous medullary immune response. Investigations reported by Noonan et al. have shown that in BM-based malignancies such as multiple myeloma, cytolytic T-cell response to autologous tumor is more than seven-fold greater in medullary lymphocytes compared to those derived from the peripheral blood (14).

Our preclinical investigations indicate that the hematopoietic effects of lenalidomide in MDS are karyotype-dependent, with direct cytotoxicity to and suppression of clones bearing the chromosome 5q31 deletion, and erythropoietin-dependent , sensitization of non-deletion 5q erythroid progenitors to rhu-erythropoietin by potentiating ligand-induced activation of STAT5 (List et al, unpublished data). Using the UT-7 erythroid progenitor cell line, lenalidomide pretreatment yields supra-additive clonogenic response to rhu-erythropoietin, whereas in the absence of the cytokine, lenalidomide has minimal effect on colony-forming capacity. Similar effects were observed on erythroid burst

formation in MDS patient specimens. Upon ligand engagement, erythropoietin receptor signaling is mediated in part through constitutively associated Janus kinase-2 (Jak2), which phosphorylates the receptor cytoplasmic tail to permit recruitment and phosphorylation of the STAT5 transcription factor. Phosphorylation of STAT5 allows its homodimerization and translocation to the nucleus, where it activates genes involved in erythroid proliferation and survival. In the UT7 cell line, lenalidomide potentiates erythropoietin-induced STAT5 phosphorylation associated with an increase in STAT5 DNA binding by relieving inhibition of Jak and lyn kinase activity. Similar findings were detected in CD71 Bright erythroid precursors by flow cytometry in primary MDS bone marrow specimens.These findings indicate that lenalidomide's ability to modulate ligand-induced response extends to erythropoietin-R activation, and suggests that combined treatment with rhu-erythropoietin may potentiate erythropoietic response in those patients experiencing sub-optimal benefit from lenalidomide monotherapy.

Serum erythropoietin concentrations were prospectively monitored in an on-going pharmacokinetic study of lenalidomide in 21 anemic patients with MDS (Unpublished data – List AF). Prior to study treatment, sEPO concentration was elevated >500 mU/ml in 12 (57%) patients, in 3 patients sEPO was <100 mU/ml, and in 6 patient - 100-500 mU/ml. During lenalidomide treatment, sEPO concentration declined 41% to 94% in 6 of the 12 non-del 5q patients with intermediate or high sEPO levels pre-study despite persistence of anemia. No patient with low sEPO pre-study (<100 mU/ml) experienced a rise in serum concentration during lenalidomide treatment. These data, if confirmed, indicate that sup-optimal endogenous EPO concentration may limit erythropoietic response to lenalidomide monotherapy in approximately 60% of patients, and thereby suggests that combined therapy with a recombinant erythropoietin may improve erythroid response.

2. Objectives

2.1 Primary Objective

To compare the rate of major erythroid response (MER) between lenalidomide monotherapy and combined treatment of lenalidomide and epoetin alfa in erythropoietin non-responsive Low/Int-1 risk MDS patients or erythropoietin-treatment naïve patients with low probability of erythropoietin benefit.

2.2 Secondary Objectives

2.2.1 To compare the time to MER by treatment assignment.

2.2.2 To evaluate the duration of MER by treatment assignment.

2.2.3 To estimate the frequency of MER to salvage combination therapy in patients who fail to experience a MER with lenalidomide monotherapy.

2.2.4 To evaluate and compare the frequency of minor erythroid response by treatment assignment.

2.2.5 To investigate the mechanism and target of lenalidomide action in patients with chromosome 5q31.1 deletion.

2.2.6 To evaluate the frequency of cytogenetic response and progression, and the relation between cytogenetic pattern and erythroid response.

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2.2.7 To evaluate the frequency of bone marrow response (CR+PR).

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2.2.8 To evaluate the relationship between erythroid response and laboratory correlates outlined below:

2.2.8.1 Pretreatment and onstudy endogenous erythropoietin level (Arm A);

2.2.8.2 To evaluate the effect of CD45 isoform profile on lenalidomide enhancement of erythropoietin-induced STAT5 phosphorylation in $CD71^{Hi}$ erythroid precursors and the relationship to erythroid response.

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2.2.8.3 To characterize molecular targets relevant to lenalidomide cytotoxicity in del5q31.1 cells.

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2.2.8.4 To evaluate the frequency of cryptic chromosome 5q31.1 deletions in patients with non-del5q31.1 MDS by array-based genomic scan, and to determine the relationship to hematologic response.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

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In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. Screening is considered to start the date that the consent is signed (Day Zero) up to 56 days later. Subjects can be registered anytime within the 56 days as long as they meet the below criteria.

ECOG-ACRIN Patient No. _____

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

M.D. Signature _____ Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

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NOTE: Results of the bone marrow biopsy and aspirate as well as Cytogenetics are mandatory to register subjects onto study, which are indispensable to determine IPSS category needed for eligibility (see Section 3.1.1.3). Please note that it is not necessary to wait for the week 16, week 32, or week bone marrow and cytogenetic results prior to starting the next cycle unless deemed necessary by the treating physician. One example of this exception can include if the subject shows signs of progression, such as increased peripheral blood blast percentage. At that juncture, the treating physician may prefer to await the results prior to starting a new cycle. If a cycle is started, and based on the bone marrow results it is felt by the treating physician that the subject should not continue on treatment, please be sure to note this information on the case report forms at end of treatment

_____ 3.1.1 **Step 1: Randomization to Arm A or Arm B**

_____ 3.1.1.1 Age ≥ 18 years.

_____ 3.1.1.2 Patient must have documented diagnosis of MDS lasting at least three months (MDS duration ≥ 3 months) according to World Health Organization (WHO) criteria (see Appendix) or non-proliferative chronic myelomonocytic leukemia (CMML) (WBC < 12,000/mcL)).

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_____ 3.1.1.3 Patient must have International Prognostic Scoring System (IPSS) categories of Low- or Intermediate-1-risk disease (see Section 6). Patients must have IPSS score determined by cytogenetic analysis prior to randomization.

Patients must have cytogenetic analysis done (to calculate IPSS). If the current bone marrow biopsy is a dry tap, patients with cytogenetic failure and < 10% marrow blasts will be eligible. Subjects with cytogenetic failure must have previous cytogenetic results (FISH is not a substitute) within the last 6 months post last type of MDS treatment (in this case, not referring to growth factors as type of MDS treatment).
IPSS score: _____Date of test: _____

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_____ 3.1.1.4 Patients must have symptomatic anemia untransfused with hemoglobin < 9.5 g/dL
≤ 8 weeks prior to randomization or with RBC transfusion-dependence (i.e., ≥ 2 units/month) confirmed for ≤ 8 weeks before randomization.

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NOTE: For non-transfusion dependent patients (i.e., receiving < 2 units/4 weeks x 8 weeks pre-study) who receive periodic transfusions, the mean 8 week pre-transfusion hemoglobin should be used to determine protocol eligibility and response reference.

For non-transfusion dependent patients, a minimum of 2 pre-transfusion or un-transfused hemoglobin values are <u>required.</u>

3.1.1.4.1 Untransfused hemoglobin: _____

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1st:_____ Date of test:_____

2nd:_____ Date of test:_____

3.1.1.4.2 RBC transfusion-dependence (i.e. ≥ 2 units/month)

Date of onset of dependence: _____

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_____ 3.1.1.5 **NOTE:** Applies only for patients without the deletion 5q 31.1. Patients must have failed treatment with an erythropoietic growth factor, or have a low probability of response to rhu-erythropoietin. Patients with Low Probability of Response to rhu-erythropoietin or prior erythropoietin failures are defined as follows:

3.1.1.5.1 *Prior erythropoietin failure* – requires a minimum trial of ≥ 40,000 Units epoetin alfa/week x 8 weeks or equivalent dose of darbepoetin alfa for 8 weeks with failure to achieve transfusion independence in dependent patients or a failure to achieve a ≥ 2g rise in hemoglobin sustained for ≥ 4 weeks in non-transfusion dependent patients.

3.1.1.5.2 *Low erythropoietin Response Profile* – rhu-erythropoietin and epoetin alfa-naïve patients receiving ≥ 2U pRBC/month for a minimum of 8 weeks, and serum erythropoietin > 500mU/mL in the 8 weeks prior to randomization for a hemoglobin < 9.5 g/dL.

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_____ 3.1.1.6 Patients must be off all non-transfusion therapy for MDS for 28 days prior to initiation of study treatment, including all types of growth factors. Patients may receive hydrocortisone prophylactically to prevent transfusion reactions.

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_____ 3.1.1.7 Patients must have a serum erythropoietin level documented before randomization and ≤ 56 days before Day 1 of study treatment.

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NOTE: Hemoglobin must be < 9.5 g/dL at time that serum erythropoietin is drawn.

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EPO:_____ Date of test:_____
HGB:_____ Date of test:_____

_____ 3.1.1.8 Patients must not have documented iron deficiency. All patients must have documented marrow iron stores. If marrow iron stain is not available, the transferrin saturation must be > 20% or a serum ferritin > 100 ng/mL.

Bone marrow iron stain available? _____(Yes or No)

If no: Transferrin saturation:_____OR Serum ferritin: _____

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_____ 3.1.1.9 Women must not be pregnant or breastfeeding:

Females of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide. A female of childbearing potential(FCBP) is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 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. FCBP must also agree to ongoing pregnancy testing.

Female of childbearing potential? _____ (Yes or No)

Date of first blood test or urine pregnancy test: _____

Date of second blood test or urine pregnancy test: _____

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_____ 3.1.1.10 Effective contraception must be used by patients participating in lenalidomide therapy, and all patients must agree to counseling by a trained counselor every 28 days

about pregnancy precautions and risks of fetal exposure. (See Appendix X: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, and also Appendix XI: Lenalidomide Education and Counseling Guidance Document):

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Females of childbearing potential (FCBP) 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 starting lenalidomide, during lenalidomide therapy, during dose interruptions, and for at least 28 days following discontinuation of lenalidomide therapy. Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed.

Males receiving lenalidomide must agree to use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy

_____ 3.1.1.11 Patients must not have prior therapy with lenalidomide.

_____ 3.1.1.12 Patients must not have a diagnosis of uncontrolled seizure or uncontrolled hypertension

_____ 3.1.1.13 Patients must not have proliferative (WBC ≥12,000/mcL) chronic myelomonocytic leukemia (CMML). WBC must be < 12,000/mcL. See Section 3.1.2.

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1st WBC: _____ Date of test: _____

2nd WBC: _____ Date of test:_____

_____3.1.1.14 Patients must not have MDS secondary to treatment with radiotherapy, chemotherapy, and/or immunotherapy for malignant or autoimmune diseases.

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_____3.1.1.15 Patients must meet the following criteria (documented on 2 occasions within 56 days prior to randomization; the 2 occasions must be separated by at least 7 days). At least one of the two CBC/Diffs and chemistry testing (including liver function tests) must be done within 7 days of registration.

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NOTE: Hematology and chemistry testing can be utilized within 56 days prior to randomization for Sections 3.1.15, 1 – 5.

_____3.1.1.15.1 Platelet count ≥ 50,000/mcL (50 x 10^9/L) without platelet transfusion.

1st:_____ Date of test:_____
2nd:_____ Date of test:_____

_____ 3.1.1.15.2 Absolute neutrophil count (ANC) ≥ 500 cells/mcL (0.5 x 10^9/L). Hence ANC must be

≥ 500/mcL without myeloid growth factor support.

1st:_____ Date of test:_____

2nd:_____ Date of test:_____

Serum creatinine ≤ 1.5x upper limit of normal (ULN)

1st:_____ Date of test:_____

2nd:_____ Date of test:_____

_____ 3.1.1.15.3 Serum SGOT/AST or SGPT/ALT ≤ 2.0 x ULN

SGOT/AST 1st:_____ Date of test:_____

2nd:_____ Date of test:_____

SGPT/ALT 1st:_____ Date of test:_____

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2nd:_____ Date of test:_____

_____ 3.1.1.15.4 Serum total bilirubin < 3.0 mg/dL

1st:_____ Date of test:_____

2nd:_____ Date of test:_____

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_____ 3.1.1.16 Prior thalidomide therapy is allowed, however, patients must not have prior ≥ grade-3 allergic reactions to thalidomide.

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_____ 3.1.1.17 Patients must not have prior history of desquamating rash from thalidomide at time of study entry.

_____ 3.1.1.18 Patients must not have clinically significant anemia resulting from iron, B_{12} or folate deficiencies, autoimmune or hereditary hemolysis, or gastrointestinal bleeding.

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_____ 3.1.1.19 Patients must not have used cytotoxic chemotherapeutic agents or experimental agents (agents that are not commercially available) for the treatment of MDS within 8 weeks of randomization.

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_____ 3.1.1.20 Patients must not have prior history of malignancy other than MDS (except basal cell or squamous skin cell carcinoma or carcinoma in situ of the cervix or breast) unless the subject has been confirmed free of disease for ≥ 3 years.

_____ 3.1.1.21 Patients must not have any serious medical condition or any other unstable medical co-morbidity, or psychiatric illness that will prevent the subject from signing the informed consent form or will place the subject at unacceptable risk if he/she participates in the study.

_____ 3.1.1.22 Patients must not have a history of thrombo-embolic events within 3 years prior to study randomization.

_____ 3.1.1.23 Patients must not have known HIV-1 seropositivity because HIV can be an alternate cause of anemia.

_____ 3.1.1.24 Patients must not have a known allergic reaction to epoetin alfa (Procrit®) or human serum albumin.

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_____ 3.1.1.25 [Deleted in Addendum #1]

3.1.2 **Crossover Registration from Arm A (Lenalidomide Alone) to Arm B (Lenalidomide and Epoetin Alfa)**

_____ 3.1.2.1 Patients must have completed 16 weeks of monotherapy with lenalidomide.

_____ 3.1.2.2 Patients must show failure to achieve MER (major erythroid response) or have achieved MER but relapsed on Arm A.

_____ 3.1.2.3 Patients must not have a limiting unresolved grade 3 or greater toxicity from lenalidomide monotherapy or drug intolerance preventing continuation of lenalidomide treatment.

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4. Registration Procedures

CTEP Investigator Registration Procedures

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

Registration requires the submission of:

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

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

CTEP Associate Registration Procedures / CTEP-IAM Account

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

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

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

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

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

CTSU Registration Procedures

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

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering

credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

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Downloading Site Registration Documents

Site registration forms may be downloaded from the **E2905** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E2905**
- Click on the Site Registration Documents link

Rev. 4/15

Requirements for E2905 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents

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

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

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.

2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
Or
B. HHS 310 Form.
Or
C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**

- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

Checking Your Site's Registration Status

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

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

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within three working days after registration.

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Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

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

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

Prior to accessing OPEN site staff should verify the following:

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

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

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Step 1: Randomization

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4.1.1 Protocol Number

4.1.1.1 Investigator Identification

4.1.1.1.1 Institution and affiliate name (Institution CTEP ID)

4.1.1.1.2 Investigator's name (NCI number)

4.1.1.1.3 Cooperative Group Credit

4.1.1.1.4 Credit Investigator

4.1.1.1.5 Protocol specific contact information

4.1.2 Patient Identification

4.1.2.1 Patient's initials (first and last)

4.1.2.2 Patient's Hospital ID and/or Social Security number

4.1.2.3 Patient demographics

4.1.2.3.1 Gender

4.1.2.3.2 Birth date

4.1.2.3.3 Race

4.1.2.3.4 Ethnicity

4.1.2.3.5 Nine-digit ZIP code

4.1.2.3.6 Method of payment

4.1.2.3.7 Country of residence

4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.Patient Identification

4.3 Stratification Factors

4.3.1 Serum erythropoietin level (≤ 500 mU/mL vs. > 500 mU/mL)

4.3.2 Prior Erythropoietic Growth Factor (Prior erythropoietin/DA vs. None)

4.3.3 All patients with del 5q31.1 karyotype will be assigned to treatment with lenalidomide monotherapy (Arm A).

4.4 Additional Requirements

4.4.1 Patients must provide a signed and dated, written informed consent form.

4.4.2 Karyotypes (Section 11.1) and pathologic materials (Section 10) must be submitted for review.

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Rev. 4/15

[Note deleted in Addendum #1]

4.4.3 Bone marrow and blood should be submitted for correlative studies as outlined in Sections 10.2.2.2 and 11.2.

4.4.4 Baseline materials submitted per E2905 Forms Packet.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E2905 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.5.

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Rev, 4/15

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

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Rev.4/15

4.5 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E2905 Forms Packet. Document the reason for not starting protocol treatment on one of the baseline forms. Also report the date and type of the first non-protocol treatment that the patient receives.

4.6 **Step 2: Cross-Over Registration**

4.6.1 Subjects who fail to achieve a MER or who achieve a MER but relapse on Arm A will be offered combined treatment on Arm B in the absence of unresolved grade 3 or greater toxicity or drug intolerance.

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4.6.2 Protocol Number

4.6.2.1 Investigator Identification

4.6.2.1.1 Institution and affiliate name (Institution CTEP ID)

4.6.2.1.2 Investigator's name (NCI number)

4.6.2.1.3 Cooperative Group Credit

4.6.2.1.4 Credit Investigator

4.6.2.1.5 Protocol specific contact information

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4.6.3 Patient Identification

4.6.3.1 Patient's initials (first and last)

4.6.3.2 Patient's Hospital ID and/or Social Security number

4.6.3.3 Patient demographics

4.6.3.3.1 Gender

4.6.3.3.2 Birth date

4.6.3.3.3 Race

4.6.3.3.4 Ethnicity

4.6.3.3.5 Nine-digit ZIP code

4.6.3.3.6 Method of payment

4.6.3.3.7 Country of residence

4.6.4 Additional Requirements

4.6.4.1 Karyotypes (Section 11.1) and pathologic materials (Section 10) must be submitted for review.

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[Note deleted in Addendum #1]

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4.6.4.2 Bone marrow and blood are to be submitted for correlative studies as outlined in Sections 10.2.2.2 and 11.2.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E2905 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.5.

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NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

4.7 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.8 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E2905 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

5. Treatment Plan

NOTE: 1 cycle = 28 days

NOTE: The use of steroids to prevent transfusion reactions must be documented on the E2905 treatment form.

5.1 Administration Schedule

5.1.1 Arm A (Lenalidomide Monotherapy)

Lenalidomide 10 mg po/day on days 1-21 followed by 7 days of no therapy. Repeat cycles every 28 days for a total of 4 cycles. (Refer to Section 5.1.3 for further treatment).

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Patients with a pretreatment platelet count of 50,000-99,000/mcL or an ANC of 500-999/mcL will receive a lenalidomide dose of 5 mg po/day on days 1-21.

5.1.2 Arm B (Lenalidomide + Epoetin Alfa)

Lenalidomide 10 mg po/day on days 1-21 followed by 7 days of no therapy and epoetin alfa 60,000 units subcutaneously (s.c.) every week. Repeat cycles every 28 days for a total of 4 cycles. (Refer to Section 5.1.3 for further treatment).

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Blood pressure and heart rate measurements will be assessed prior to each dose of epoetin alfa.

Patients with a pretreatment platelet count of 50,000-99,000/mcL or an ANC of 500-999/mcL will receive a lenalidomide dose of 5 mg po/day on days 1-21.

5.1.3

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Patients on Arm A or Arm B who achieve a Major Erythroid Response (MER) according to modified International Working Group (IWG) criteria described in Section 6 may continue the assigned treatment in the absence of limiting toxicity or disease progression.

Rev. 10/09

Patients on Arm A who do not achieve a MER will have the option to cross over to Arm B (see Section 5.2). If they choose not to cross over, they will then discontinue protocol treatment.

Patients on Arm B who do not achieve a MER will discontinue treatment.

If the treating MD and/or PI feels that the subject is receiving benefit from study (in the way of decreasing RBC transfusion frequency and/or HGB increase outside RBC transfusion influence) but does not meet MER, subjects may remain on treatment if they have achieved a **minor** erythroid response until demonstrating signs of lack of continued response (example: increase in RBC transfusion dependence, or decreased HGB on consistent basis outside of the influence of RBC transfusions). See Section 6.1.2.3 for reference. If there are questions regarding this item, please have the treating MD and/or PI email Dr. List for further discussion on a case by case basis.

Rev. 4/15

Treatment with white cell growth factors is allowed for the management of neutropenia at the discretion of the treating investigator.

5.2 Cross-Over Treatment

Patients who fail to achieve a MER on Arm A AND patients on Arm A who relapse will be offered to cross over to Arm B to receive combined treatment in the absence of limiting toxicity precluding continuation of lenalidomide treatment. The dose for Arm B crossover is the dose of lenalidomide that would otherwise be implemented for continuation of therapy according to Section 5.5. If a patient does not choose to cross over, he/she will then discontinue study treatment.

Response to cross-over treatment will be assessed after 16 weeks (4 cycles) of combined therapy (i.e., study week 32). Arm A patients that cross over to Arm B that do not achieve a MER after 16 weeks of combined treatment (i.e. week 32) will discontinue protocol treatment.

Rev. 6/14

5.3 Adverse Event Reporting Requirements

5.3.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E2905 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.3.2 Determination of reporting requirements

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

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study arm includes both investigational and commercial agents, the following rules apply.

- ***Concurrent administration:*** **When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.**

Steps to determine if an adverse event is to be reported in an expedited manner:

Rev. 8/10

Step 1: *Identify the type of event:* The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until September 30, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning October 1, 2010.

Rev. Add14

UPDATE: CTEP has released CTCAE Version 5.0 and effective April 1, 2018, all expedited adverse event reporting done through CTEP-AERS will utilize version 5 of the CTCAE. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Step 2: *Grade the event using the NCI CTCAE* v 5.0.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is **NOT** listed in:

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- **Arm A** – the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER)

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- **Arm B** – the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER) for the investigational agent or package insert/protocol for the commercial agent.

Rev. 6/13

NOTE: The NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) is included in Section 5.4 of the protocol. FOR THIS PROTOCOL, events listed in the SPEER should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER. The SPEER is presented in the last column of the CAEPR and identified with bold and italicized text.

Step 5: *Review the "Additional instructions, requirements, and exceptions for protocol E2905" table in Section 5.3.6 for protocol*

and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the NCI AdEERS Help Desk: 301-897-7497.

Rev. 6/13

5.3.3 Reporting methods

Rev. Add15

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the NCI (301-897-7497)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 897-7404) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

Rev. Add15

5.3.4 When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Section 5.3.6). Please complete a 24-Hour Notification Report via the NCI CTEP-AERS website (http://ctep.cancer.gov) within 24 hours of learning of the event. The full CTEP-AERS report must be completed and submitted via CTEP-AERS within 5 calendar days.

If the CTEP-AERS system is down, a 24-hour notification call must be made to ECOG-ACRIN (857-504-2900) and to NCI (301-897-7497). Once the system is restored, a 24-hour Notification Report must be entered into the CTEP-AERS system by the original submitter of the report at the site.

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section 5.3.6.

NOTE: Adverse events that meet the reporting requirements in Section 5.3.6 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited

adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Section 5.3.6 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.3.5 Other recipients of adverse event reports

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

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

5.3.6 Expedited reporting for investigational agents

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Investigational Agent Lenalidomide in this Study (Arm A and B) OR Within 30 Days of the Last Dose of Any Protocol Treatment.

Attribution	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				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 <u>greater</u> 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 a 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. See NOTE below regarding how to report a death due to progressive disease.

Please see additional information below under section entitled “Additional instructions, requirements, and exceptions for protocol E2905”

March 2005

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

Rev. Add14 **NOTE:** A death due to progressive disease should be reported as a Grade 5 “Disease progression” under the System Organ Class (SOC) “General disorder and administration site conditions”. Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be.

Rev. Add14 **NOTE:** A death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 10 calendar days of learning of the event.

- Expedited AE reporting timelines:
  - **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 disability/incapacity, congenital anomaly, or birth defect** must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

  * Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via CTEP-AERS.

Additional instructions, requirements and exceptions for protocol E2905

1. Additional Instructions:

- With respect to determining the specific day by which the event must be reported, the day the reporter learns of the adverse event constitutes "Day 0"
- For grade 2 and 3 unexpected events, CTEP-AERS reporting is only required if the event is related to the investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

  NOTE: For grade 3 unexpected events with hospitalization lasting ≥ 24 hours (or prolonged hospitalization), an CTEP-AERS report is required even if the event is unrelated to the investigational agent(s).
- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

2. ECOG-ACRIN and Protocol Specific expedited reporting requirements:

The adverse events listed below also require expedited reporting for this trial:

ECOG-ACRIN specific expedited reporting requirements:

- **Hospitalizations:** Any grade 1 or 2 adverse event which precipitates a hospitalization lasting ≥ 24 hours (or prolongs hospitalization) must be reported via CTEP-AERS within 10 calendar days of learning of the event regardless of the attribution and designation as expected or unexpected.

Protocol specific expedited reporting requirements:

- ***All grade 3 expected events*** with an attribution of definite, probable, or possible, regardless of whether the patient is hospitalized, must be reported via CTEP-AERS within 10 calendar days or learning of the event.
- ***All ≥ grade 3 thrombo-embolic events***, regardless of the attribution and designation as expected or unexpected and whether the patient is hospitalized, must be reported via CTEP-AERS within 10 calendar days of learning of the event.

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- **Pregnancies**

  Pregnancies and suspected pregnancies (including a positive/inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on Lenalidomide, or within 28 days of the subject's last dose of Lenalidomide, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.** Please refer to Appendix XIV for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

Rev. 11/13

All occurrences of primary red cell aplasia (PRCA) or a report of anti-erythropoietin antibodies must be reported via CTEP-AERS within 10 calendar days of learning of the event. Report under 'Blood/Bone Marrow - Bone Marrow Cellularity' as grade 4 events.

3. Protocol specific expedited reporting exceptions:

For study arms A and B, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

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- Grade 4 expected myelosuppression (unless it results in a hospitalization, in which case, an CTEP-AERS report is required).

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5.3.7 Reporting Second Primary Cancers

All cases of second and secondary malignancies [including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)], regardless of attribution, that occur following treatment on NCI-sponsored trials must be reported as follows:

1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at:

   ECOG-ACRIN Operations Office - Boston
   FSTRF
   900 Commonwealth Avenue
   Boston, MA 02215

2. Report the diagnosis via CTEP-AERS, regardless of attribution, at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, c.) treatment related secondary malignancy, or d.) Neoplasm Other, malignant (grade 3 or 4)

3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.

4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: 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.

Whenever possible, the CTEP-AERS report should include the following:

- tumor pathology
- history of prior tumors
- prior treatment/current treatment including duration
- any associated risk factors or evidence regarding how long the tumor may have been present
- when and how the tumor was detected
- molecular characterization or cytogenetics or the original tumor (if available) and of any new tumor
- tumor treatment and outcome (if available).

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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5.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Lenalidomide (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. Frequency is provided based on 4081 patients. Below is the CAEPR for lenalidomide (CC-5013).

NOTE: FOR THIS PROTOCOL, events listed in the SPEER column should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER.

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)***
	Vomiting		***Vomiting (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%)**	
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)***

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%)**	
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		
	Hyperglycemia		
	Hyperuricemia		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		
	Hypophosphatemia		
	Iron overload		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Bone pain		
	Generalized muscle weakness		
	Muscle cramp		***Muscle cramp (Gr 2)***
	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]	

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%)**	
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			
		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)		

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%)**	
		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.

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5.5 Dose Modifications

NOTE: Although effective April 1, 2018, expedited adverse event reporting done via CTEP-AERS (see Section 5.3) will use CTCAE version 5.0 terminology and grading, routine adverse event reporting and dose modifications outlined below will continue to be based on CTCAE version 4.0 terminology and grading.

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The toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/).

5.5.1 Subjects will be evaluated for adverse events (AEs) at each visit.

Rev. 6/11

5.5.2 Dose Reductions for Lenalidomide

Table 1 gives the dose levels for the dose reduction steps for adverse events.

Table 1

Dose reductions for Lenalidomide	**Pre-treatment ANC>/= 1,000 And PLT >/= 100,000**	**Pre-treatment ANC >/= 500-999 And PLT >/= 50,000-99,000**
Starting dose	10 mg po/day on days 1-21, followed by 7 days of no therapy	5 mg po/day, days 1-21, followed by 7 days of no therapy
Dose level -1	5 mg po/day on days 1-21, followed by 7 days of no therapy	5 mg po every other day for 28 days
Dose level -2	5 mg po every other day for 28 days	2.5 mg po every other day for 28 days

Patients who experience limiting cytopenias after prolonged treatment with 2.5 mg every other day may resume treatment at the same dose upon hematologic recovery.

5.5.3 Dose Modifications for Neutropenia

Hold lenalidomide for a decline in neutrophil count to < 500/mcL that is not supported by myeloid growth factor administration. Lenalidomide should be resumed at the next dose reduction step when neutrophil count is > 500/mcL. Patients who do not experience neutrophil recovery within 8 weeks should be removed from study treatment and complete all off-study evaluations.

5.5.4 Dose Modifications for Thrombocytopenia

Some MDS patients may develop thrombocytopenia precipitously within the first month of lenalidomide therapy. Therefore, weekly CBCs are assessed during the first eight weeks of the study.

The following are dose interruption/modification guidelines for subjects who develop thrombocytopenia.

5.5.4.1 **For patients with a baseline platelet count ≥ 100,000/mcL;**

5.5.4.1.1 Hold lenalidomide when the platelet count falls to < 30,000/mcL. Lenalidomide should be resumed within eight weeks at the next dose reduction step when the platelet count recovers to ≥ 50,000/mcL. Subsequent cycles should continue at that dose reduction level.

Rev. 10/09

Patients who do not experience platelet recovery within 8 weeks should be removed from study treatment and complete all off-study evaluations.

5.5.4.2 **For patients with a baseline platelet count <100,000/mcL;**

5.5.4.2.1 Hold lenalidomide for decline in the platelet count ≥ 50% of the baseline value. Lenalidomide treatment should be resumed at the next dose reduction step upon platelet count recovery to ≥ 50,000/mcL. Subsequent cycles should continue at that dose reduction level.

Rev. 10/09

Patients who do not experience platelet recovery within 8 weeks should be removed from study treatment and complete all off-study evaluations.

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Baseline plt count	Hold for counts of	Must recover to*
≥ 100,000	< 30,000	≥ 50,000
≥ 60,000 – 99,999	50% of baseline	≥ 50,000
< 60,000	50% of baseline	> 30,000

* Then dose reduce for remainder of cycle. Maintain dose reduction for next cycles, as long as subject meets requirements to start next cycle.

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5.5.5 **Combined Treatment (Arm B)**: If, at any time, the Hgb level rises to > 12g/dL, regardless of Hgb rate of rise, the epoetin alfa dose will be withheld until the Hgb level decreases to < 11 g/dL and will be resumed at a decreased dose, as outlined below:

- Epoetin alfa 60,000 U sc QW → 40,000 U sc QW
- Epoetin alfa 40,000 U sc QW → 30,000 U sc QW
- Epoetin alfa 30,000 U sc QW → 20,000 U sc QW
- Epoetin alfa 20,000 U sc QW → 10,000 U sc QW

NOTE: If the Hgb rises due to a transfusion, epoetin alfa will continue to be administered, and the dose level will not change.

If Hgb rate of rise is > 1 g/dL in the 1-week or 2-week period immediately preceding the next epoetin alfa dose or the Hgb level exceeds 11.5 g/dL (and the Hgb is ≤ 12 g/dL), the epoetin alfa dose will be decreased immediately, as described, but will not be withheld. For example, at the week 5 scheduled dosing visit, assess Hgb rate of rise between weeks 4 and 5 and weeks 3 and 5.

NOTE: Dose re-escalation may be allowed in the event of an increased, and then decreased, Hgb. Follow the recommendations for Epoetin alfa adjustment when reinstituted for decline in Hgb.

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5.5.6 **Lenalidomide Monotherapy (Arm A)**: For those patients experiencing a rise in hemoglobin ≥ 14 g/dL on Arm A, lenalidomide should be withheld until the hemoglobin is ≤ 12 g/dL, at which time treatment can be resumed according to the dose adjustment recommendations in Table 1 of Section 5.5.2. For those patients previously adjusted to the lowest lenalidomide dose, the lenalidomide schedule should be changed to a 2 week treatment schedule every 4 weeks.

5.5.7 Dose Modifications for Other Adverse Events

Dose interruption and modification guidelines for other adverse events are in Table 2. Lenalidomide should be held for any ≥ grade 3 adverse events with suspected drug association until resolution to < grade 2. For any patient who does not experience resolution to < grade 2 within 6 weeks should be removed from protocol treatment and complete all off-study evaluations. For patients with thromboembolic events, both agents should be discontinued and not resumed until resolution with proper prophylaxis according to the discretion of the treating investigator.

NOTE: Patients will be removed from study treatment if lenalidomide is held for > 6 weeks for treatment-related toxicity.

NOTE: For patients on Arm B, epoetin alfa will continue while lenalidomide is being held for toxicity.

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5.5.8 Dose Reduction for Patients with Renal Insufficiency

Defined as creatinine >1.5 mg/dl that does not resolve to grade 1.

Rev. 6/11

[Deleted in Addendum #4]

- Patients with CLcr <60 mL/min and >/= 30 mL/min should be monitored closely for possibly excess myelosuppression or other toxicity, and dose reduce by 50% upon recovery.

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[Deleted in Addendum #4]

Table 2: Dose Modifications for Lenalidomide

System	NCI CTCAE Grade	Action
Coagulation	**Venous thrombosis/embolism ≥ Grade 3**	• Hold (interrupt) dose and start anticoagulation; resume lenalidomide at investigator's discretion (maintain dose level).
Skin	**Desquamating (blistering) rash**	• Discontinue study treatment.
	Non- desquamating rash Grade 2	• If Grade 2, interrupt lenalidomide therapy. Resume lenalidomide when the rash resolves to ≤ Grade 1 (decrease one dose level).
	Grade ≥ 3	• Hold lenalidomide study drug.
Neurology	**Neuropathy Grade 3**	• If Grade 3, interrupt lenalidomide 3 therapy. Resume lenalidomide when the neuropathy resolves to ≤ Grade 1 (decrease one dose level).
	Grade 4	• Hold lenalidomide study drug.
Allergy	**Allergic reaction Grade 2**	• If Grade 2, interrupt lenalidomide therapy. Resume lenalidomide when symptoms resolve to ≤ Grade 1 (decrease one dose level).
	≥ Grade 3	• Hold lenalidomide study drug.
Gastrointestinal	**Constipation ≥ Grade 3**	• Hold (interrupt) dose. Initiate bowel regimen, and resume lenalidomide when constipation resolves to ≤ grade 2 (decrease one dose level).
Endocrine	**Hyperthyroidism or hypothyroidism**	• Interrupt lenalidomide and initiate appropriate medical therapy. Resume lenalidomide at investigator's discretion (maintain dose level).
Cardiac Arrhythmias	**Sinus bradycardia/other cardiac arrhythmia Grade 2**	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1resume at next lower dose level.
	≥ Grade 3	• Hold lenalidomide study drug.
Other Toxicity	**Other non-hematologic toxicity assessed as lenalidomide-related ≥ Grade 3**	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 resume at next lower dose level.

5.6 Supportive Care

5.6.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.6.2 Therapies considered necessary for the patient's well being may be administered at the discretion of the Investigator. These therapies include antibiotics, analgesics, antihistamines, or other medications, and transfusions of red blood cells, platelets, or fresh frozen plasma given to assist in the management of complications associated with MDS or study treatment.

5.6.3 Packed RBCs: Transfusions of two units of packed RBCs should be considered for decline in hematocrit (HCT) to < 25% or symptoms of cardiovascular compromise. The following **transfusion thresholds and guidelines** are recommended for study participants: HCT < 25%, two units of packed RBCs; HCT < 21%, three units of packed RBCs; HCT < 18%, four units of packed RBCs.

5.6.4 Platelets: Eight to ten units of random donor platelets or one cytopheresis unit of single donor platelets should be administered to all subjects with signs of hemostatic failure (i.e., bleeding or petechiae) or life threatening thrombocytopenia (i.e., platelet count < 10,000/mcL).

5.6.5 Patients should not receive androgens or steroids for treatment of their anemia or thrombocytopenia as part of supportive therapy.

5.6.6 Patients may receive hydrocortisone prophylactically to prevent transfusion reactions. Steroids given for adrenal failure, hormones administered for non-cancer-related conditions (e.g. insulin for diabetes), and intermittent uses of dexamethasone as an antiemetic are permitted concomitantly with study drug. Short courses of steroids to treat study drug-induced skin rashes are also permitted. Use of steroids and reasons should be documented in the E2905 Forms Packet.

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5.6.7 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 the Celgene Pregnancy Prevention Counseling Program (CPPCP). Registration for CPPCP is done by completing the form found in Appendix XIII 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 CTSU for documentation. Sites may not order lenalidomide until documentation for two trained counselors is provided to the appropriate office." The CTSU operations office fax number for CPPCP training certificates: (1-888-691-8039).

5.7 Duration of Therapy

Patients will receive protocol therapy unless:

5.7.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E2905 Forms Packet.

5.7.2 Patient withdraws consent.

5.7.3 Adverse event(s) (AEs) occur that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.

5.7.4 Lack of therapeutic effect while on either Arm A (for those patients that are not eligible or do not wish to cross over to Arm B) or Arm B.

5.7.5 Patient’s disease converts to acute myeloid leukemia or disease progression.

5.7.6 Patient is lost to follow-up.

5.8 Duration of Follow-up

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For this protocol, all patients, including those who discontinue protocol treatment early, will be followed for response until relapse/progression, and for 6 months from end of protocol treatment. Arm A patients that cross over to Arm B that do not achieve a MER after 16 weeks of combined treatment (i.e. week 32) will discontinue protocol treatment.

6. Measurement of Effect

6.1 **MDS Response Criteria:** Modified International MDS Working Group (IWG) Criteria for Measurement of Response/Treatment Effect in MDS will be used to assess response.

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6.1.1 International Prognostic Scoring System (IPSS) for MDS

Prognostic Variable	Survival and AML Evolution Score Value				
	0	0.5	1.0	1.5	2.0
Marrow Blasts (%)	<5	5 to 10	N/a	11 to 20	21 to 30
Karyotype	Good Normal or any 1 of: -Y (del(5q) del(20q)	Intermed. Any other abnormality	Poor chromosome 7 anomalies; Complex: ≥ 3 abnormalities	n/a	n/a
Cytopenias Neutrophil Count < 1800/mcL Platelets < 100,000 mcL Hemoglobin < 10 g/dL	0 or 1	2 or 3	n/a	n/a	n/a

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Low: total score = 0
Int-1: total score 0.5-1.0
Int-2: total score 1.5-2.0
High: total score ≥ 2.5

6.1.2 MDS Response Criteria

6.1.2.1 Bone Marrow Response (CR or PR must last ≥ 8 weeks)

1. Complete Remission (CR)

Bone marrow evaluation: Bone marrow showing < 5% myeloblasts with normal maturation of all cell lines, with no evidence for dysplasia (see dysplasia qualifier under peripheral blood evaluation). When erythroid precursors constitute < 50% of bone marrow nucleated cells, the percent of blasts is based on all nucleated cells; when there are ≥ 50% erythroid cells, the percent blasts should be based on the non-erythroid cells.

- Peripheral Blood Counts (Absolute values must last ≥ 8 weeks)
  - Hemoglobin greater than 11 g/dL.
  - Neutrophils 1500/mm^3 or more (not on a myeloid growth factor)
  - Platelets 100 000/mm^3 or more (not on a thrombopoetic agent)
  - Blasts – ≤ 5%
  - No dysplasia. The presence of mild megaloblastoid changes may be permitted if they are thought to be consistent with treatment effect.

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However, persistence of pretreatment abnormalities (e.g., pseudo-Pelger Huet cells, ringed sideroblasts, dysplastic megakaryocytes) is not consistent with CR.

2. Partial Remission (PR)

- All of the CR criteria (if abnormal prior to treatment), except
  - Bone marrow evaluation: Blasts decreased by 50% over pretreatment, or a less advanced MDS WHO classification than pretreatment. Cellularity and morphology are not relevant.

3. Stable Disease

- Failure to achieve at least a PR, but with no evidence of progression for ≥ 2 months.

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4. Failure

- Death during treatment or disease progression characterized by worsening of cytopenias, with increase in the percent of bone marrow blasts (as defined in Section 6 below), and/or progression to an MDS FAB subtype more advanced than pretreatment.

5. Relapse (following a CR or PR)

- One or more of the following:
  - Return to pretreatment bone marrow blast percentage.
  - Decrement of > 50% from maximum remission response levels in neutrophils or platelets.
  - RBC transfusion dependence (≥ 2 units RBC transfusions over an 8 week period) or a reduction in hemoglobin concentration by ≥ 2 g/dL in the absence of acute infection, gastrointestinal bleeding, hemolysis, treatment hiatus etc.

6. Disease Progression

- A 50 % increase in blasts, depending on baseline blast percent.
  - For patients with < 5% blasts: increase to ≥ 10% blasts
  - For patients with 5% to 10% blasts: ≥ 50% increase to > 10% blasts
  - For patients with 10% to 20% blasts: ≥ 50% increase to ≥ 20% blasts

7. Disease Transformation

- Transformation to AML (≥ 20% blasts).

6.1.2.2 Cytogenetic Response

Requires 20 analyzable metaphases when using conventional techniques. Analysis of data will require 20 metaphases before and after treatment, which must be done on bone marrow only (peripheral blood is not a substitute). Fluorescent *in situ* hybridization (FISH) may be used as a supplement to follow a specifically defined cytogenetic abnormality, but it is not a substitute for conventional cytogenetic studies. Cytogenetic response is defined as follows:

Complete response: Restoration of a normal karyotype in patients with a documented pre-existing clonal (>2 metaphases abnormal) chromosome abnormalities.

Partial response: > 50% reduction in the percentage of bone marrow metaphases with only clonal abnormality.

6.1.2.3 Hematologic Improvement

Improvements must last ≥ **8 consecutive weeks**.

1. Erythroid Response

- *Major Erythroid Response:* Transfusion-independence for ≥ 8 consecutive weeks for patients who were RBC transfusion-dependent at baseline AND a ≥ 1 g/dL hemoglobin rise compared to mean pre-transfusion baseline value; or a > 2 g/dL rise in hemoglobin without transfusion for non-transfusion dependent patients.
- *Minor Erythroid Response:* The mean hemoglobin is sustained 1.0 to 2.0 g/dL above the baseline value for a minimum of 8 weeks; or a 50% or greater decrease in 8-week RBC transfusion requirements compared to baseline.

2. Platelet Response

- *Major Platelet Response:* For patients with a pretreatment count < 100,000/mm^3, an absolute increase of ≥ 30,000/mm^3; for platelet transfusion-dependent patients, stabilization of platelet counts and platelet transfusion independence.
- *Minor Platelet Response:* For patients with a pretreatment platelet count < 100,000/mm^3, a > 50% increase in platelet count with a net increase > 10,000/mm^3 but < 30,000/mm^3.

3. Neutrophil Response

- Major Neutrophil Response: For pretreatment ANC < 1500/mm^3, ≥ 100% increase, or an absolute increase of ≥ 500/mm^3, whichever is greater.
- Minor Neutrophil Response: For ANC > 1500/mm^3 before therapy, ANC increase of at least 100%, but absolute increase less than 500/mm^3, lasting greater than 8 weeks (56 days).

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4. Progression/Relapse Following Erythroid Hematologic Improvement

- For patients who achieve RBC transfusion independence: requirement for ≥ 2 units RBC transfusion in an 8 week period or a reduction in hemoglobin concentration by ≥ to 2 g/dL in the absence of acute infection, gastrointestinal bleeding, hemolysis, etc., reaching a hemoglobin < 9.5 g/dL.
- For patients who achieve ≥ 50% decrease in RBC transfusions: return to pre-treatment RBC transfusion requirement over an 8 week period.

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6.1.2.4 Duration of Response

Time to disease progression (as per Bone Marrow Responses above) or progression/relapse following hematologic improvement (as per Hematologic Improvement above).

7. Study Parameters

7.1 Therapeutic Parameters

1. All CBCs and RBC transfusion values for the eight weeks prior to randomization are required to establish transfusion-dependence and baseline hemoglobin. Transfusion number and dates must be documented for the eight weeks preceding initiation of study treatment.
2. For non-transfusion dependent patients (i.e., receiving < 2 units/4 weeks x 8 weeks pre-study) who receive periodic transfusions, the mean pre-transfusion hemoglobin should be used to determine protocol eligibility and response reference.

   NOTE: For non-transfusion dependent patients, a minimum of 2 pre-transfusion or un-transfused hemoglobin values are required.

Rev. 10/09, 6/11

3. [Deleted in Addendum #4]

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4. All required prestudy chemistries, as outlined in Section 3 (at least one set of the two required sets), should be done within 7 days before randomization. CBC/Diff and chemistries should also be performed on Day 1 of each cycle.
5. Prestudy non-transfused Hgb, Hct, WBC, ANC, Plt should be documented on
   2 occasions over 56 days prior to randomization. The 2 occasions must be separated by at least 7 days.

Response Assessment

Hematologic, pathologic and cytogenetic response will be assessed according to criteria outlined in Section 6.1.2.

NOTE: When recording prestudy results on the ECOG-ACRIN forms, please make sure that ALL relevant dates are clearly given. Do ***not*** put all the results under the date for Day 1 of protocol treatment unless they were actually done that day. Record the actual dates.

Rev.	Assessment	Screening[1] (56 days prior to randomization unless otherwise noted)	Weekly	Day 1 of each cycle[15]	Every 8 weeks[15]	Week 16 and Treatment Discontinuation	Follow-Up
Rev. 10/09 Rev. 4/15	Medical History	X					
	Prior MDS Treatment	X					
	ECOG Performance Status	X		X		X	
	Pregnancy test[2]	X[3]		X[4]		X	
	Physical examination	X[9]		X			
	ECG	X					
Rev. 6/13 Rev. 10/09	Thyroid function tests[5]	X				X	X[11]
Rev. 6/11	Serum erythropoietin (when Hgb < 9.5 g/dL pre-study)	X			X	X	
Rev. 10/09	Serum chemistry[6,7]	X		X		X	X[11]
Rev. 10/09	Hematology[8]	X	X[10]	X[9]		X	X[11]
	RBC Transfusion History[8]	X					
	Serum ferritin level				X		
Rev. 10/09	Response assessment[13]			X	X	X	X[11]
Rev. 10/09 6/11	Toxicity assessment[14]		X	X	X	X	X[11]
Rev. 10/09	Bone marrow aspirate & biopsy[12]	X				X	X

Rev. 6/13 **NOTE:** For patients receiving epoetin alfa (Procrit) through the ESA Apprise Oncology Program, please refer to the REMS requirements of the ESA Apprise Oncology Program for the guidelines for use, e.g, for hemoglobin testing, as they may differ from the protocol assessments requested in the Section 7 Assessment table above.

Rev. 4/15 **NOTE:** Results of the bone marrow biopsy and aspirate as well as Cytogenetics are mandatory to register subjects onto study, which are indispensable to determine IPSS category needed for eligibility (see Section 3.1.1.3). Please note that it is not necessary to wait for the week 16, week 32, or week bone marrow and cytogenetic results prior to starting the next cycle unless deemed necessary by the treating physician. One example of this exception can include if the subject shows signs of progression, such as increased peripheral blood blast percentage. At that juncture, the treating physician may prefer to await the results prior to starting a new cycle. If a cycle is started, and based on the bone marrow results it is felt by the treating physician that the subject should not continue on treatment, please be sure to note this information on the case report forms at end of treatment.

1. Pertains to subjects enrolled in arms A or B.

Rev. 7/11 2. Females of child bearing potential only. Serum or urine pregnancy testing for β-HCG with a sensitivity of at least 25 mIU/mL. For further requirements for pregnancy testing and birth control, please see Sections 3.1.9 and 3.1.10. See Section 7.3 for testing, counseling, and drug schedules.

Rev. 6/11 3. Within 10-14 days prior to the start of the study drug and again within 24 hours prior to the start of the study drug.

Rev. 7/11 4. Females of child bearing potential only. Weekly pregnancy testing during the first cycle of protocol treatment. Every 4 weeks while on study drug if menstrual cycles are regular. Every 2 weeks if menstrual cycles are irregular. See Section 7.3 for testing, counseling, and drug schedules.

Rev. 10/09 5. TSH (thyroid-stimulating hormone), T3, and T4 levels should be done at screening, at 8 and 16 weeks, then every 3 months and at time of treatment failure and/or study discontinuation.

Rev. 10/09 6. Both sets of CBC/Diffs and chemistries should be collected after patient signs consent (see Section 3).

Rev. 10/09 7. Includes sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (SGOT/AST) or glutamic pyruvic transaminase (SGPT/ALT), lactate dehydrogenase (LDH), and uric acid (at least one of the two required, see Section 3) to be done within 7 days prior to randomization.

Rev. 10/09 8. Red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count and differential, absolute neutrophil count (ANC), and platelet count required for protocol therapy must be done < 24 hours prior to the treatment cycle. Pre-study CBC with differential and chemistries (at least one of the 2 required, see Section 3) should be done within 7 days of randomization.

9. Repeat on Day 1.

10. Perform weekly for 8 weeks, then every 2 weeks until the completion of 16 weeks on study, and then every 4 weeks thereafter.

Rev. 4/15 11. Repeat every 3 months from last day of protocol treatment. No specific requirements if patient is more than 6 months from last protocol treatment. There is a +/- 2 week window for follow-up visits.

Rev. 10/09
Rev.4/15 12. Bone marrow aspirate and biopsy with cytogenetic analysis and iron stains performed pre-study, after 16 weeks of study treatment, at week 32, and year 1 (if still receiving treatment) in addition to end of treatment or relapse or progression. The BMBx performed after 16 weeks of study treatment should be completed by the last week of the cycle 4 in order for the information from the results to be available for those considering crossing over to Arm B, whether to continue treatment, etc. If the subject has been on hold from starting a new cycle, then the BMBx should fall on the last week of cycle 4. Additional biological studies obtained with bone marrow aspiration are summarized in Section 7.2.

13. Hematologic, pathologic, and cytogenetic response will be assessed according to criteria outlined in Section 6.1.2.

Rev. 6/11 14. Toxicity assessment schedule will follow the hematology schedule. See schedule in Footnote 10.

Rev. 4/15 15. There is a +/- 5 business day window for all post-screening (on treatment) testing.

7.2 Biological Sample Submissions

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1. Submission of karyotypes (Section 11.1) for cytogenetic review and pathologic materials (Section 10) for diagnostic review and classification is mandatory in order for the patient to be considered evaluable. Failure to submit the required materials may render the case unevaluable.

2. Submission of bone marrow and blood for correlative studies should be submitted as outlined in Sections 10.2.2.2 and 11.2. Collection of bone marrow and blood should be limited to those patients who have given written informed consent to participate in the correlative studies.

NOTE: An informed consent MUST be signed prior to the submission of any samples for the mandatory diagnostic reviews and correlative studies. Samples for correlative studies should be submitted only from patients who have given written consent for the use of their samples for these purposes.

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Rev, 4/15

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

Rev. 6/11

NOTE: It is required that biological sample submissions be logged into the ECOG-ACRIN Sample Tracking System (STS) (see Section 10.5) for purposes of monitoring compliance.

	Baseline	Week 16 [5]	Week 32	Year 1	Relapse/Progression/ End of Treatment
Rev. 10/09					
Diagnostic Slides/Smears[*1]	X	X	X	X	X
Rev. 10/09					
BM Biopsy Block [+2, 6]	X	X	X	X	X
Rev. 10/09					
Peripheral Blood (Sodium Heparin tubes) [+3]	X	X	X	X	X
Rev. 10/09, 7/11					
BM Aspirate (EDTA tube)+[3,6]	X	X	X	X	X
Rev. 10/09					
Karyotypes[*4]	X	X	X	X	X

*Mandatory

[+]Submit per patient consent.

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1. Submit to the ECOG-ACRIN CBPF as outlined in Section 10 at baseline, week 16, week 32, year 1 and progression.

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2. Submit to the ECOG-ACRIN CBPF per Section 10 from patients consenting to participate in the optional laboratory studies. If blocks cannot be submitted, please submit five (5) unstained bone marrow biopsy level slides. If you have questions please call Lynn Moscinski at (813) 979-3001.

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3. Submit to Dr. Alan List's Laboratory as indicated in Section 11.2 from patients consenting to participate in the optional laboratory studies. Direct questions to Kathy McGraw or Ashley Basiorka at (813) 745-8271.

4. All study participants/cooperative groups must submit two original karyotypes to Mayo Clinic Cytogenetic Laboratory as indicated in Section 11.1.

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[Note deleted in Addendum #1]

5. 16 weeks after the first dose of drug.

Rev. 10/09, 6/11, 7/11 Rev.4/15

6. Patient must sign consent before collection of baseline bone marrow biopsy/aspirate and peripheral blood (collect Monday-Thursday only, do not collect on Fridays or the day before a holiday, and ship day of collection). Submit initial bone marrow aspirate to Dr. Alan List's Laboratory using the Generic Specimen Submission Form (#2981) as outlined in Section 10.5.1. Please call Dr. List's laboratory prior to shipping. Once the patient is randomized please call the receiving laboratories with the ECOG-ACRIN patient sequence number and enter the information into the ECOG-ACRIN STS.

Rev. 7/11

7.3 Schedule for pregnancy testing, education and counseling, and dispensing schedule for lenalidomide.

Procedure	Screening	Cycle 1				Subsequent cycles		Study drug discontinuation
	≤ 28 days from baseline (first day of study drug administration)	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	3-4 weeks from the last of day of last cycle
Pregnancy testing[1]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Education and counseling[3]		X[3]				X[3]		X[3]
Dispense lenalidomide		X[4]				X[4]		

[1]Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 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).

[2]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 study treatment (including breaks in treatment); 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 study treatment (including breaks in treatment), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix X: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

[3]The Lenalidomide Education and Counseling Guidance Document (Appendix XI) 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 XII) 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.

[4]Only enough lenalidomide for 28 days or one cycle of study treatment (whichever is shorter) may be provided to the patient each cycle.

8. Drug Formulation and Procurement

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Rev. 5/17
Rev. Add15

NOTE: As of Addendum #13, all patients who register to the study will use commercial supply of Procrit. Patients who previously received Procrit from the NCI will be switched to the commercially supplied Procrit. Sites will register to the REMS program, via the ESA APPRISE Oncology Program, for commercially supplied epoetin alfa (Procrit). In addition, each site should inform the hospital compliance group responsible for the ESA that the epoetin alfa (Procrit) is being used as part of an approved protocol. Please contact the ESA APPRISE Oncology Program at 1-866-284-8089. Patients/insurance will be charged for the commercial supply of epotin alfa (Procrit). Only brand Procrit should be ordered through the REMS. Epogen may not be substituted for Procrit.

Vial sizes available:

Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL (3).

Multidose vial containing benzyl alcohol: 20,000 Units/2 mL and 20,000 Units/1 mL (3).

Overview of Steps - ESA Apprise Oncology Program:

Steps for Hospitals and Hospital/Institution-affiliated Outpatient Facilities That Dispense ESAs to Patients With Cancer

Select a Hospital Designee: This individual is designated by hospital management to assume authority and responsibility to internally coordinate and oversee the ESA APPRISE Oncology Program in the hospital (e.g., pharmacy director, Head of Hematology/Oncology Department).

Complete Training: The Hospital Designee must complete the ESA APPRISE Oncology Program training for the Hospital Designee.

Enroll: The Hospital Designee must enroll in the ESA APPRISE Oncology Program by completing the ESA APPRISE Oncology Program Enrollment Form for Hospitals.

Implement: The Hospital Designee must establish or oversee the establishment of a system, order sets, protocols, or other measures designed to ensure that ESAs are only dispensed to patients with cancer after verifying:

- That the Healthcare Provider (HCP) who prescribed Procrit® for patients with cancer has enrolled in the ESA APPRISE Oncology Program.

  If an HCP who prescribes Procrit® is not enrolled in the ESA APPRISE Oncology Program, the prescriber will be notified that he/she is not able to prescribe Procrit® for patients with cancer.

- That the discussion between the patient and ESA APPRISE Oncology Program-enrolled prescriber on the risks of Procrit® therapy is documented by patient and prescriber signatures on the ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgment Form prior to initiation of each new course of Procrit® therapy".

  https://www.esa-apprise.com/ESAAppriseUI/public/ESA_APPRISE_Oncology_Program_Hospital_Process_Overview_Flashcard.pdf

For complete details on the REMS for ESA Apprise please call 1-866-284-8089.

Availability

Rev. 6/13, 11/13
Rev. Add15

Maintenance of NCI drug accountability records is required. Lenalidomide **(NSC# 703813)** may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug 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 – see general information). Completed Clinical Drug Requests (NIH-986): 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

Rev. Add15

<https://ctepcore.nci.nih.gov/OAOP>. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account

Rev. Add15

<https://ctepcore.nci.nih.gov/iam/> and the maintenance of an "active" account status and a "current" password, and active person registration status. The NCI Clinical Drug Request form is available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

Rev. 5/17
Rev. Add15

NOTE: As of the activation of Addendum #13, all patients will receive epoetin alfa **(Procrit) through the commercial channels, or through the ESA Apprise Oncology program.**

NCI Supplied Agent(s) – General Information

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Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time, or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

8.1 Lenalidomide (NSC# 703813)

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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

8.1.1 Other Names

IMiD CC-5013, Revlimid®

8.1.2 Classification

Immunomodulatory drug

8.1.3 Mode of Action

Lenalidomide, 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.

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8.1.4 Storage and Stability

How Supplied: Celgene supplies and CTEP, NCI, DCTD distributes lenalidomide 2.5 mg (size 4) and 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 capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

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Storage: The capsules should be stored at room temperature (15-30°C) away from moisture and direct sunlight.

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Stability: Refer to the package labeling for expiration date. Lenalidomide stability is adequate for at least 28 days after transferring to a pharmacy vial.

8.1.5 Dose Specifics

Lenalidomide 10 mg po/day x 21 days (5 mg dose for moderate neutropenia or thrombocytopenia-see Section 5.1). To be repeated every 28 days until relapse or progression.

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8.1.6 Route of Administration

Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules.

8.1.7 Potential Drug Interactions

In vitro, lenalidomide did not significantly inhibit marker enzyme activities for CYP1A2, CYP2C9, CYP2C19, CYP2E1, or CYP3A4. In rats, no induction of any CYP450 enzymes was observed. These data suggest that lenalidomide is not likely to cause metabolic drug interactions in man.

8.1.8 Availability

Lenalidomide is an investigational agent supplied by the National Cancer Institute. See Section 8 for ordering instructions.

Available as both a 5 mg and a 2.5 mg hard gelatin capsule.

8.1.9 Side Effects

Please refer to Section 5.4.

8.1.10 Nursing/Patient Implications

1. Effective contraception must be used by patients for at least 4 weeks before beginning lenalidomide therapy, during lenalidomide therapy, during dose interruptions and for 4 weeks following discontinuation of lenalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been postmenopausal naturally for at least 24 consecutive months. Two reliable forms of contraception must be used simultaneously, by females, unless continuous abstinence from heterosexual sexual contact is the chosen method. Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 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).

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   Males receiving lenalidomide must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a vasectomy.

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   Before prescribing lenalidomide, females of childbearing potential should have 2 negative pregnancy tests (sensitivity of at least 25 mIU/mL). The first test should be performed within 10 – 14 days, and the second test 24 hours prior to prescribing lenalidomide. A prescription for lenalidomide for a female of childbearing potential must not be issued by the prescriber until negative pregnancy tests have been verified by the prescriber.

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2. Caution patient not to drive or use hazardous machinery until the potential sedative effects of the drug are known in the patient.
3. Caution patient to report leg swelling or shortness of breath, because of the risk of thrombosis/embolism
4. Counsel patient to report abnormal sensations in hands or feet, such as decreased sensation or dysesthesia. Paresthesias are often noted early before neuropathy develops.
5. Advise patient to immediately report rashes or fever.

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8.1.11 Dispensing

Only a 28-day supply may be dispensed at one time. Sites may not mail lenalidomide to patients.

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8.1.12 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 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.

Definition of female of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 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 mIU/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 XI) 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 XII) will be supplied with each medication dispense."

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8.1.13 References

1. Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002; 100:3063-7.
2. Richardson P, Jagannath S, Schlossman R, et al. A Multi-center, Randomized, Phase 2 Study to Evaluate the Efficacy and Safety of 2 CDC-5013 Dose Regimens When Used Alone or in Combination with Dexamethasone (Dex) for the Treatment of Relapsed or Refractory Multiple Myeloma (MM). Blood 2003; 102:235a.
3. Zangari M, Tricot G, Zeldis J, Eddlemon P, Saghafifar F, Barlogie B. Results of Phase I Study of CC-5013 for the Treatment of Multiple Myeloma (MM) Patients Who Relapse after High Dose Chemotherapy (HDCT). Blood 2001:775a (A3226).
4. Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood 2001; 98:210-6.

8.2 Epoetin Alfa (NSC# 628281)

Experience in Subjects with Cancer

A randomized controlled clinical study, previously summarized in the label and published in 2005, entitled, "Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study" (BEST) evaluated 939 women with metastatic breast cancer receiving chemotherapy. Patients received either weekly Epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when Epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The study was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% Epoetin alfa vs. 0.2% placebo) in the first 4

months of the study were observed among patients treated with Epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the Epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).[6]

A multicenter, randomized, double-blind, placebo-controlled trial in which patients with advanced non-small cell lung cancer unsuitable for curative therapy were treated with Epoetin alfa targeting hemoglobin levels between 12 and 14 g/dL or placebo. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favor of patients in the placebo group was observed (63 vs. 129 days; HR 1.84; p = 0.04).[7]

A preliminary report from a clinical study (DAHANCA) evaluated 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy. Patients were randomized to darbepoetin alfa (a different erythropoietin drug) or placebo. An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among darbepoetin alfa-treated patients (p = 0.01). At the time of study termination, there was a trend toward worse survival in the darbepoetin alfa-treated arm (p = 0.08).[8]

A recently completed phase 3, double-blind, randomized, placebo-controlled 16-week clinical study evaluated 989 patients with active malignant disease not receiving chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. In addition, there were more deaths in the darbepoetin alfa treatment group [26% (136/515)] than the placebo group [20% (94/470)] at 16 weeks (completion of treatment phase). With a median survival follow up of 4.3 months, the absolute number of deaths was greater in the darbepoetin alfa treatment group [49% (250/515)] compared with the placebo group [46% (216/470); HR 1.29, 95% CI: 1.08, 1.55].[9]

NOTE: Refer to epoetin alfa package insert for more information.

8.2.1 Other Names

Erythropoietin, rhu-erythropoietin, EPO, Epogen, Procrit.

8.2.2 Classification

Colony stimulating factor; cytokine.

8.2.3 Mode of Action

Stimulates red cell production. It stimulates the division and differentiation of committed erythroid progenitors in the bone marrow.

8.2.4 Storage and Stability

Epoetin alfa is stored in the refrigerator (2-8°C). Do not freeze or shake. If the epoetin alfa solution freezes, it must not be used. The solution should be brought to room temperature prior to injection.

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The 1 mL vial single-dose vial contains no preservative. Use one dose per vial. Do not re-enter vial; discard unused portions.

The 1 mL or 2mL multidose vials contain preservative. Store at 2° to 8° C after initial entry and between doses. Discard 21 days after initial entry. Epoetin alfa should be drawn up into a plastic syringe and

administered subcutaneously according to standard sterile techniques.

8.2.5 Dose Specifics

60,000 subcutaneously weekly. Repeated every 28 days for four cycles.

8.2.6 Preparation

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Usually single-dose vials are administered undiluted, although preservative-free solutions may be mixed with bacteriostatic NS containing benzyl alcohol 0.9% in a 1:1 ratio.

Admixing is not necessary when using the multidose vials of epoetin alfa containing benzyl alcohol. Do not dilute or administer in conjunction with other drug solutions.

8.2.7 Route of Administration

Subcutaneous

8.2.8 Availability

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Those patients who had previously received Procrit from the NCI will be switched to the commercially supplied Procrit.

As of Addendum #13, all patients will receive epoetin alfa (Procrit) through the commercial channels, or through the ESA Apprise Oncology Program.

Vial sizes available:

Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL (3).

Multidose vial containing benzyl alcohol: 20,000 Units/2 mL and 20,000 Units/1 mL (3).

NOTE: See Section 8 for updated drug ordering instructions.

8.2.9 Incompatibilities

Epoetin Alfa is contraindicated in subjects with the following:

- Uncontrolled hypertension
- Known hypersensitivity to the active substance or any of the excipients

8.2.10 Side Effects

1. Fever (29%).
2. Gastrointestinal: Diarrhea (21%), nausea (17%), vomiting (17%).
3. Cardiovascular: Edema (17%), hypertension with dialysis patients.
4. Neurologic: Paresthesia (11%); increased incidence of seizures in dialysis patients.
4. Dermatologic: Local erythema; rash (mild, rare, and transient).

5. Thrombotic events: Pulmonary embolisom, cerevral vascular accident.

6. Other: Potential to increase tumor growth.

Thrombovascular Events

TVEs, such as myocardial ischemia, myocardial infarction, cerebrovascular accidents (cerebral hemorrhage and cerebral infarction), transient ischemic attacks, deep venous thrombosis, arterial thrombosis, pulmonary emboli, retinal thrombosis, and clotting of an artificial kidney or shunt have been associated with the use of erythropoietic agents as reflected in the labeling of all currently marketed products. Additionally, there is a potential for an increased rate of TVE occurrence when recombinant human erythropoietin is used in non-anemic subjects. Published findings from a study evaluating survival in subjects with cancer has indicated that there may be an increased risk of TVE associated with recombinant human erythropoietin treatment of non-anemic cancer subjects.[10]

In summary, the occurrence of TVE is associated with epoetin alfa treatment whether used in anemic or non-anemic subjects.

8.2.11 Nursing Implications

1. Monitor for central venous catheter occlusion or generalized thrombosis.

2. Administer antipyretics, antiemetics and analgesics as needed. Diphenhydramine PO may decrease erythema at the subcutaneous injection site.

3. Inform patient of possible side effects.

4. Encourage patient to keep scheduled laboratory visits, as frequent blood tests are needed to determine the correct dose of epoetin alfa.

5. Monitor blood pressure and heart rate prior to each dose of epoetin alfa.

6. Self-administration of epoetin alfa is not permitted for patients on protocol treatment.

8.2.12 Allergic Responses

There may be a risk of developing an allergic reaction to rhu-erythropoietin. Rare allergic symptoms following epoetin alfa treatment (e.g., skin rash, itching and hives) have been reported, It is possible for more serious allergic reactions to occur. These possible reactions include a whole body rash, shortness of breath, wheezing, sudden drop in blood pressure, swelling around the mouth or eyes, rapid pulse or sweating. If a serious allergic or anaphylactic reaction occurs, epoetin alfa should be immediately and permanently discontinued and appropriate therapy should be administered.

8.2.13 Antibodies

Pure red cell aplasia (PRCA) in association with neutralizing antibodies to native erythropoietin has been observed in patients treated with recombinant erythropoietins. This has been reported predominately in patients with chronic renal failure. PRCA has been reported in a limited number of subjects exposed to other recombinant erythropoietin products prior to exposure to darbepoetin alfa; therefore, the contribution of epoetin alfa to the development of PRCA is unclear. Any patient with loss of response to rhu-erythropoietin should be evaluated for the etiology of loss of effect. Rhu-erythropoietin should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to epoetin alfa, native erythropoietin, and any other recombinant erythropoietin administered to the patient. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, epoetin alfa should be discontinued. (Source for reviewer: USPI)

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Serological screening to investigate the presence of neutralizing antibody to epoetin alfa can be arranged by contacting Janssen Products, LP, at 1-800-526-7736.

All occurrences of PRCA, loss of effect (LOE) of epoetin alfa in the treatment of anemia and/or a report of the presence of antibodies to erythropoietin, will be defined as a SAE and reported and tracked as such.

Any patient who develops a sudden loss of response to epoetin alfa therapy, (unexplained drop in Hb >2g/dL), accompanied by a low reticulocyte count should be appropriately evaluated for etiology (e.g. iron or vitamin deficiency, blood loss, hemolysis, infection or inflammation, progression of underlying malignancy, aluminum intoxication). In the absence of another etiology, serum should be tested for the presence of antibodies to erythropoietin.

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In the event that erythropoietin testing is deemed necessary in the setting of PRCA, a consent form for the testing of erythropoietin antibodies is required. Refer to Appendix , Addendum 1.

8.2.14 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women (pregnancy category C); therefore, epoetin alfa should not be used during pregnancy. In addition, it is not known if epoetin alfa is excreted in human milk, therefore, lactating mothers should stop nursing before participating in any epoetin alfa study.

8.2.15 Geriatric Use

Please refer to the epoetin alfa drug insert for specific information on geriatric use.

8.2.16 References

Abels RI, *et al.* Recombinant human erythropoetin (rhu-EPO) for the treatment of the anemia of cancer. Proc Beijing Symposium. Murphy MJ, Jr. (ed.) Dayton, Ohio: Alpha Med Press, 1991.

Nelson RA, *et al.* Long-term treatment of anemic cancer patients with recombinant human erythropoetin. American Society of Hematology 34th Annual Meeting. December, 1992.

Case DC, *et al.* Recombinant human erythropoetin therapy for anemic cancer patients on chemotherapy. J NCI 1993; 85.

Leyland-Jones B, for BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol. 2003, 4 (8): 459-460. (J & J sponsored EPREX [an epoetin alfa that is marketed outside the U.S.] study.)

Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study. JCO. 2005; 23(25): 1-13.

Wright JR, Ung YC, Julian JA, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Erythropoietin in Non-Small-Cell Lung Cancer with Disease-Related Anemia. *JCO.* 2007; 25(9): 1-6.

http://frejacms.au.dk/dahanca/get_media_file

http://www.clinicalstudyresults.org/documents/company-study_2157_0.pdf

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9. Statistical Considerations

The overall goal of this study is to improve the rate of MER through combined therapy of lenalidomide and epoetin alfa (arm B) by 20% over that of arm A of lenalidomide monotherapy, in which the rate of MER is estimated at 30%, in an MDS population without chromosome 5q31.1 deletion. The anticipated improvement in response is based upon the potentiation of erythroid colony-forming capacity in cell line models. MER will be evaluated at 16 weeks after start of study treatment. Patients without 5q31.1 deletion will be randomly assigned to one of two treatment arms, stratified by serum erythropoietin level (≤500 mU/mL vs. > 500 mU/mL) and prior erythropoietin/DA treatment (yes vs. no). Patients with 5q31.1 deletion will be assigned to arm A only for correlative studies, and will not be included in the comparative analysis of the study. The original design required 236 total patients (212 to be randomized) in order to obtain 80% power for the primary comparison. Due to an interruption in drug supply, the study was suspended and epoetin alfa treatment was held on September 24, 2010. At that time, 67 patients were enrolled. Among them, 57 were randomized (29 on arm A, 28 on arm B). 7 patients on Arm B were still within 16 weeks treatment. New supply of epoetin alfa was available for arm B patients on October 27, 2010 and the study was reopened on February 4, 2011. Due to this unexpected drug supply issue, the comparison of the primary endpoint may lose some power. To minimize the potential effect on the primary endpoint, in the revised design, 14 patients (7 on arm A; 7 on arm B) randomized between May 19, 2010 and September 24, 2010 will be excluded from the primary analysis. The total accrual will be increased to 252 (226 to be randomized). This revised statistical considerations section is to incorporate this change.

9.1 Accrual

This study requires 212 patients (226 to be randomized) without 5q31.1 deletion for the primary endpoint comparison. Assuming that 10% of patients in the MDS population as defined in this study have the 5q31.1 deletion, a total of 252 patients will be entered. Accrual for E1996, a previous study in this patient population was lower than expected. However, since the proposed regimens (lenalidomide, lenalidomide + epoetin alfa) are different from the regimen used in E1996 (erythropoietin vs. supportive care) with promising activity in multi-center phase II trials, and this study will be an intergroup study, we anticipate no accrual impediment. In fact, based on the accrual to the study before its suspension, we anticipate that the accrual rate will be approximately 60 patients per year, and thus, the accrual will be completed in approximately five years, taking the suspension time into account. The feasibility of achieving the accrual goal will be monitored closely by the ECOG-ACRIN Data Monitoring Committee (DMC) and the NCI. According to NCI guidelines, if quarter 5-6 accrual (the number of patients enrolled on trial during quarters 5 and 6 after activation) is $\leq$ 20% of projected rate, then the trial will be closed; If quarter 5-6 accrual is < 50% and > 20% of projected rate, then the study team will be given 6 months to improve accrual. If the average accrual rate in quarter 8 is below 50% then the trial will have to be amended to reflect actual accrual.

9.2 Primary Endpoint

The primary endpoint in this phase III study of previously erythropoietin/DA-treated MDS patients or erythropoietin/DA-naïve patients but with high transfusion frequency or high endogenous erythropoietin level is major erythroid

response (MER), defined as sustained transfusion independence in transfusion-dependent patients or a rise in hemoglobin > 2 g/dL in transfusion-independent patients with anemia for a minimum of eight consecutive weeks. The objective MER will be assessed 16 weeks after start of study treatment. At the time of objective MER assessment, patients who fail to achieve MER on Arm A will be allowed to crossover to Arm B.

When patients were treated with lenalidomide alone in phase II trials, the MER rates were 25%-34% in patients without a chromosome 5q31.1 deletion and 67% with a chromosome 5q31.1 deletion. There is limited clinical information for the combination of lenalidomide with epoetin alfa. In a pilot study involving 40 patients that had failed erythropoietin monotherapy, 5 of 18 patients who received the lenalidomide and epoetin alfa combination treatment achieved an erythroid response after failing to respond to lenalidomide alone, including 3 MER (12). When UT7 erythroid progenitor cells are treated with lenalidomide and in vitro, clonogenic response and STAT5 activation is additive or greater. Thus, we anticipate that MER rate for the combination of lenalidomide with epoetin alfa will be even higher. Based on this information, we hypothesize that the MER rate in Arm A (lenalidomide) will be 30% and anticipate that the MER rate in Arm B (lenalidomide + epoetin alfa) will be at least 50%. Thus the study is designed to detect an improvement of 20% in the MER rate from 30% to 50%, comparing Arm A to Arm B. Using the statistical package EaSt (Cytel Software Corporation, 1993) to account for multiple interim looks in a sequential design for binomial distribution with continuity correction, a sample size of 212 cases will provide approximately 80% power to detect improvement in MER rate with an overall one-sided type I error rate of 0.025. The primary comparison of the MER rates will be performed on all patients randomized before May 19, 2010 and after September 24. The 14 patients (7 on arm A; 7 on arm B) randomized between May 19, 2010 and September 24, 2010 will be excluded. A secondary analysis will include all 226 patients randomized to this study.

9.3 Secondary Objectives

All analyses on secondary endpoints will be performed on 212 patients randomized before May 19, 2010 and after September 24. The 14 patients (7 on arm A; 7 on arm B) randomized between May 19, 2010 and September 24, 2010 will be excluded.

Time to MER is defined in responders as the time from randomization to the documented date of MER. For transfusion independent patients, the date of MER is the first date of the elevation in hemoglobin level of more than 2 g/dL that has been sustained for at least 8 weeks. For transfusion dependent patients, the date of MER is the beginning date of the time interval of transfusion independence that has been sustained for at least eight weeks.

Time to MER will be compared between lenalidomide monotherapy and combined treatment of lenalidomide and epoetin alfa in MER responders, using a one-sided log-rank test at the significance level of 0.025. Data from a prior study, MDS-001, of patients with MDS show that the median to MER is 11.5 weeks for patients on the lenalidomide schedule of 10 mg/day for 21 days (10). Under the assumption that the proportions of major erythroid responders are 30% for the monotherapy and 50% for the combined therapy, the log-rank test will have 80% power to detect a hazard ratio of 1.88 of the combined therapy over the

monotherapy. If time to MER follows an exponential distribution, this difference corresponds to an improvement in median time to MER from 11.5 weeks to 6.1 weeks.

Duration of MER response is defined as the time interval between the documented date of MER and the earliest date of resumption of RBC transfusions ≥ 2 units in an 8 week period, a reduction in hemoglobin concentration ≥ 2 g/dL in the absence of acute infection, gastrointestinal bleeding and hemolysis, or death.

Duration of MER response will be summarized by Kaplan-Meier method for patients who achieve MER by treatment arms. A secondary analysis will be done on duration of MER response by excluding all patients on arm B whose epoetin alfa treatment was interrupted by the drug supply issue occurred in September 2010.

The 90% confidence interval of the rate of MER to salvage combination therapy will be computed in patients who fail to achieve an MER with lenalidomide monotherapy and cross over to the combination therapy. Since it is assumed that the MER rate on the monotherapy arm is 30%, 74 patients from the monotherapy arm will fail to achieve MER. If among them 60 patients cross over to the combination therapy arm, the 90% confidence interval of the MER rate of the 60 patients will be no wider than 22.5%. A secondary analysis will be done on the rate of MER to salvage combination therapy by excluding those cross over patients whose epoetin alfa treatment was interrupted by the drug supply issue occurred in September 2010.

The minor erythroid response rate will be compared between treatment arms by Fisher's exact test. In a prior study MDS-001 of patients with MDS, 2 minor erythroid responses were observed from 17 patients who were on the lenalidomide schedule of 10 mg/day for 21 days (10). If the minor erythroid response rate is 10% for the monotherapy arm and 30% for the combination therapy arm, there is 94% power to detect this difference at a two-sided significance level 0.05.

Cytogenetic response rate will be calculated by treatment arm among patients with cytogenetic abnormalities, along with its 90% confidence interval. If 45% of patients are expected to have genetic abnormalities, the 90% confidence interval of the response rate is no wider than 25.6% for each arm.

Bone marrow response (CR+PR) rate and its 90% Confidence Interval will be calculated by treatment arm. The 90% Confidence Interval of the bone marrow response rate is no wider than 16.8% for each arm.

9.4 Interim Analyses

All interim analyses will be performed on patients randomized before May 19, 2010 and after September 24. The 14 patients (7 on arm A; 7 on arm B) randomized between May 19, 2010 and September 24, 2010 will be excluded.

The interim analyses will be conducted every six months, in conjunction with scheduled ECOG-ACRIN DMC meetings, starting at 25% information time, unless small increments of information (<10%) are gained during six months. Taking the delay of the initiation of accrual and the study suspension into account, the first and final analyses are anticipated to take place at

approximately 2.5 and 5.5 years after the study begins active accrual. The formal interim analyses will be conducted using the truncated O'Brien Fleming group sequential boundaries as described in Freidlin et.al. (1999).

Table 1 summarizes the operating characteristics of this design. For example, this trial can be stopped early at the fourth interim analysis (63% information time) in favor of an alternative hypothesis of adding lenalidomide to epoetin alfa improves the MER rate if the standardized test statistic comparing two MER rates is greater than 2.6523.

Table 1: Operating Characteristics

Analysis	Information Time	Eligible Cases for Two Arms	Upper Boundary	Nominal Significance level
1	0.25	53	3.2905	0.0005
2	0.38	80	3.2905	0.0005
3	0.51	108	3.0606	0.0011
4	0.63	133	2.6523	0.004
5	0.75	159	2.4101	0.008
6	0.88	186	2.2094	0.014
7	1.00	212	2.0703	0.019

Since lenalidomide in combination with epoetin alfa might not significantly improve the MER rate compared to lenalidomide alone, this study will be monitored for early stopping in favor of null hypothesis. Using repeated confidence interval methodology similar to that described by Jennison and Turnbull, at each interim analysis, a nominal 1-α confidence interval on the difference in MER rates will be computed using the nominal one-sided significance level of the use function boundary at the information fraction at the particular analysis time. The results will be provided to the DMC as a guideline to use when evaluating the study. If the confidence interval does not contain the alternative of interest, 20%, consideration may be given to early termination of the study.

9.4.1 Early Stopping for Excessive Toxicity

All toxicities will be monitored closely and reported using ECOG-ACRIN's standard AE mechanism. Since the proposed regimen of lenalidomide or lenalidomide + epoetin alfa has not been examined in a cooperative group setting, the tolerability of these regimens will be initially tested in the first 30 patients in Arm A and Arm B. We will consider each regimen tolerable if the grade 3 or higher thrombo-embolic events is 1% or less, and intolerable if the rate is 10% or higher. In addition to thrombo-embolic events, we will consider each regimen tolerable if the grade 3 or higher regimen related other toxicity rate is 30% or less, and intolerable if the rate is 50% or greater with proper dose adjustment. Hematologic toxicities are expected effects of the regimens and therefore will not be considered in the stopping rule. If, in the first 30 patients treated in Arm A or Arm B, we observe 2 or more patients with grade 3 or higher thrombo-embolic events, or 13 or more patients with grade 3 or higher related other toxicity after proper dose adjustment, the study will be terminated to further accrual. Assuming statistical independence of occurrence of thrombo-embolic events and other regimen related toxicities, with this

design, the probability of terminating the study early is 0.12 if the true but unknown rate of grade 3 or higher thrombo-embolic events is 1% and the true but unknown rate of grade 3 or higher other toxicity is 30%; the probability of terminating the study early is at least 0.83 if the true but unknown rate of grade 3 or higher thrombo-embolic events is 10% or the true but unknown rate of grade 3 or higher other toxicity is 50%. If the study does not meet those toxicity early stopping rules after the first 30 patients in arm B, additional 9 patients on arm B will be closely monitored for grade 3 or higher thrombo-embolic and other regimen related toxicities and the results will be reported to DMC.

9.5 Statistical Analysis for Correlative Studies

We expect that at least 60-70% of samples collected for correlative studies will be adequate for analysis. The statistical plan for the first and the third aim is based on the assumption of 132 patients (62% samples of 212 patients randomized before May 19, 2010 and after September 24) are available for analysis of correlative studies. The statistical plan for the second aim is based on the assumption of 16 del5q31.1 patients (62% samples of 26 del5q31.1 patients enrolled to the study) are available for analysis of correlative studies.

9.5.1 Evaluate the effect of CD45 isoform profile on lenalidomide enhancement of erythropoietin-induced STAT5 phosphorylation in $CD71^{Hi}$ erythroid precursors and the relationship to erythroid response.

The association between the CD45 isoform profile and ex vivo augmentation of STAT5 phosphorylation by lenalidomide will be assessed by simple regressions. The phosphorylation delta (PD) as quantified by the $\log_{10}$ ratio of p-STAT5 geometric mean fluorescence intensity (MFI) with lenalidomide (LEN)+ erythropoietin versus erythropoietin treatment alone (i.e., LEN+erythropoietin:EPO) will be regressed on RA:RO, RB:RO ratios separately. With 132 non-del5q31.1 patients, there is 83% and 94% power to test this association at a two-sided significance level of 0.05, if the true but unknown correlation between PD and RA:RO (or RB:RO) ratio is 0.25 and 0.3 respectively. The relationship between the CD45 isoform profile and MER response status will be assessed by treatment arm. RA:RO and RB:RO ratios will be compared between MER responders and non-responders within each treatment arm using the Wilcoxon rank sum test. The same assessment will be performed on the relation between PD and MER response status, and on the relation between apoptosis reduction and MER response status.

Prior studies show that response rate to erythropoietin varies for patients with different serum erythropoietin levels. To investigate if the addition of DA benefits the group of patients with sub-optimal erythropoietin production at baseline, MER response rates will be compared between treatment arms in the subset of patients with low serum erythropoietin levels at baseline (defined as <500 mU/ml) using Fisher's exact test. Furthermore, to investigate if primary resistance to lenalidomide monotherapy is due to low endogenous erythropoietin production, the change in serum erythropoietin levels at 16 weeks

from baseline of non- del5q31.1 patients on the monotherapy arm will be compared between MER responders and non-responders using Wilcoxon rank sum test. It is hypothesized that the decline in serum erythropoietin levels correlates with non-response.

The correlation between the magnitude of erythropoietin/STAT5-PD induced ex vivo by lenalidomide in pretreatment specimens and the magnitude of in vivo activation will be assessed using simple regressions by treatment arms. With 66 non- del5q31.1 patients per arm, there is 84% and 93% power to test this association at a two-sided significance level of 0.05, if the true but unknown correlation between PD and RA:RO (or RB:RO) ratio is 0.35 and 0.4 respectively.

Characterize molecular targets relevant to lenalidomide cytotoxicity in del5q31.1 cells

To determine whether lenalidomide modulates the phosphatase activity of Cdc25C and PP2A in bone marrow MNC from MDS patients with or without del5q31.1, a series of comparisons will be made. The RNA and protein expression level of Cdc25C, PP2A and their phosphatase substrates, Cdc2phospho-Tyr15 and Cdc25Cphospho-Ser216 will be compared between 16 MDS patients with del5q31.1, 20 MDS patients with normal cytogenetics that are not receiving active therapy and 20 age-matched normal volunteers. Pair-wise comparisons will be conducted by using t-test. Under the assumption of equal variances of groups, with the above number of samples per group, the t-test has at least 82% power to detect an effect size of 1 standard deviation for each pair-wise comparison at a two-sided significance level of 0.05.

In the factorial experiment for the investigation of whether reduction of either Cdc25C or PP2A alone or in combination leads to lenalidomide sensitization in patients with normal karyotype, each patient's sample will be aliquotted to 4 equal portions which are randomly exposed to 4 conditions, the cross of inhibition or not inhibition of gene expression of Cdc25C and PP2A by siRNAs. This experiment will be performed in samples from twenty patients. Assume that 50% of MDS cases enrolled to the E2905 trial will have normal cytogenetics by conventional metaphase karyotyping and that 5% of MDS cases with normal cytogenetics may contain minor abnormalities in the 5q31.1 CDR by SNA arrays, to arrive at 20 patients with normal karyotype, 45 bone marrow samples (each from an individual MDS patient) eligible for analysis need to be obtained. Apoptosis and cell cycle from this randomized blacks design will be analyzed by using Analysis of Variance (ANOVA) with the blocking variable patient as the random effect.

9.5.2 Evaluate the frequency of cryptic chromosome 5q31.1 deletions in patients with non- del5q31.1 MDS by array-based genomic scan, and to determine the relationship to hematologic response

Signal intensity will be analyzed and SNP calls determined using Gene Chip Genotyping Analysis Software Version 4.0 (GTYPE). Copy number will be investigated using a Hidden Markov Model and Copy

Number Analyzer for Affymetrix GeneChip Mapping 1000K arrays (CNAG v.3.0)22. Segmental LOH will be identified by a statistical assessment of the likelihood that consecutive SNP loci would exhibit heterozygosity given the corresponding allelic frequency of particular SNP in the normal population (CNAG). Lesions identified by SNP arrays will be compared with the Cancer Genome Anatomy Project database (http://cgap.nci.nih.gov). The two-sided Fisher's Exact test will be used to analyze the difference between the distributions of dichotomized variables among the groups. Normal copy number polymorphisms will be identified according to http://projects.tcag.ca/variation/.

LOH that correlates with response/refractoriness will be identified through the following approach. Frequencies of LOH within q-arm of chromosome 5 will be compared between hematologic responders and non-responders using Fisher's exact test. To control for false positives, nominal p-values from Fisher's exact tests will be adjusted such that the FDR (false positive rate) is controlled under 5%. Distribution of cryptic copy number changes of SNP on the q-arm of chromosome 5 will also be compared between hematologic responders and non-responders using the Chi-square test. False positives will also be controlled as in the LOH analysis. Analogous calculations are planned for the exploration of presence of "any lesion" throughout the genome, numbers of lesions and each specific lesion type (e.g. 7q, UPD7q etc) and its association with response/non-response.

9.6 Gender and Ethnicity

Based on previous data from E1996 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	2	2
Not Hispanic or Latino	93	157	250
Ethnic Category: Total of all subjects	93	159	252
Racial Category			
American Indian or Alaskan Native	0	2	2
Asian	0	2	2
Black or African American	2	7	9
Native Hawaiian or other Pacific Islander	0	0	0
White	91	148	239
Racial Category: Total of all subjects	93	159	252

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.7 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DMC. Any DMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DMC Policy can be obtained from the ECOG-ACRIN Operations Office - Boston.

10. Pathology Review

NOTE: ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.5.

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Pathology materials should be submitted for diagnostic review, classification and correlative studies.

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Rev.4/15

10.1 Pathology Submission

When a patient is registered to receive protocol therapy, the submitting pathologist and clinical research associate should refer to Appendix (Pathology Submission Guidelines) which provides the following:

10.1.1 Instruction Sheet from ECOG-ACRIN Central Biorepository and Pathology Facility providing details for the Submission of Pathology Materials.

10.1.2 Memorandum to the submitting pathologist from Stanley Hamilton, M.D., chair, ECOG-ACRIN Laboratory Science and Pathology Committee, providing details for the Submission of Pathology Materials.

10.1.3 A list of required materials.

10.2 Materials required for this protocol:

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[Note deleted in Addendum #1]

Rev. 7/11

10.2.1 Sample Tracking System Shipping Manifest Form

Rev. 10/09

In addition to the surgical pathology report, if immunologic studies (ex. flow cytometry) have been performed at the home institution, it is necessary that these be forwarded as well.

Rev. 7/11

10.2.2 Biological Sample Submissions

10.2.2.1 Pathology Review (Mandatory):

Rev. 7/11

Baseline, Weeks 16 and 32, Year 1, and Progression/End of Treatment

Rev. 10/09

- Two (2) stained bone marrow smears to include one (1) Wright-Giemsa (W-G) stain and one (1) Iron Stain

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- One (1) H&E stained bone marrow biopsy slide

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- One (1) W-G stained peripheral blood smear

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[Note Deleted in Addendum #1]

NOTE: Submission of pathologic materials for diagnostic review is mandatory in order for the patient to be considered evaluable. Failure to submit pathologic materials may render the case unevaluable.

10.2.2.2 Correlative Studies (Optional Based on Patient Consent)

Paraffin blocks from bone marrow trephine biopsies should be submitted at the following time points:

- Baseline
- Week 16
- Week 32
- Year 1
- Relapse/End of Treatment

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NOTE: If blocks cannot be submitted, please submit five (5) unstained bone marrow biopsy level slides. If you have questions, please call Lynn Moscinski at (813) 979-3001.

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10.3 Shipping Procedures

Log the shipment into the ECOG-ACRIN Sample Tracking System (STS) the day of shipment.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager

10.3.1 Submission Schedule

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10.3.1.1 The required initial diagnostic materials must be submitted within one month of patient registration. Materials should be submitted within one month of collection for the additional time points.

10.3.1.2 For the blocks for correlative studies, materials should be submitted within one month of collection (Section 10.2.2.2).

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10.3.2 Shipping Address:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Boulevard
Houston, TX 77030
Toll Free Phone: (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

Access to the FedEx shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all sample submissions.

10.4 ECOG-ACRIN Central Biorepository and Pathology Facility: Sample Processing and Routing

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Rev. 4/15

Pathology review materials for confirmation of diagnosis, pathologic response and at progression will be forwarded to John Bennett, M.D. for review. Materials for the correlative studies will be forwarded to Dr. Lynn Moscinski at Moffitt Cancer Center.

10.5 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all biological samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). All sites, regardless of group affiliation, are required to use the ECOG-ACRIN STS. As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN username or password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

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Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

A shipping manifest form must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog-acrin.tst@jimmy.harvard.edu.

10.5.1 Study Specific Notes

Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at time of sample submission. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN Central Biorepository and Pathology Facility
- ECOG-ACRIN Cytogenetic Laboratory
- Dr. Alan List Laboratory/H. Lee Moffitt Cancer Center

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Rev.4/15

NOTE: When collecting and shipping baseline research specimens (such as bone marrow and peripheral blood), there will be no screening # available. Please note patients must sign consent before the collection of the baseline bone marrow and peripheral blood. Therefore, Dr. List's laboratory (813-745-8271) must be notified of specimen arrival, and then the specimens must be logged into the ECOG-ACRIN STS post-randomization, once the patient has an ECOG-ACRIN sequence number. Please call the receiving laboratories with the ECOG-ACRIN patient sequence number once the patient is randomized.

Retroactively enter all specimen collection and shipping information when STS is available.

10.6 Banking

Residual blocks and/or slides will be retained for banking at the ECOG-ACRIN Central Tissue Repository for possible use in future ECOG-ACRIN approved studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11. Correlative Studies

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NOTE: ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System. An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.5.

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Rev. 4/15
Rev. 7/11

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

11.1 Cytogenetic Review (Mandatory)

The cytogenetic review will be performed by the ECOG-ACRIN Cytogenetic Laboratory at Mayo Clinic.

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NOTE: All study participants/cooperative groups must submit karyotypes to the ECOG-ACRIN Cytogenetic Laboratory as outlined below.

11.1.1 Sample Submission Schedule

Within 30 days of chromosome study for each applicable time point, investigators will send original karyotypes, cytogenetic laboratory report, and completed form #365R to the ECOG-ACRIN Cytogenetic Committee.

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Karyotypes must be submitted at:

- Baseline
- Week 16 (after study treatment)

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- Week 32
- Year 1

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- Relapse/Progression/End of Treatment

NOTE: Karyotypes are required at all time points.

Direct questions to Gary Hicks at Tel: (507) 284-2950 or Fax: (507) 284-0043.

11.1.2 Sample Preparation Guidelines

The following materials are to be submitted within one month after each time point:

- Two original karyotypes per clone
- Institution's cytogenetic laboratory report
- The Leukemia Cytogenetics Form (#365R)

11.1.3 Shipping Procedures

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Log the shipment into the ECOG-ACRIN STS the day of shipment. If the STS is unavailable, an Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

The forms and original karyotypes are to be sent to:

Gary Hicks

Mayo Clinic Cytogenetics Laboratory
970 Hilton
200 First Street, S.W.
Rochester, MN 55905
Tel: (507) 284-2950
Fax: (507) 284-0043

An STS shipping manifest form must be generated and shipped with all sample submissions.

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NOTE: If cytogenetic studies are not successful, submit the laboratory report and #365R form to Gary Hicks by mail or fax.

Original karyoptypes will be returned upon written request when the review and analysis are complete.

11.2 Additional Laboratory Studies

Biomarker studies described in the Statistical Section that are intended to investigate biological mechanisms of response and resistance to treatment will be performed under the direction of Dr. Alan List at the Moffitt Cancer Center.

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Peripheral blood and bone marrow aspirate samples are requested at the intervals indicated below.

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Sample Type	Baseline	Week 16	Week 32	Year 1	Relapse or End of Treatment
Peripheral Blood (Two 10 mL Sodium Heparin tubes)	X	X	X	X	X
Bone Marrow Aspirate (5 mL EDTA tube)	X	X	X	X	X

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If you have any questions, please contact Kathy McGraw or Ashley Basiorka at (813) 745-8271.

NOTE: If patient has prior documentation of a chromosome 5q deletion, please make note in the comments section of the Sample Tracking System (STS).

11.2.1 Sample Preparation Guidelines

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All samples should be clearly labeled with detailed patient information, ECOG-ACRIN Protocol Number, ECOG-ACRIN Patient Sequence Number, Patient Initials, Date, and Type of Sample: Bone Marrow (BM)/Peripheral Blood (PBL).

11.2.1.1 Bone Marrow Aspirate

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BM aspirate samples should be collected after coating the syringe with a small amount of preservative-free sodium heparin then transfer it to sterile vacutainer tube(s) containing EDTA preservative (purple tops) for immediate

shipment. The tube must be wrapped in absorbable material and then be placed in an airtight/leakproof container (such as a zip lock bag) and placed in a padded styrofoam container. Express mail envelopes alone are NOT adequate.

11.2.1.2 Plasma

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Peripheral blood should be drawn into two (2) standard 10 mL sodium heparin tubes.

11.2.2 Shipping Procedures

Log the shipment into the ECOG-ACRIN STS the day of shipment. If the STS is unavailable, an Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

Heparinized bone marrow aspirates and plasma should be shipped overnight on cool packs (warm weather months), wrapping the vials to insure that the marrow does not freeze. Specimens must be shipped via next day delivery on the day the specimen is obtained.

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DO NOT USE DRY ICE OR WET ICE. During hot summer days, place a cold pack in the container to keep the temperature in the container cool.

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Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

Access to the FedEx shipping account can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

Call Kathy McGraw or Ashley Basiorka at (813) 745-8271 on the day of expected shipment to confirm delivery date.

Shipping Address:

For WEEKDAY Shipping (for ARRIVAL on Monday-Friday):

H. Lee Moffitt Cancer Center
Kathy McGraw, Dr. Alan List Laboratory
Rev. 10/09, 4/15 SRB3/23234/K Rocha/x8271
12902 Magnolia Drive
Tampa, FL 33612
Phone: 813-745-8271

An STS shipping manifest form must be generated and shipped with all sample submissions.

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Please only ship on Monday through Thursday. Please do not ship on Fridays or the day before a holiday. Specimens cannot be accepted on the weekends.

11.2.3 Studies to be Performed:

11.2.3.1 To evaluate the effect of CD45 isoform profile on lenalidomide enhancement of erythropoietin-induced STAT5 PHN in $CD71^{Hi}$ erythroid precursors and the relation to erythroid response

The goal of the proposed studies is to delineate the value of CD45 isoform profile and the capacity of LEN to augment erythropoietin/STAT5 PHN in $CD71^{Hi}$ erythroid precursors to predict response to study treatment, and to confirm the role of the CD45 PTP as a key negative regulator of the erythropoietin-R signal in non-del5q MDS. We hypothesize that LEN promotes erythropoiesis in non-del5q MDS by relieving CD45 suppression of JAK2/Lyn kinase-mediated STAT5 activation after erythropoietin-R/ligand engagement. Dual features of (a) large CD45 isoform predominance, and (b) enhancement of erythropoietin/STAT5 activation by LEN in $CD71^{Hi}$ erythroid precursors, therefore, may identify non-del5q patients with rhu-erythropoietin resistance and potential responsiveness to LEN treatment. Moreover, these studies will further characterize the impact of CD45 isoform profile on erythropoietin-R signal capacity and erythroid progenitor survival.

To validate this hypothesis, we will assess CD45-RA, -RB and -RO isoform distribution in pretreatment BM erythroid precursors ($CD71^{Hi}$), and the magnitude of erythropoietin-induced STAT5 PHN in the presence and absence of LEN using a sensitive flow cytometry assay. *Ex vivo* augmentation of STAT5 PHN by LEN in $CD71^{Hi}$ cells (i.e., the *PHN delta, PD)* will be quantified by the $\log_{10}$ ratio of p-STAT5 geometric mean fluorescence intensity (MFI) with LEN (LEN)+ erythropoietin versus erythropoietin treatment alone (i.e., LEN+erythropoietin: erythropoietin). CD45 isoform profile in $CD71^{Hi}$ cells will be assessed by the RA:RO and RB:RO isoform geometric MFI ratios. Magnitude of LEN enhancement of erythropoietin/STAT5 PHN (i.e., *PD*) according to CD45 isoform ratio and the linkage between isoform ratio and LEN associated reduction in erythroid apoptotic fraction will be evaluated as a continuum to determine the *PD* and isoform ratio associated with a threshold necessary for clinical response and augmentation of erythroid survival. Moreover, the capacity for LEN augmentation of STAT5 activation will be confirmed *in vivo* by comparing STAT5 PHN intensity in erythroid precursors by immunohisto-chemistry in fixed BM biopsy sections from pre-treatment and week16, post-treatment BM specimens. Because our investigations indicate that the erythropoietic effects of LEN in non-del5q MDS are erythropoietin-dependent, clinical resistance to

LEN monotherapy (Arm A) may arise from endogenous erythropoietin under-production despite evidence for *ex vivo* erythropoietin/STAT5 activation. PB plasma erythropoietin concentration will be assessed prior to treatment and at week 16 of LEN monotherapy by enzyme-linked immunosorbant assay (ELISA) and the findings correlated with treatment response and results of *ex vivo* p-STAT5 *PD* in the pre-treatment BM specimen. The proposed studies will be the first to characterize the erythropoietin-R signal axis in MDS, its regulation by a key PTP, and the application of a pharmaco-dynamic model to identify patients responsive to a targeted therapeutic in a large, uniformly treated MDS population. Moreover, primary and secondary treatment failure specimens provide a valuable resource to explore mechanism(s) of treatment resistance and the relationship to erythropoietin-R signal suppression.

11.2.3.2 To characterize molecular targets relevant to lenalidomide cytotoxicity in del5q

We have shown that LEN inhibits the PPT activity of both Cdc25C and PP2A *in vitro*. We hypothesize that enforced reduction in Cdc25V expression, using siRNA, mimics the naturally occurring events of haplo-deficiency in del5q AML and MDS cells. The goal of this specific aim, using U937-siCdc25c cells as a model, is to determine whether inhibition of Cdc25C mediates the cellular apoptotic events associated with LEN treatment. We will further define whether Cdc25C and PP2A coordinately regulate cell survival in U937 cells. Finally, we will utilize a siRNA retroviral-based expression system targeting Cdc25C and PP2A to determine whether coordinated disruption of these two PPTs induce apoptosis in cells from non-del5q MDS patients *in vitro*. Through experiments proposed in this specific aim, we will provide important biochemical and molecular information about LEN mechanisms of action. Understanding the signaling mechanisms of LEN will better enable the development of targeted drug therapy for MDS; selecting inhibitors for key signaling events that mediate survival and transformation of the leukemic clones.

11.2.3.3 To evaluate the frequency of cryptic chromosome 5q31 deletions in patients with non-del5q MDS by array-based genomic scan, and to determine the relationship to hematologic response.

The main goal of the proposed studies is to delineate sub-microscopic chromosome 5q31 deletions that are not resolved by conventional metaphase cytogenetics. For that purpose, high-density array-based genome mapping will be performed to characterize molecular markers for response and identify cryptic chromosomal lesions that

may explain clinical heterogeneity of patients with and without 5q31 deletions with regard to the speed of disease progression, response failure or emergence of treatment resistance. Our strategy is to perform, in addition to routine metaphase cytogenetic analysis, a high density genomic scan of hematopoietic cells to detect clonal somatic chromosomal defects. We hypothesize that micro-deletions, smaller previously cryptic defects and/or UPD of 5q regions may be associated with responsiveness to LEN in patients with non 5q31 metaphase cytogenetics. Furthermore, we suggest that resistance, whether primary or developed in the course of therapy, may be associated with additional previously cryptic lesions affecting other chromosomal regions. First, we will correlate the presence of specific defects with the therapy response or refractoriness and subsequently we will monitor detection/appearance of new aberrations that may convey resistance. Finally, we plan to study the commonly affected regions of characteristic shared lesions for the presence of genes that can play a role in the pathogenetic mechanisms.

11.3 Banking

The residuals and/or derivatives of bone marrow and blood samples collected for the correlative studies will be retained at the ECOG-ACRIN Leukemia Translational Studies Laboratory for possible use in ECOG-ACRIN approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.4 Sample Inventory Submission Guidelines

Inventories of all samples collected and aliquoted, and used on the above mentioned laboratory correlative studies will be submitted to the ECOG-ACRIN Operations Office - Boston on a monthly basis. Inventories will be submitted electronically or by diskette by any laboratory holding and/or using any specimens associated with this study. Electronic submissions should be submitted to ecog.labdata@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Translational Science Team.

11.5 Lab Data Transfer Guidelines

The data collected on the above mentioned correlative studies will be submitted to the ECOG-ACRIN Operations Office - Boston by the central laboratories on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates. Electronic submissions should be submitted to ecog.labdata@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Translational Science Team.

12. Records to Be Kept

Please refer to the E2905 Forms Packet for the forms submission schedule and copies of all forms. The E2905 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

12.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years from the date of the FDA review
- two years from the notification of the withdrawal of the IND

Please contact the ECOG-ACRIN Operations Office - Boston prior to destroying any source documents.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

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Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

Version Date: 9/22/2011

Appendix I

Informed Consent Template for Cancer Treatment Trials
(English Language) [DELETED IN ADDENDUM #7]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E2905

Rev. 4/15

4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Rev. 4/15

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)

Instructions:

1. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material to the appropriate pathologist.
2. The pathologist should return the required pathology samples and surgical pathology reports. If any other reports are required, they should be obtained from the appropriate department at this time.
3. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)
   Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.
4. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Boulevard
   Houston, TX 77030
   Toll Free Phone: (844) 744-2420 (713-745-4440 Local or International Sites)
   Fax: (713) 563-6506
   Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone (844) 744-2420 or by email eacbpf@mdanderson.org.

List of Required Material

E2905:	Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

Rev. 10/09, 7/11

All samples submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS) and an STS shipping manifest form included with every shipment. See Section 10.5.

Rev. 7/11
Rev. 4/15

Baseline, Weeks 16 and 32, Year 1 and Progression/End of Treatment

1. Generic Specimen Submission Form (#2981)
2. Institutional pathology report ***(must be included with EVERY pathology submission)***.
3. Materials submitted for:
   a. Pathology Review:

Rev. 10/09
- Two (2) stained bone marrow smears to include one (1) Wright-Giemsa (W-G) stain and one (1) Iron Stain

Rev. 10/09
- One (1) H&E stained bone marrow biopsy slide

Rev. 10/09
- One (1) W-G stained peripheral blood smear

Rev. 10/09

NOTE: Submission of pathology materials for diagnostic review is mandatory in order for the patient to be considered evaluable. Failure to submit pathologic materials may render the case unevaluable.

   b. Correlative Studies:

Paraffin blocks from bone marrow trephine biopsies should be submitted at the following time points:

- Baseline
- Week 16
- Week 32
- Year 1

Rev. 10/09
- Relapse/End of Treatment

Rev. 10/09

NOTE: If blocks cannot be submitted, please submit five (5) unstained bone marrow biopsy level slides.

MEMORANDUM

TO: (Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

Rev. 11/13
Rev. 4/15

DATE:

SUBJECT: Submission of Pathology Materials for E2905, Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

A patient has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review and correlative studies.

Please return, the surgical pathology report(s), the slides and/or blocks, and any other required material (see attached List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

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Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for use in future ECOG-ACRIN approved studies.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, therefore the block may not be returned.

If you have any questions regarding this request, please feel free to contact the Central Biorepository and Pathology Facility at Tel: (844) 744-2420 or email: eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

Appendix IV

World Health Organization (WHO) Diagnostic criteria for MDS

Once a diagnosis of MDS is established, eight subtypes of MDS are recognized in the WHO classification that are distinguished by the percentage of myeloblasts, the presence of ringed sideroblasts, number of dysplastic lineages, and karyotype as summarized in the following table:

World Health Organization Classification and Criteria for the Myelodysplastic Syndromes (MDS)		
MDS Subtype	**Blood Findings**	**Bone Marrow Findings**
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia *only* < 5% blasts < 15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia *only* > 15% ringed sideroblasts < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bi- or pancytopenia) No or rare blasts No Auer rods <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in 2 or more myeloid cell lines < 5% blasts in marrow No Auer rods < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bi- or pancytopenia) No or rare blasts No Auer rods <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in 2 or more myeloid cell lines ≥ 15% ringed sideroblasts <5% blasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias <5% blasts No Auer rods <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 5% to 9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias <5% to 19% blasts Auer rods ± <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes <5% blasts No Auer rods
MDS associated with isolated del(5q)	Anemia <5% blasts Platelets normal or increased	Normal to increased megakarocytes with hypolobated nuclei < 5% blasts No Auer rods Isolated del(5q)
Adapted from reference 14. (see Section 14 of protocol)		

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Appendix V

ECOG Performance Status Score

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

Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

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Appendix VI

[DELETED IN ADDENDUM #4]

Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

Appendix VII

Cooperative Research and Development Agreement (CRADA)

NCI/ DCTD Standard Protocol Language

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

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) 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"
Rev. 4/15 (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing 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 as described in the IP

Option to Collaborator
Rev. 4/15 (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

Rev. 4/15 6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

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

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Appendix VIII

Medication Diary

Please complete this diary on a daily basis. Write in the amount of the dose of lenalidomide that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

If you experience any health/medical complaints or take any medication other than lenalidomide or epoetin alfa, please record this information.

For patients on Arm B, epoetin alfa will be administered by a health care professional. As a result, patients do not have to record their epoetin alfa injections in this diary.

Cycle # (Month):

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
lenalidomide							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
lenalidomide							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
lenalidomide							

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
lenalidomide							

Week of: _____

HEALTH/MEDICAL COMPLAINTS

Please record all health/medical complaints you may have experienced below.

Please describe what you experienced	Date started	Date stopped

OTHER MEDICATION

Record only medication (prescription and/or over-the-counter, including herbal medications and vitamins) taken other than lenalidomide or prednisone.

Name of Medication	Why did you take the medication?	Date medication started?	Date medication stopped

_____
Patient Signature

_____
Date

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Appendix IX

Specimen Submission Instructions for Southwest Oncology Group Patients
[DELETED IN ADDENDUM #1]

Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

Appendix X

Rev. 7/11

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 any woman, regardless of sexual orientation, or whether they have undergone tubal ligation, 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.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence 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.

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Appendix XI

Lenalidomide Education and Counseling Guidance Document

Rev. 7/11

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: □

Do Not Dispense study drug if:

- **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].**

FCBP:

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

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Appendix XII

Lenalidomide Information Sheet

Rev. 7/11

FOR PATIENTS 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.

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Appendix XIII

CPPCP Site Counselor Form

Rev. 7/11, 6/14, 4/15

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 888.314.2392**
- **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 coop_ma@celgene.com**

General Information

Principal Investigator: _____Institution Name: _____

CTEP site ID: _____

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: _____

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Rev. 11/13

Appendix XIV

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Lenalidomide, or within 28 days of the patient's last dose of Lenalidomide must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via NCI's Adverse Event Expedited Reporting System (CTEP-AERS) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/CTEP-AERS.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office - Boston. Please contact the ECOG-ACRIN Operations Office - Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an amendment to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if

the outcome of the pregnancy occurred on a subsequent cycle, a new CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the NCI Medical Help Desk at 301-897-7497 or CTEP-AERSmd@tech-res.com, for it will need to be discussed on a case by case basis.

Rev. Add14 **Reporting a Pregnancy Loss**

A pregnancy loss is defined in CTCAE as "A death in utero."

It must be reported via CTEP-AERS as Grade 4 "Pregnancy loss" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions".

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Rev. Add14 **Reporting a Neonatal Death**

A neonatal death is defined in CTCAE as "A death occurring during the first 28 days after birth" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the in utero exposure to Lenalidomide must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "*Death Neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Rev. Add15 **Additional Required Forms:**

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the CTEP 'Pregnancy Information Form' must be completed and faxed along with any additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)