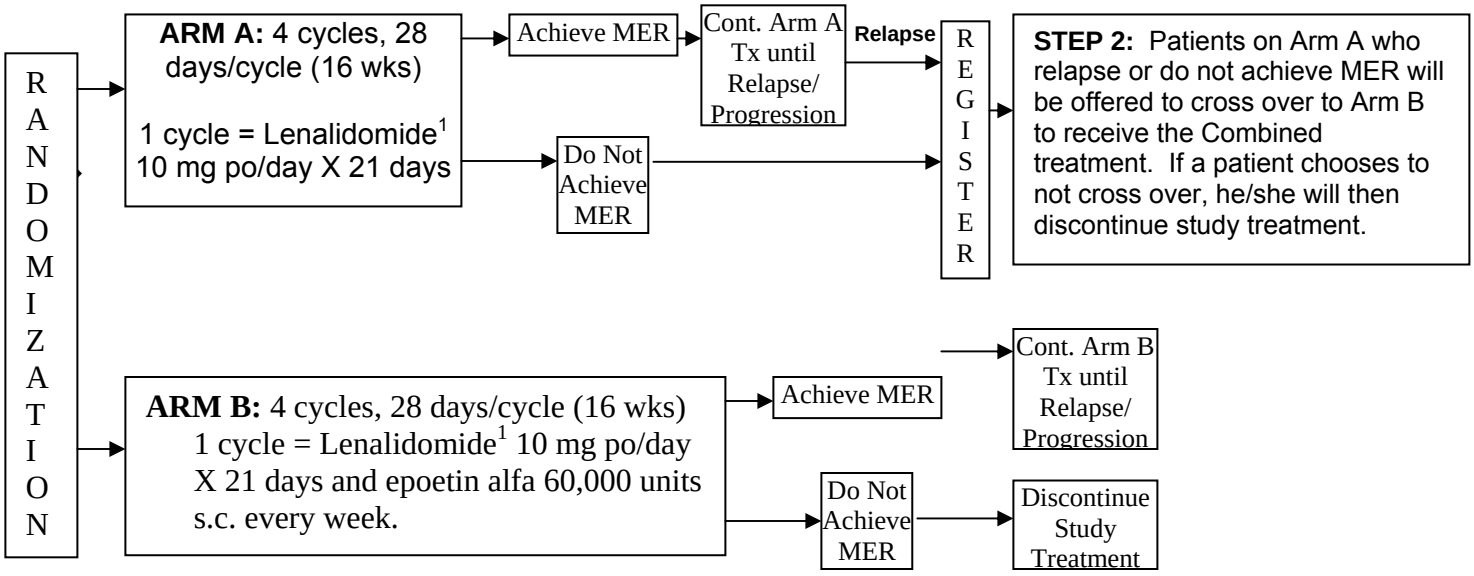
E2905: Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid) Alone and in Combination with Epoetin Alfa (Procrit) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia



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

MAJOR ELIGIBILITY CRITERIA: At least 18 years of age

- MDS duration ≥ 3 months, according to WHO criteria or non-proliferative CMML (WBC < 12,000/mcL)
- IPSS of low- or intermediate-1-risk disease. Patients with cytogenetic failure and < 10% marrow blasts will be eligible
- Symptomatic anemia un-transfused with hemoglobin ≤9.5 or with RBC transfusion-dependence confirmed for ≤ 8 wks before randomization
  - For non-transfusion dependent patients who receive periodic transfusions, the mean pre-transfusion hgb should be used to determine protocol eligibility and response reference
  - For non-transfusion dependent patients, a minimum of 2 pre-transfusion or un-transfused hgb values are required
- Must have failed treatment with an erythropoietic growth factor, or have low probability of response to erythropoietin. Low probability of response or prior erythropoietin failures are define as follows:
  - Prior failure: minimum trial of ≥ 40,000 units Procrit (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 failure to achieve a ≥ 2g rise in hgb sustained for ≥ 4 weeks in non-transfusion dependent patients
  - Low Response Profile: rhu-erythropoietin and epoetin alfa-naïve patients receiving ≥ 2U RBC/month, and serum erythropoietin > 500 mU/mL in the 8 weeks prior to randomization for hgb ≤ 9.5
- Must be off all non-transfusion therapy for MDS for 28 days prior to initiation of study treatment. Patients may receive hydrocortisone prophylactically to prevent transfusion reactions
- Must not have documented iron deficiency; must have documented marrow iron stores
  - If no marrow iron stain, the transferrin saturation must be > 20% or serum ferritin > 100 ng/mL
- Patients must meet the following criteria (twice within 21 days of randomization, must be separated by 7 days):
  - Platelet ≥ 50,000 w/o platelet transfusion ,ANC ≥ 500 without myeloid growth factor support
  - Serum creatinine ≤ 1.5 x ULN, Serum SGOT/AST or SGPT/ALT ≤ 2.0 x ULN, Serum total bilirubin < 3.0 mg/dL
- None of the following:
  - Women who are pregnant or breastfeeding; prior therapy with lenalidomide; diagnosis of uncontrolled seizure or uncontrolled hypertension; proliferative CMML; MDS secondary to treatment with radiotherapy, chemotherapy, and/or immunotherapy for malignant or autoimmune diseases; prior ≥ grade 3 allergic reaction to thalidomide; prior desquamating rash at time of study entry; clinically significant anemia resulting from iron, B_{12}, or folate deficiencies, autoimmune or hereditary hemolysis, or gastrointestinal bleeding; use of cytotoxic chemotherapeutic agents, erythropoietin, or experimental agents for the treatment of MDS within 8 weeks of randomization; prior history of malignancy other than MDS unless disease free for ≥ 3 years (except basal cell or squamous skin cell carcinoma or carcinoma in situ of cervix or breast); serious medical condition or any other unstable medical co-morbidity, or psychiatric illness; history of thrombo-embolic events within 3 years prior to study randomization; known HIV-1 seropositivity; known allergic reaction to epoetin alfa (Procrit) or human serum albumin

Crossover Registration from Arm A to Arm B

- Completion of 16 weeks of monotherapy with lenalidomide
- Failure to achieve MER (major erythroid response) or have achieved MER but relapsed on Arm A
- No limiting unresolved toxicity ≥ G 3 from lenalidomide monotherapy or drug tolerance preventing continuation of lenalidomide treatment

PRE-STUDY LABS AND TESTS: (Consent needs to be signed prior to screening bone marrow biopsy-study samples need to be sent)
< 56 days prior to randomization: ECG; TSH, T3, T4; serum erythropoietin; bone marrow biopsy/aspirate with iron stains and cytogenetics
Documentation of serum erythropoietin level during screening (≤56 days prior to randomization) and just prior to randomization
- **Hgb must be < 9.5**

Study samples: Mandatory: 2 unstained marrow smears, 1 H&E stained marrow slide, 1 peripheral smear.
Optional: marrow paraffin block, 1-10ml green top peripheral blood, 1-5ml EDTA (lavender top) tube of marrow)
Required twice prior to randomization: 21-14 days prior to randomization and within 7 days prior to randomization: CBC, diff, retic, lytes, Ca, BUN, creatinine, glucose, albumin, protein, alk phos, total bili, AST, ALT, uric acid, Mg, phosphorus, LDH
Pregnancy test to be done 10-14 days prior to first treatment and again within 24 hours of start of treatment
Day 1: CBC, differential, reticulocyte count

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