



Submitted by:
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Dear NCCN Myelodysplastic Syndromes Guidelines Panel:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for Myelodysplastic Syndromes (MDS) review the enclosed recently published Phase III data on the use of REVLIMID® (lenalidomide) in International Prognostic Scoring System (IPSS) Low or Intermediate-1 Risk MDS patients with red blood cell transfusion-dependent (RBC-TD) symptomatic anemia, without deletion 5q (del(5q)) abnormality. The submission of this publication is in follow-up to a previous submission dated December 22, 2014 (enclosed for your reference).

Specific Changes: Recommend the use of lenalidomide in patients with IPSS low/intermediate-1 risk MDS with symptomatic anemia without del(5q) and are ineligible for or refractory to ESAs as a preferred treatment option, with a *Category 1* rating. In addition, we request an update to the discussion section to include a description of these Phase III data, recently published in the Journal of Clinical Oncology.

FDA Clearance: REVLIMID is not approved for the treatment of non-del(5q) MDS. REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities (Celgene Corporation, 2015).

Please see the enclosed REVLIMID Prescribing Information for additional indications.

Rationale:

The MDS-005 study was an international, multicenter, randomized, double-blind Phase III trial comparing the efficacy and safety of lenalidomide to placebo in RBC-TD patients with IPSS low or intermediate-1 risk non-del(5q) MDS -ineligible for or refractory to ESAs (Santini et al., 2016). Two hundred thirty nine patients were randomized 2:1 to receive either lenalidomide (n=160) 10 mg orally

daily (5 mg daily for patients with creatinine clearance 40-60 mL/min) or placebo (n=79) (both on 28-day cycles). Median age of the patients was 71 years (range, 43-87 years) and baseline characteristics were similar. The primary endpoint of RBC transfusion independence (RBC-TI) for ≥ 8 weeks was achieved by significantly more patients treated with lenalidomide (26.9%) versus placebo (2.5%) ($P < 0.001$); RBC-TI for ≥ 24 weeks was observed in 17.5% vs. 0%, respectively. Ninety percent of patients responded within 4 cycles of treatment and the median duration of RBC-TI ≥ 8 weeks was 30.9 weeks (95% confidence interval [CI], 20.7, 59.1).

In a univariate analysis, response was significantly higher in patients with baseline EPO ≤ 500 mU/mL than in patients with EPO > 500 mU/mL (34% vs. 15.5%; $P = .015$). Median OS has not yet been reached; data are not mature enough to permit a definitive analysis. Collection of long term (≥ 5 years) follow-up data for OS is ongoing. The incidence of AML progression was 1.91 (95% CI, 0.80, 4.59) and 2.46 (95% CI, 0.79, 7.64) per 100 person-years for lenalidomide vs. placebo patients, respectively.

Grade 3/4 hematologic and non-hematologic treatment-emergent adverse events (TEAEs; $\geq 5\%$) in the lenalidomide vs. placebo arms, respectively, included: neutropenia (61.9% vs. 12.7%), thrombocytopenia (35.6% vs. 3.8%), infection (14.4% vs. 3.8%), hepatic disorder (5% vs. 2.5%) and cardiac arrhythmia (1.3% vs. 5.1%).

A copy of the 2016 publication is enclosed for your review (Santini et al., 2016).

Your consideration of this submission is greatly appreciated.

Sincerely,



June Keane, PharmD
Sr. Manager, Global Medical Information



Mary Sugrue, MD, PhD
Executive Director, US Medical Affairs Disease Lead-MDS, AML

Cited References:

1. Celgene Corporation. Revlimid (lenalidomide). Summit, NJ. 2015; <http://www.revlimid.com/>.
2. Santini V, Almeida A, Giagounidis A, et al. Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents. *J Clin Oncol*. 2016;:1-11. <http://www.ncbi.nlm.nih.gov/pubmed/27354480>.