



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 presented 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, who were unresponsive or refractory to erythropoiesis stimulating agents (ESAs).

Specific Changes: Recommend the use of lenalidomide in patients with IPSS low/intermediate-1 risk MDS with symptomatic anemia with no del(5q) and are unresponsive 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 recently presented Phase III data.

FDA Clearance: The FDA has not approved REVLIMID for the treatment non-del(5q) MDS. REVLIMID is indicated for the treatment of (Revlimid Prescribing Information):

- 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

Please see the enclosed REVLIMID Prescribing Information for additional indications.

Rationale:

The MDS-005 study, recently presented at the *Annual Meeting and Exposition of the American Society of Hematology (ASH)* on December 8, 2014, 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 MDS without del(5q) abnormality who were unresponsive or refractory to ESAs (Santini et al. 2014b; Santini et al. 2014a). 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). 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 17.3% vs. 0%, respectively. Ninety percent of patients responded within 4 cycles of treatment and the median duration of RBC-TI ≥ 8 weeks was 32.9 weeks (95% confidence interval [CI], 20.7, 71.1). Grade 3/4 hematologic and non-hematologic treatment-emergent adverse events (TEAEs) in the lenalidomide vs. placebo arms, respectively, included: neutropenia (61.9% vs. 12.7%), thrombocytopenia (35.6% vs. 3.8%), infections (14.4% vs. 3.8%), hemorrhage (1.9% vs. 0), hepatic disorder (5% vs. 2.5%), cardiac arrhythmia (1.3% vs. 5.1%), diarrhea (2.5% vs. 0%), cutaneous reactions (1.3% vs. 0%) and constipation (0% vs. 2.5%); deep vein thrombosis (DVT) was reported in 1.9% of lenalidomide treated patients.

The results of the Phase III MDS-005 study corroborate the results of the Phase II, MDS-002 study of lenalidomide in lower risk transfusion-dependent non-del(5q) MDS patients, in which 26% of lenalidomide-treated patients achieved RBC-TI. These data are already described within the NCCN guidelines for MDS (Raza et al. 2008).

A copy of the oral presentation from ASH 2014 is enclosed for your review (Santini et al. 2014a). Additional data regarding the efficacy and safety of lenalidomide in support of the proposed change can be found in the following citation: (Toma et al. 2013).

In closing, we believe these Phase III data support the use of lenalidomide as a treatment option for RBC-TD, low or intermediate-1 risk MDS patients without del(5q) who are unresponsive or refractory to ESAs. Your consideration of this submission is greatly appreciated.

Sincerely,



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

Cited References:

1. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1-risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood* 2008; 111(1): 86-93.
<http://www.pubmed.gov/17893227>
2. Revlimid (lenalidomide) Prescribing Information. Summit, NJ: Celgene Corporation.
<http://www.revlimid.com/>
3. Santini V, Almeida A, Giagounidis A, et al. Efficacy and Safety of Lenalidomide (LEN) Versus Placebo (PBO) in RBC-Transfusion Dependent (TD) Patients (Pts) with IPSS Low/Intermediate (Int-1)-Risk Myelodysplastic Syndromes (MDS) without Del(5q) and Unresponsive or Refractory to Erythropoiesis-Stimulating Agents (ESAs): Results from a Randomized Phase 3 Study (CC-5013-MDS-005) [oral]. *Oral presented at: 56th Annual Meeting and Exposition of the American Society of Hematology (ASH)* 2014a; December 6-9; San Francisco, CA; USA.
4. Santini V, Almeida A, Giagounidis A, et al. Efficacy and Safety of Lenalidomide (LEN) Versus Placebo (PBO) in RBC-Transfusion Dependent (TD) Patients (Pts) with IPSS Low/Intermediate (Int-1)-Risk Myelodysplastic Syndromes (MDS) without Del(5q) and Unresponsive or Refractory to Erythropoiesis-Stimulating Agents (ESAs): Results from a Randomized Phase 3 Study (CC-5013-MDS-005) [abstract]. *Proceedings of the 56th Annual Meeting and Exposition of the American Society of Hematology (ASH)* 2014b; December 6-9; San Francisco, CA; USA: Abstract #409.
5. Toma A, Chevret S, Kosmider O, et al. A randomized study of lenalidomide (LEN) with or without EPO in RBC transfusion dependent (TD) IPSS low and int-1 (lower risk) myelodysplastic syndromes (MDS) without del 5q resistant to EPO [abstract]. *Proceedings of the 49th Annual Meeting of the American Society of Clinical Oncology (ASCO)* 2013; May 31-June 4; Chicago, IL; USA: Abstract #7002.