Bristol Myers Squibb™

April 1, 2021
Kaleen Barbary, PharmD
Bristol Myers Squibb
86 Morris Avenue
Summit, NJ 07901

NCCN Guidelines® Panel: Myelodysplastic Syndromes

On behalf of Bristol Myers Squibb, we respectfully request the Myelodysplastic Syndromes Panel to review updated data presented at the Society of Hematologic Oncology (SOHO) 2020 Meeting on the use of REBLOZYL® (luspatercept-aamt) for the treatment of patients with myelodysplastic syndromes.

Specific Changes: We respectfully request the panel's consideration of the enclosed data for inclusion of REBLOZYL within the algorithms for the treatment of myelodysplastic syndromes without ring sideroblasts anemia with a Category 2A recommendation (MDS-4 and MDS-5) and an update to the discussion section (MDS-24 and MDS-33).

FDA Clearance: REBLOZYL is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).[1]

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.[1]

REBLOZYL is not indicated for the treatment of patients with MDS without ring sideroblasts.

Rationale: This data is being submitted in response to a standing request from the NCCN® for consideration of new data.

Please note there was a previous submission to NCCN on November 20, 2019 regarding data from the Phase II PACE-MDS study, which contained data on the treatment of patients with MDS without ring sideroblasts from an earlier data cutoff (March 4, 2016), that was published in *Lancet Oncology*. This submission also included data from the Phase III MEDALIST study which evaluated the use of luspatercept for the treatment of lower-risk MDS (LR-MDS) with ring sideroblasts which was presented at the American Society of Hematology 2019 Meeting.

Chronic anemia is one of the primary symptoms affecting patients with LR-MDS. Addressing the underlying anemia and decreasing the overall burden of red blood cell transfusions is the principal aim of treatment. Patients with non-del 5q MDS have limited effective treatment options.[2] LR-MDS patients with <15% ring sideroblasts treated with erythropoiesis-stimulating agent (ESA) therapy have been shown to have lower response rates and require higher doses to attain clinical benefit.[3,4] Furthermore, this subgroup of MDS patients carries a high unmet medical need, especially after failure of ESA therapy.[4,5]

PACE-MDS was a phase II, multicenter, open-label, dose-finding study in adult patients with low or intermediate-1 risk MDS or non-proliferative chronic myelomonocytic leukemia associated-anemia with or without red blood cell transfusion support.[6] Patients were administered luspatercept subcutaneously every 21 days with dose concentration ranging from 0.125 to 1.75 mg/kg for up to 5 doses over a maximum of 12 weeks. After assessment for response and safety in the base study, patients were considered for enrollment into an extension study. Patients in the extension study, received either the same luspatercept

dose concentration last received in the base study or 1 mg/kg every 3 weeks with titration allowed up to 1.75 mg/kg for treatment up to 5 years. The primary endpoint was the proportion of patients achieving hematological improvement (HI-E; as defined by the International Working Group 2006 criteria). Secondary endpoints included safety and the proportion of patients achieving red blood cell transfusion independence (RBC-TI) for 8 weeks or longer.

The final results from the PACE-MDS study (data cutoff May 20, 2020) were recently presented at the 8th SOHO 2020 Annual Meeting and included expanded data from a subgroup of heterogeneous LR-MDS patients without ring sideroblasts.[7] In the overall PACE-MDS study population, 54% (58/108) and 44% (32/73) of luspatercept-treated patients achieved the primary and secondary study endpoints of HI-E and RBC-TI >8 weeks, respectively. Among subjects with a diagnosis of LR-MDS without ring sideroblasts, 36% (16/44) and 35% (10/29) achieved the primary and secondary endpoints, respectively. All study subjects were evaluable for the HI-E primary endpoint while only those subjects with a RBC transfusion burden of >2 units over 8 weeks at baseline were evaluable for the RBC-TI secondary endpoint.

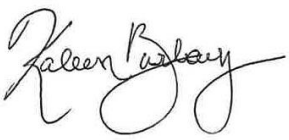
Majority of adverse events (AEs) were grade 1 or 2. AEs occurring in ≥5% of patients include fatigue (7%), headache (7%), and hypertension (6.1%). Eight Grade 3 AEs and four serious AEs occurred.

As part of the submission, a copy of the SOHO 2020 presentation on the updated long-term data from the PACE-MDS study (Platzbecker et al.) and the original PACE-MDS 2017 *Lancet Oncology* publication (Platzbecker et al.) are enclosed for your review.

We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

Thank you for your consideration of this request.

Sincerely,



Kaleen Barbary, PharmD
Director, Worldwide Scientific Content & US Market Capabilities, Hematology

Michael S. Ondovik, PharmD, MBA
Senior Director, US Medical Affairs, Hematology

References:

1. REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use [Package Insert]. Summit, NJ: Celgene Corporation. April 2020.

2. Almeida A, Fenaux P, List AF, et al. Recent advances in the treatment of lower-risk non-del(5q) myelodysplastic syndromes (MDS). *Leuk Res*. 2017; 52:50-57.
3. Negrin RS, Stein, R, Doherty K, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. *Blood*. 1996; 87(10):4076-81.
4. Kelaidi C, Park S, Sapena R, et al. Long-term outcome of anemic lower-risk myelodysplastic syndromes without 5q deletion refractory to or relapsing after erythropoiesis-stimulating agents. *Leukemia*. 2013;27(6):1283-90.
5. Park S, Hamel JF, Toma A, et al. Outcome of Lower-Risk Patients With Myelodysplastic Syndromes Without 5q Deletion After Failure of Erythropoiesis-Stimulating Agents. *J Clin Oncol*. 2017;35(14):1591-1597
6. Platzbecker U, Germing U, Götze KS, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. *Lancet Oncol*. 2017;18:1338-47.
7. Platzbecker U, Kiewe P, Germing U, et al. Long-term Efficacy and Safety of Luspatercept in Lower-Risk Myelodysplastic Syndromes (MDS): Phase 2 PACE-MDS Study. Presented at: 8th Society of Hematologic Oncology (SOHO); September 9-12, 2020; Virtual.