



Submitted by:

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Dear NCCN B-Cell Lymphoma Guidelines Panel:

On behalf of MorphoSys US Inc. and Incyte Corporation, we respectfully request that the NCCN Guidelines Panel for B-Cell Lymphoma review the enclosed data for the recent FDA approval of MONJUVI® (tafasitamab-cxix) in combination with lenalidomide (LEN) in Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL).

**Specific Changes:** We respectfully recommend tafasitamab-cxix as a preferred option for the treatment of previously-treated adult patients with R/R DLBCL who are ineligible for stem cell transplantation.

**FDA Clearance:** On July 31, 2020, the FDA approved MONJUVI, a CD19-directed cytolytic antibody, in combination with lenalidomide for the treatment of adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT). This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).<sup>1</sup> Please refer to the enclosed prescribing information for the full FDA-approved product information.

**Rationale:** In support of the proposed change and enclosed for your review are results from the Phase II L-MIND study (NCT02399085) which combined tafasitamab with lenalidomide for 12 cycles followed by tafasitamab monotherapy upon progression in patients who are transplant ineligible R/R DLBCL.<sup>1</sup> Data from the L-MIND study submitted to the US FDA led to approval by the US FDA.<sup>2</sup> L-MIND is a phase II, open-label, multicenter, single arm trial (NCT02399085) that evaluated the efficacy and safety of MONJUVI in combination with lenalidomide followed by MONJUVI as monotherapy.<sup>2</sup> Eligible patients (n=81) had R/R DLBCL after 1 to 3 prior systemic therapies, including a CD20-directed cytolytic antibody, and were not candidates for high dose chemotherapy (HDC) followed by ASCT. Patients received MONJUVI 12 mg/kg intravenously in combination with lenalidomide (25 mg orally on Days 1 to 21 of each 28-day cycle) for maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity as follows:

- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle;
- Cycle 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle;
- Cycles 4 and beyond: Days 1 and 15 of each 28-day cycle.

The primary endpoint was the proportion of patients with an objective response, defined as the proportion of patients with a complete response (CR) plus those with a partial response (PR), as assessed by an independent review committee (IRC). Secondary endpoints included, disease control rate, duration of response (DOR), progression-free survival (PFS) and overall survival (OS), adverse events, and pharmacokinetics.

The IRC-assessed overall response rate (ORR) (n=80) was 60% (48/80), with 43% (34/80) of the patients achieving a CR and 18% (14/80) achieving a PR.<sup>2</sup> In a cohort of 71 patients with DLBCL confirmed by central laboratory who received the combination therapy, the ORR was 55% (39/71), with 37% achieving a CR and 18% achieving a PR.<sup>1</sup> Consistent response rates were observed across multiple subgroups, including primary refractory patients and patients who had one prior line of therapy. Median duration of response (DOR) was 21.7 months (95% CI: 21.7-NR), and median progression-free survival (PFS) was 12.1 months (95% CI: 5.7-NR). At a median follow-up of 19.6 months, median OS was not reached (95% CI: 18.3-NR).

The most frequently reported grade  $\geq 3$  hematological treatment-emergent adverse events (TEAEs) were neutropenia (48%), thrombocytopenia (17%), febrile neutropenia (12%), leukopenia (8%), and anemia (7%). The most frequently reported grade  $\geq 3$  non-hematological TEAEs were rash (all) (9%), pneumonia (6%) and hypokalemia (6%). The tafasitamab plus lenalidomide combination did not show any occurrence of serious or life-threatening adverse events.<sup>1</sup> The most common treatment-emergent adverse event grade 3 or higher were neutropenia (40/81 [49%]), thrombocytopenia (14/81 [17%]), febrile neutropenia (10/81 [12%]).

In a subsequent analysis conducted after  $\geq 2$  years of follow-up, an ORR of 59 (47/80)% including 41% (33/80) of patients achieving a CR and 18% (14/80) achieving a PR.<sup>3</sup> The IRC-assessed median PFS was 16.2 months, and DOR was 34.6 months (95% CI: 26.1-34.6). Median OS was 31.6 months (95% CI: 18.3-NR) with a median follow-up of 31.8 months (95% CI: 27.2-35.9).

Jurczak et al conducted a phase IIa study to evaluate the safety and efficacy of MONJUVI monotherapy in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL).<sup>4</sup> Patients aged 18 years, with relapsed or refractory NHL progressing after 1 prior rituximab-containing regimen were enrolled into subtype-specific cohorts including DLBCL, follicular lymphoma (FL), other indolent (i) NHL and mantle cell lymphoma (MCL). Among 35 patients enrolled in the DLBCL cohort, the ORR was 26% (9/35), including 6% (2/35) achieving CR and 20% (7/35) achieving PR. The median duration of response was 20.1 months (range 1.1-26.5). Across all cohorts (n=92), the most frequently reported grade  $\geq 3$  non-hematological TEAEs were dyspnea 4% and pneumonia 3%. The most frequently reported grade  $\geq 3$  hematologic TEAEs were neutropenia (9%), thrombocytopenia (4%), and anemia (3%).

To evaluate the additive effectiveness of tafasitamab to lenalidomide, a non-interventional real-world data study of patients treated with LEN monotherapy (RE-MIND, NCT04150328) was conducted.<sup>5</sup> A Propensity Score-Based 1:1 matched comparison of an L-MIND cohort with a lenalidomide monotherapy cohort (RE-MIND) showed statistically superior ORR of 67.1% (95% CI: 55.4-77.5) for the L-MIND cohort versus 34.2% (95% CI: 23.7-46.0) for the RE-MIND cohort (odds ratio 3.89; 95% CI: 1.90-8.14;  $p < 0.0001$ ).<sup>4</sup> The CR rate was 39.5% (95% CI: 28.4-51.4) in the L-MIND cohort and 13.2% (95% CI: 6.5-22.9) in the RE-MIND cohort. A significant difference in OS favored the L-MIND cohort (HR=0.499; 95% CI: 0.317-0.785). ORR and CR outcomes in the RE-MIND cohort were similar to the published literature for LEN monotherapy in R/R DLBCL patients.

A case study showed sustained remission achieved from Anti-CD19 CAR T Cell Therapy administered post treatment with anti-CD19 antibody tafasitamab in a patient with R/R DLBCL. This case report indicates that treatment with the anti-CD19 monoclonal antibody tafasitamab may not preclude patients from anti-CD19 CAR T cell therapy, despite previously targeting the same antigen.<sup>6</sup>

The following references are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of these publications.

1. MONJUVI [tafasitamab-cxix] prescribing information. Boston, MA. MorphoSys US Inc. 2020.
2. Salles G, Duell J, Gonzalez-Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicenter, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020. Accessed on July 20, 2020. doi: 10.1016/S1470-2045(20)30225-4.
3. Salles G, Duell J, Gonzalez-Barca E, et al. Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. Presented at: The European Hematology Association (EHA). 2020.
4. Jurczak W, Zinzani PL, Gaidano G, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Ann Oncol* 2018;29:1266-1272.
5. Nowakowski et al. RE-MIND Study: A Propensity Score-Based 1:1 Matched Comparison of Tafasitamab + Lenalidomide (L-MIND) Versus Lenalidomide Monotherapy (Real-World Data) in Transplant-Ineligible Patients With Relapsed/Refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL). *J Clin Oncol* 38: 2020 (suppl; abstr 8020).
6. Oliai C, et al. *Blood* (2019) 134 (Supplement\_1): 5360. Case Report: Sustained Remission Achieved from Anti-CD19 CAR T Cell Therapy Despite Prior Treatment with Anti-CD19 Antibody Tafasitamab (MOR208) in a Patient with Relapsed and Refractory Diffuse Large B-Cell Lymphoma.

Your consideration of this submission is greatly appreciated.

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