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NCCN Guidelines Panel: B-Cell Lymphomas

NCCN B-Cell Lymphomas Panel:

Please find enclosed a request for your review regarding Gazyva® (obinutuzumab) in combination with lenalidomide.¹⁻³

Requests:

1. Consider inclusion of Gazyva in combination with lenalidomide into the guideline as a treatment option in both the first-line and second-line/subsequent therapy settings based on the results from the Phase II Lymphoma Study Association (LYSA) study¹⁻³ evaluating the use of this regimen in separate cohorts, including patients with advanced untreated follicular lymphoma and patients with relapsed/refractory follicular lymphoma. The results for the advanced untreated follicular lymphoma cohort were presented on December 2, 2018 at the American Society of Hematology (ASH) Annual Meeting.¹

Rationale:

The LYSA group conducted an open label, multicenter, Phase Ib/II trial to evaluate the efficacy and safety of Gazyva in combination with lenalidomide. This chemotherapy-free regimen was studied in separate cohorts, including patients with advanced untreated follicular lymphoma and patients with relapsed/refractory follicular lymphoma (NCT01582776). Results are summarized below.

Advanced untreated follicular lymphoma:

Morschhauser et al.¹ recently presented updated Phase II results from the trial evaluating Gazyva in combination with lenalidomide in a cohort of 100 patients with advanced untreated follicular lymphoma (NCT01582776). The primary endpoint was complete response (CR)/CR unconfirmed (CRu) rate by investigator assessment at the end of induction based on IWG 1999 criteria. At a median follow-up of 2.1 years, the CR/CRu rate was 47% per IWG 1999 criteria, and 59% per 2007 criteria. The overall response rate (ORR) was 91% and 96%, per IWG 1999 and 2007, respectively. Overall survival (OS) at 2 years was 96.9%, while progression-free survival (PFS) was 85.0%. The duration of response (DOR) at 2 years was 85.5%.

The most common adverse events (AEs) reported in >10% of patients during induction (% all grades/% grades 3/4) were neutropenia (43/42), asthenia (35/2), constipation (32/0), infusion-related reactions (23/3), diarrhea (21/2), rash (21/2), cough (18/0), nausea (13/0), pruritus (12/1), weight decrease (12/0), bronchitis (11/0), muscle spasms (11/1), and pyrexia (11/0). Febrile neutropenia was reported in 2% of patients. Eight second primary malignancies were reported in 8 patients, including 2 deemed unrelated due to misdiagnosis at baseline. Three patients had died, one each due to lymphoma, toxicity of additional treatment, and intestinal adenocarcinoma.

Relapsed/refractory follicular lymphoma:

Morschhauser et al.^{2,3} also have published results for Gazyva in combination with lenalidomide in a cohort of 89 patients with relapsed/refractory follicular lymphoma (NCT01582776). A total of 86 patients were assessable for efficacy. At a median follow-up of 18.1 months, the CR/CRu rate at the end of induction was 39.5% and 44.2% per IWG 1999 and 2007 criteria, respectively. The

overall response rate (ORR) was 80.2% and 74.4%, respectively. The 1-year OS rate was 75.5% in all patients, with 74.8% for early relapse patients (defined as relapse within 24 months of first-line treatment) and 65.5% for refractory patients. The 1-year PFS rate was 88.8% for all patients, with 86.9% for early relapse patients and 71.5% for refractory patients .

The most common AEs reported in >20% of patients during induction (% all grades/% grades 3/4) were gastrointestinal disorders (76.1/2.3), infections (62.5/6.8), asthenia (52.3/2.3), neutropenia (30.7/28.4), muscle spasms (30.7/0), and cough (20.7/0). Febrile neutropenia occurred in 3.4% of patients. Some AEs of special interest included rash (19.3/0), peripheral neuropathy (17.0/1.1), infusion-related reactions (14.8/3.4), and venous thrombosis (1.1/0). Six second primary malignancies were reported in 3 patients (5 basal carcinoma and 1 myelodysplastic syndrome).

FDA Clearance:

- Gazyva in combination with lenalidomide is not an FDA-approved regimen.
- Gazyva is a CD20-directed cytolytic antibody indicated:
 - in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia
 - in combination with bendamustine followed by Gazyva monotherapy, for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen
 - in combination with chemotherapy followed by Gazyva monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma
- Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at: http://www.gene.com/download/pdf/gazyva_prescribing.pdf

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Thank you for your consideration and I hope this information is helpful to you. If you have any questions, please contact us at the phone number and email provided above.

Respectfully submitted,
Oscar Merino, PharmD

References:

1. Morschhauser F, Salles G, Casasnovas, R, et al. A Phase II Lysa Study of Obinutuzumab Combined with Lenalidomide for Advanced Untreated Follicular B-Cell Lymphoma in Need of Systemic Therapy. Oral presentation at: American Society of Hematology 60th ASH Annual Meeting & Exposition; December 1-4, 2018; San Diego, CA. Available at: <https://ash.confex.com/ash/2018/webprogram/Paper112805.html>. Accessed December 2, 2018.
2. Morschhauser F, Salles G, Le Gouill S, et al. An open-label phase 1b study of obinutuzumab plus lenalidomide in relapsed/refractory follicular B-cell lymphoma. *Blood*. 2018;132(14):1486-1494.
3. Morschhauser F, Le Gouill S, Feugier P, et al. A phase II Lysa study of obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma [abstract]. *Hematological Oncology*, 2017, suppl 2 35:52-53. Available at: https://onlinelibrary.wiley.com/doi/10.1002/hon.2437_36. Accessed December 2, 2018.