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Submitted by:
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NCCN Guidelines Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

On behalf of Genentech, Inc., I respectfully request the NCCN CLL/SLL Guideline Panel to consider the following enclosed data for:

- **Gazyva® (obinutuzumab):** CLL First-Line
    - Sharman J, Yimer H, Boxer M, et al. Results of the Phase II, multicenter study (GIBB) of obinutuzumab plus bendamustine in patients with previously untreated chronic lymphocytic leukemia. Presented at the 2017 ASCO Annual Meeting in Chicago, IL; June 2–6, 2017. ASCO Poster #7523.

Specific Changes:

- For your updating purposes, please consider the efficacy and safety results from the GIBB trial which was conducted to evaluate the use of Gazyva plus bendamustine in patients with previously untreated CLL.

FDA Clearance:

- Gazyva is FDA-approved:
    - in combination with chlorambucil, for the treatment of patients with previously untreated CLL
    - 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
- Gazyva in combination with bendamustine is not FDA approved for the treatment of previously untreated CLL.
- Please refer to the product prescribing information for the full FDA-approved indications and safety information.
    - Full Gazyva® prescribing information available at:
        - http://www.gene.com/download/pdf/gazyva_prescribing.pdf

Rationale:

The GIBB trial evaluated the efficacy and safety of Gazyva plus bendamustine in patients (n=102) with previously untreated CLL in a multi-center, open-label, single-arm Phase 2 study. The primary endpoint was investigator-assessed complete response (CR) according to iwCLL criteria. Secondary endpoints included overall response rate (ORR), progression free survival (PFS), overall survival (OS), and minimal residual disease (MRD). MRD was assessed as <1 CLL cell detected in 10,000 leukocytes [sensitivity 10^{-4}].

After 6 cycles of treatment, the investigator-assessed CR/CRi rate was 49% (95% CI, 39-59.1) and ORR was 89.2% (95% CI, 81.5-94.5).[1] At the end of the 6 cycles, 32 of 75 (42.7%) evaluable patients achieved MRD-negativity in the peripheral blood and 31 of 51 (60.8%) in the bone marrow, using 4-color flow cytometry. In the 50 patients with CR/CRi at end-of induction, MRD negativity was achieved in 43 (86%) patients in peripheral blood, 23 (46%) in bone marrow, and 21 (42%) in both peripheral blood and bone marrow at any time after induction. After a median follow-up of 11 months, PFS and OS data are immature.

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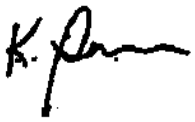
The most common adverse events (AE) [≥35%] were infusion related reactions (IRRs) [72.5%], nausea (52%), and pyrexia (36.3%).[1] Neutropenia (26.5%) was the most common Grade 3/4 AE, and 47.1% of patients received pre-treatment with G-CSF. Additional Grade 3/4 AEs occurring in ≥5% of patients included decreased neutrophil count (10.8%), thrombocytopenia (7.8%), anemia (7.8%), IRRs (7.8%), and pneumonia (5.9%). Adverse events of special interest were reported in 12 patients and included serious infection (n=3), abnormal liver function (n=1), tumor lysis syndrome (TLS) (n=2), serious IRR (n=2), and serious neutropenia (n=4). There were 3 deaths reported, none of which were deemed related to study treatment or CLL disease (congestive heart failure [n=1]; myocardial infarction [n=1]; and cardiac arrest/unknown [n=1]).

Additional trials have been conducted to evaluate the combination of Gazyva plus bendamustine in patients with previously untreated CLL.[1,2]

Respectfully submitted,



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Supplemental References:

1. Stilgenbauer S, Ilhan O, Woszczyk D, et al. Safety and efficacy of obinutuzumab plus bendamustine in previously untreated patients with chronic lymphocytic leukemia: subgroup analysis of the GREEN study. Presented at the 57th ASH Annual Meeting and Exposition in Orlando, FL; December 5–8, 2015. *ASH* Oral presentation.
2. Brown JR, O'Brien S, Kingsley CD, et al. Obinutuzumab plus fludarabine/cyclophosphamide or bendamustine in the initial therapy of CLL patients: the Phase 1b GALTON trial. *Blood* 2015;125:2779-2785.