

Submitted by:
Danielle Dishmon, Pharm.D.
Managed Care Medical Communications, Medical Affairs
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
Phone: (650) 515-9723
Email: genentechmedinfo-d@gene.com
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NCCN Guidelines Panel: Non-Hodgkin's Lymphoma

On behalf of Genentech, Inc., I respectfully request the NCCN Non-Hodgkin's Lymphoma Guideline Panel to review the enclosed recent key presentation and poster for:

- **Gazyva® (obinutuzumab):** Untreated or relapsed/refractory CLL

Goede V, Fischer K, Bosch F, et al. Updated survival analysis from the CLL11 study: obinutuzumab versus rituximab in chemoimmunotherapy-treated patients with chronic lymphocytic leukemia. Presented at the 57th ASH Annual Meeting and Exposition in Orlando, FL; December 5–8, 2015. ASH Poster.

- **Gazyva® (obinutuzumab):** Previously untreated CLL

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.

Specific Changes:

Please consider the Goede et al. and Stilgenbauer et al. for your updating purposes.

FDA Clearance:

Gazyva is FDA approved in combination with chlorambucil for the treatment of patients with previously untreated CLL.

Please refer to the product prescribing information for the full FDA-approved indications and safety information.

- Full prescribing information available at:
http://www.gene.com/download/pdf/gazyva_prescribing.pdf

Rationale:

Goede et al.:

The GREEN study is an ongoing, non-randomized, multi-cohort Phase 3b study designed to evaluate Gazyva alone or in combination with chemotherapy in patients with previously untreated or relapsed/refractory CLL. Safety was the primary endpoint. Safety and efficacy from Cohort 1 (n=158) in patients with previously untreated CLL who received Gazyva + bendamustine were recently presented at the ASH congress. The most common Grade ≥3 adverse events (AEs) included neutropenia (50%), infusion related reactions (15.2%), infections (12.7%), thrombocytopenia (12.7%), tumor lysis syndrome (10.1%), and hemorrhagic events (0.6%). Response rates are shown in the table below.

GREEN Phase 3b Study Response to Therapy from Patients in Cohort 1

	All Patients (n=158)	Fit [†] Patients (n=74)	Non-Fit [†] Patients (n=84)
ORR, %	78.5	81.1	76.2
CR/CRi, %	32.3	29.7	34.5
PR, %	46.2	51.4	41.7
SD, %	10.8	10.8	10.7
PD, %	0.6	0	1.2
Missing, %	10.1	8.1	11.9

Notes: * Patients with CrCl \geq 70 mL/min and CIRS score \leq 6. [†] Patients with CrCl <70 mL/min and CIRS score >6.
Abbreviations: CIRS=Cumulative Illness Rating Scale; CrCl=creatinine clearance; CR=complete response; CRi=complete response with incomplete hematologic recovery; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease

Minimal residual disease (MRD), a secondary endpoint, was assessed in patients with evaluable samples at 3 months end-of-treatment. In the intent-to-treat population, MRD-negativity was 58.9% (93/158) in the peripheral blood and 27.8% (45/158) in the bone marrow.

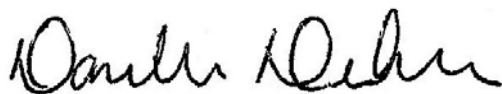
An additional study has been conducted to evaluate Gazyva + bendamustine in CLL.¹

Stilgenbauer et al.:

The CLL11 study was a Phase 3, open-label, randomized, 2-stage, 3-arm trial that was conducted to compare the safety and efficacy of Gazyva with chlorambucil (G-Clb) vs chlorambucil (Clb) alone (Stage 1a) and vs Rituxan with Clb (R-Clb; [Stage 2]) in patients with previously untreated CLL. Results from these studies were previously submitted.²⁻⁴ The updated interim analysis of the CLL11 study showed that after a median observation time of 42.4 months, median progression-free survival (PFS) was 31.1 months in the G-Clb arm and 11.1 months in the Clb arm (hazard ratio [HR]=0.20; 95%CI, 0.15-0.26; p<0.0001). The median time to new anti-leukemic treatment (TTNT) was 51.1 months in the G-Clb arm and 15.1 months in the Clb arm (HR=0.24; 95% CI, 0.17-0.34; p<0.0001). Median overall survival (OS) was not reached in the G-Clb arm and 58.5 months in the Clb arm (HR=0.62; 95% CI, 0.42-0.92; p=0.0167). For Stage 2, after a median observation time of 39 months, the median PFS was 28.7 months in the G-Clb arm vs 15.7 months in the R-Clb arm (HR=0.46; 95%CI, 0.38-0.55; p<0.0001). The median TTNT was 51.1 months in the G-Clb arm vs 38.2 months in the R-Clb arm (HR=0.57; 95% CI, 0.44-0.74; p<0.0001). The OS analysis for G-Clb vs R-Clb reported a hazard ratio of 0.77 (95% CI, 0.57-1.05; p=0.0932). Median OS had not been reached in either arm. No new safety signals were reported.

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Respectfully submitted,



Danielle Dishmon, Pharm.D.

Supplemental References

1. 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.
<http://www.ncbi.nlm.nih.gov/pubmed/25769620>
2. Goede V, Fischer K, Humphrey K, et al. Obinutuzumab (GA101) + chlorambucil (Clb) or rituximab (R) + Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): final stage 1 results of the CLL11 (BO21004) Phase 3 trial.

Presented at the American Society of Clinical Oncology 2013 Annual Meeting in Chicago, IL; May 31–June 4, 2013. ASCO Oral Presentation.

3. Goede V, Fischer K, Busch R, et al. Head-to-head comparison of obinutuzumab (GA101) plus chlorambucil (Clb) versus rituximab plus Clb in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): final Stage 2 results of the CLL11 trial. Presented at the 55th ASH Annual Meeting and Exposition in New Orleans, LA; December 7–10, 2013. ASH Oral Presentation.
4. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014;370:1101-1110.
<http://www.ncbi.nlm.nih.gov/pubmed/24401022>

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