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
  

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

**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.


**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.
<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=158)</th>
<th>Fit Patients (n=74)</th>
<th>Non-Fit† Patients (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>78.5</td>
<td>81.1</td>
<td>76.2</td>
</tr>
<tr>
<td>CR/CRi, %</td>
<td>32.3</td>
<td>29.7</td>
<td>34.5</td>
</tr>
<tr>
<td>PR, %</td>
<td>46.2</td>
<td>51.4</td>
<td>41.7</td>
</tr>
<tr>
<td>SD, %</td>
<td>10.8</td>
<td>10.8</td>
<td>10.7</td>
</tr>
<tr>
<td>PD, %</td>
<td>0.6</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td>Missing, %</td>
<td>10.1</td>
<td>8.1</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Notes: * Patients with CrCl >70 mL/min and CIRS score ≤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**


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.


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