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Submitted by:
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NCCN Guidelines Panel: Non-Hodgkin's Lymphomas

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

- **Gazyva (obinituzumab)**: Previously Untreated Follicular Lymphoma

  Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized Phase 3 GALLIUM study. Presented at the 58th ASH Annual Meeting and Exposition in San Diego, CA ; December 3–6, 2016. ASH Oral Presentation.

  Pott C, Hoster E, Kehden B, et al. Minimal residual disease in patients with follicular lymphoma treated with obinutuzumab or rituximab as first- line induction immunochemotherapy and maintenance in the Phase 3 GALLIUM study. Presented at the 58th ASH Annual Meeting and Exposition in San Diego, CA ; December 3–6, 2016. ASH Oral Presentation.

- **Gazyva (obinituzumab)**: Previously Untreated Diffuse Large B-cell Lymphoma

  Vitolo U, Trneny M, Belada D, et al. Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-Cell lymphoma: final results from an open-label, randomized Phase 3 study (GOYA). Presented at the 58th ASH Annual Meeting and Exposition in San Diego, CA ; December 3–6, 2016. ASH Oral Presentation.

- **Gazyva (obinituzumab)**: Relapsed or Refractory Follicular Lymphoma

  Cheson BD, Trney M, Bouabdallah K, et al. Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin Lymphoma: updated results of the GADOLIN study. Presented at the 58th ASH Annual Meeting and Exposition in San Diego, CA ; December 3–6, 2016. ASH Oral Presentation.

Specific Changes:

Please consider the above presentations for your updating purposes.

FDA Clearance:

- Gazyva is FDA-approved:
  - in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (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 is not FDA approved for the treatment of previously untreated follicular lymphoma or previously untreated diffuse large B-cell lymphoma.

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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:

- **Previously Untreated Follicular Lymphoma**

  Marcus et al.: The Phase 3 GALLIUM study evaluated the efficacy and safety of obinutuzumab with chemotherapy followed by maintenance obinutuzumab versus rituximab with chemotherapy followed by maintenance rituximab in previously untreated follicular lymphoma or marginal zone lymphoma.

  In patients with follicular lymphoma, treatment with obinutuzumab with chemotherapy was associated with a significant improvement in the primary endpoint of investigator-assessed progression-free survival over rituximab with chemotherapy (HR 0.66; 95% CI, 0.51- 0.85; p=0.0012). Independent review committee progression-free survival was similarly improved (HR 0.71; 95% CI 0.54-0.93; p=0.0138). Overall survival was not significantly improved with G-chemo (HR=0.75; 95% CI, 0.49-1.17;p=0.21). Time to new anti-lymphoma treatment was significantly improved with G-chemo (HR=0.68; 95% CI, 0.51-0.91; p=0.0094).

  The most common Grade ≥3 adverse events with obinutuzumab with chemotherapy were neutropenia (43.9%), infections (20%), leukopenia (8.6%), febrile neutropenia (6.9%), infusion-related reactions (6.7%), and thrombocytopenia (6.1%).

  Pott et al. reported results of MRD assessment at mid-induction and end-of-induction in FL patients enrolled in the GALLIUM study. In patients receiving obinutuzumab with chemotherapy, 92% of minimal residual disease (MRD) evaluable patients were MRD-negative at end-of-induction versus 84.9% of patients receiving rituximab with chemotherapy (p=0.0041).

  Additional studies have been conducted to evaluate Gazyva for the treatment of previously untreated follicular lymphoma.[1-2]

- **Previously Untreated Diffuse Large B-cell Lymphoma**

  Vitolo et al.: The Phase 3 GOYA study evaluated obinutuzumab with cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP) versus rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with previously untreated diffuse large B-cell lymphoma.

  In this study, G-CHOP did not significantly improve investigator-assessed progression-free survival (PFS) compared with R-CHOP. The 3-year PFS, assessed by investigator, was 69.6% in the G-CHOP arm and 66.9% in the R-CHOP arm (HR 0.92; 95% CI, 0.76-1.11; p=0.3868). Adverse events were more common in the G-CHOP arm compared to the R-CHOP arm. Ninety-seven percent of patients in the G-CHOP arm and 93.5% of patients in the R-CHOP arm experienced an adverse event of any grade. Serious adverse events were reported in 42.6% and 37.6% of patients in the G-CHOP and R-CHOP arms, respectively. Grade 3-5 adverse events were reported in 73.7% of patients in the G-CHOP arm and 64.7% of patients in the R-CHOP arm.
  Additional studies have been conducted to evaluate Gazyva for the treatment of previously untreated diffuse large B-cell lymphoma.[3]

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- **Relapsed or Refractory Follicular Lymphoma**

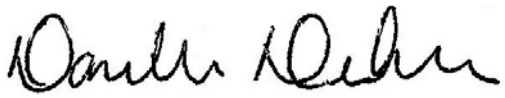
  The GADOLIN study compared a combination of obinutuzumab and bendamustine followed by obinutuzumab maintenance (GB) to bendamustine monotherapy (B) in indolent NHL patients who are refractory to rituximab-based therapy or who relapsed within 6 months of a rituximab-based therapy.

  The overall survival results for the follicular lymphoma patient population from the GADOLIN study were previously submitted.[4]

  Cheson et al.: Updated outcomes after a median follow-up of 31.8 months from the GADOLIN trial were presented and revealed a statistically significant difference in OS, favoring the GB arm (HR 0.67; 95% CI, 0.47-0.96; p=0.0269).

  Additional supplemental references, including the GADOLIN full publication, to evaluate Gazyva in relapsed or refractory follicular lymphoma are included for review.[5-7]

Respectfully submitted,



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Supplemental References

1. Dyer MJS, Grigg A, González-Díaz M, et al. Obinutuzumab (GA101) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or bendamustine in patients with previously untreated follicular lymphoma: results of the Phase 1b GAUDI study (BO21000). Presented at the 54th American Society of Hematology Annual Meeting and Exposition in Atlanta, GA; December 8–11, 2012. ASH Poster.
2. Dyer MJS, Grigg AP, Diaz MG, et al. Obinutuzumab (GA101) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine for the first-line treatment of follicular non-Hodgkin lymphoma: final results from the maintenance phase of the Phase Ib GAUDI study. Presented at the 56th ASH Annual Meeting and Exposition in San Francisco, CA; December 6–9, 2014. ASH Abstract #1743.
3. Zelenetz AD, Mobasher M, Costa LJ, et al. Safety and efficacy of obinutuzumab (GA101) plus CHOP chemotherapy in first-line advanced diffuse large B-cell lymphoma: results from the Phase 2 GATHER study (GAO4915g). Presented at the 55th ASH Annual Meeting and Exposition in New Orleans, LA; December 7–10, 2013. ASH Poster #1820.
4. Sehn LH, Chua N, Mayer J, et al. GADOLIN: primary results from a Phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-hodgkin lymphoma. Presented at the American Society of Clinical Oncology 2015 Annual Meeting in Chicago, IL; 2015 May 29 - June 2. ASCO Oral presentation.
5. Sehn LH, Chua N, Mayer JM, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, Phase 3 trial. Lancet Oncol 2016;17:1081-1093.
6. Sehn LH, Chua N, Mayer J, et al. GADOLIN: primary results from a Phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-hodgkin lymphoma. Presented at the American Society of Clinical Oncology 2015 Annual Meeting in Chicago, IL; May 29–June 2, 2015. ASCO Oral presentation.
7. Pott C, Belada D, Danesi N, et al. Analysis of minimal residual disease in follicular lymphoma patients in GADOLIN, a Phase III study of obinutuzumab plus bendamustine versus

bendamustine in relapsed/refractory indolent non-Hodgkin lymphoma. Presented at the 57th ASH Annual Meeting and Exposition in Orlando, FL; December 5–8, 2015. ASH Abstract #3978.