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NCCN Guidelines Panel: Non-Hodgkin's Lymphoma

On behalf of Genentech, I respectfully request the NCCN Non-Hodgkin's Lymphomas (NHL) Guideline Panel to reconsider the following enclosed Gazyva® (obinutuzumab) Phase III trial data for the treatment of patients with indolent NHL.

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.

Specific Changes:

In addition to your recent inclusion of Gazyva as a maintenance therapy option for follicular lymphoma, please consider Gazyva + bendamustine as a treatment option for Second-line and Subsequent Therapy of follicular lymphoma (FOLL-B 1 of 3), consistent with the design of the Phase III GADOLIN study.

FDA Clearance:

Gazyva is not currently FDA-approved for the treatment of indolent NHL. Please refer to the product prescribing information for the full FDA-approved indication and safety information.

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

Based on the results of the GADOLIN study, the FDA has accepted for priority review a supplemental Biologics License Application (sBLA) for Gazyva in the treatment of patients with follicular lymphoma who relapsed after or are refractory to a rituximab-containing regimen.¹

Rationale:

In the follicular lymphoma setting, Gazyva is only listed in the NCCN guidelines as a maintenance therapy option based on the results of the GADOLIN study. However, the GADOLIN study was designed and powered to evaluate the overall safety and efficacy of a treatment strategy combining Gazyva and reduced dose bendamustine (90mg/m²) for induction treatment followed by Gazyva maintenance as compared to the full labeled dose of bendamustine induction treatment (120mg/m²). The study results were achieved with both induction and maintenance therapy and not maintenance therapy alone.

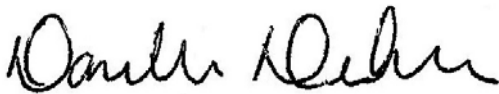
GADOLIN is a Phase III, multicenter, open-label, randomized trial that was conducted to compare bendamustine monotherapy with Gazyva + bendamustine followed by Gazyva maintenance in patients with indolent NHL whose disease did not respond or progressed within 6 months after rituximab-based therapy (either monotherapy or in combination with chemotherapy). The primary endpoint was progression-free survival (PFS) assessed by an independent radiology facility (IRF). After a median follow up of 21 months, the IRF-assessed PFS was significantly prolonged in patients treated with Gazyva + bendamustine followed by Gazyva maintenance compared with those treated with bendamustine alone (median PFS=not reached and 14.9 months, respectively; stratified hazard ratio [HR]=0.55, 95% CI 0.4-0.74; p=0.0001). The investigator-assessed median PFS, a secondary endpoint, was 29.2 months for patients treated with Gazyva + bendamustine followed by Gazyva maintenance and 14 months for patients treated with bendamustine alone (stratified HR=0.52, 95% CI 0.39-0.70; p<0.0001). At the time

of the report, median overall survival was not reached in either arm, and no significant differences in overall response rates were observed. No new safety signals were identified. Grade 3-4 adverse events that occurred in >5% of patients treated with either Gazyva + bendamustine or bendamustine alone included neutropenia (33% vs 26.3%), infusion-related reactions (10.8% vs 5.6%), thrombocytopenia (10.8% vs 16.2%), and anemia (7.7% vs 10.1%).²

An additional exploratory analysis of the minimal residual disease (MRD) results at the end of induction from the GADOLIN trial was recently presented at the 2015 ASH congress.³ Additional studies have been conducted to evaluate Gazyva + bendamustine in indolent NHL.⁴⁻⁵

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Respectfully submitted,



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Supplemental References

1. Roche. (2015). New data from pivotal study showed Roche's Gazyva/Gazyvaro induced deep remissions and provided meaningful quality of life improvements in people with difficult-to-treat indolent non-Hodgkin lymphoma [Press release]. Retrieved from <http://www.roche.com/media/store/releases/med-cor-2015-12-07.htm>
2. 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.
3. 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 Poster.
4. 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.
5. Dyer MJS, Grigg A, 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 1b GAUDI study. Presented at the 56th ASH Annual Meeting and Exposition in San Francisco, CA; December 6–9, 2014. ASH Poster #1743.

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