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July 23, 2014
Non-Hodgkin's Lymphoma Panel

On behalf of Gilead Sciences, I respectfully request that the NCCN Non-Hodgkin's Lymphoma Panel review the enclosed data for inclusion of Idelalisib in the Non-Hodgkin's Lymphoma NCCN Clinical Practice Guidelines for patients with relapsed Chronic Lymphocytic Leukemia (CLL) and relapsed indolent Non-Hodgkin's Lymphoma (iNHL).

Specific Changes: Initial recommendation for Idelalisib in combination with rituximab therapy for patients with relapsed CLL and as single agent therapy for patients with relapsed follicular B cell non-Hodgkin lymphoma and relapsed small lymphocytic lymphoma.

FDA Clearance: Idelalisib 150 mg orally, twice daily is FDA approved for the following indications:

Chronic Lymphocytic Leukemia

Zydelig is indicated for the treatment of relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

Follicular B-cell Non-Hodgkin Lymphoma

Zydelig is indicated for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.

Small Lymphocytic Lymphoma

Zydelig is indicated for the treatment of relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

Rationale: On July 23, 2014 Gilead received FDA approvals for idelalisib for the treatment of relapsed CLL, FL, and SLL. The approvals were based on the results of studies 312-116 (CLL) and 101-09 (iNHL). The FDA granted idelalisib a "Breakthrough" therapy designation for relapsed CLL based on interim results from study 312-116; the breakthrough therapy designation was granted after Gilead's NDA submission for iNHL.

CLL

Evidence in support of the proposed Specific Changes includes: Idelalisib was evaluated in a randomized, double-blind, placebo-controlled Phase 3 study (Study 312-116, n=220) in patients with relapsed CLL. At a pre-specified interim analysis, idelalisib + rituximab was superior to placebo + rituximab for both the primary endpoint of PFS and for overall survival (OS) and the trial was stopped early by Gilead due to "overwhelming efficacy" (Furman et al. NEJM 2014) based on a recommendation of the Data and Safety Monitoring Board. Importantly, the treatment effect of idelalisib + rituximab was consistent across all pre-specified subgroups, regardless of adverse cytogenetic markers (including del (17p) or TP53 mutations, and un-mutated IGHV). The median PFS for patients treated with placebo and rituximab was 5.5 months, while it was not reached for patients treated with idelalisib and rituximab (hazard ratio 0.18, $p < 0.0001$). Both the ORR of 74.5% versus 14.5% (odds ratio 17.28, $p < 0.0001$) and OS (hazard ratio 0.37, $p = 0.037$) favored idelalisib + rituximab as superior to the control group.

The safety and tolerability of idelalisib + rituximab in this study was acceptable and generally consistent with the population of patients with advanced CLL who are receiving anti-CD20 antibody therapy.

iNHL

Evidence in support of the proposed Specific Changes includes: Idelalisib was studied in a single-arm open-label, Phase 2 study (Study 101-09, n=125), in heavily pretreated patients (i.e., median of 4 prior therapies) with relapsed FL, SLL

and other iNHLs who were refractory to rituximab therapy and to alkylating agent-containing chemotherapy. This difficult to treat patient cohort demonstrated an overall response rate (ORR) of 57%, progression free survival (PFS) of 11 months, and a duration of response of 12.5 months. These responses were rapid (median time to response 1.9 months) and durable with continued administration of idelalisib to the patients as an oral tablet twice daily. Other non-cytotoxic agents have been associated with similar efficacy but these agents were studied in patients who received less extensive prior therapy than the patients taking idelalisib in this study.

In this heavily pretreated population, idelalisib had an acceptable toxicity profile with low rates of discontinuation due to AEs as indicated in the prescribing information and as reported in the NEJM study referenced below.

The following articles are submitted in support of this proposed change to the guidelines. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors on some of these publications.

CLL

Coutre, S. E., R. R. Furman, et al. (2014). Second Interim Analysis of a Phase 3 Study Evaluating Idelalisib and Rituximab for Relapsed CLL [Poster 7012]. American Society of Clinical Oncology (ASCO) 50th Annual Meeting, Chicago, IL.

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014; 370:997-1007.

Sharman, J.P., Coutre, S.E., et al. (2014). Efficacy of idelalisib (GS-1101), a selective inhibitor of PI3Kδ, in high risk CLL subpopulations harboring del17p and other adverse prognostic factors American Society of Clinical Oncology (ASCO) Annual Meeting; May 30-June 3, 2014 Chicago, Illinois.

Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3 kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood*, doi: 10.1182/blood-2013-11-535047, Prepublished online March 10, 2014

Barrientos JC, Leonard JP, Furman RR, et al. Update on a Phase 1 Study of the Selective PI3Kδ Inhibitor, Idelalisib (GS-1101) in Combination with Rituximab and/or Bendamustine in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia [Presentation]. Paper presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4 2013; Chicago, Illinois.

Barrientos JC, Wagner-Johnston ND, De Vos S, et al. Chemo-Immunotherapy Combination of Idelalisib with Bendamustine/Rituximab or Chlorambucil/Rituximab in Patients with Relapsed/Refractory CLL Demonstrates Efficacy and Tolerability [Poster 4176]. Paper presented at: 55th ASH Annual Meeting and Exposition; December 7-10, 2013; New Orleans, LA.

O'Brien SM, Lamanna N, Kipps TJ, et al. A phase 2 study of the selective phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor idelalisib (GS-1101) in combination with rituximab in treatment-naïve patients ≥65 years with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) [Presentation]. Paper presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4 2013; Chicago, Illinois.

Furman RR, Barrientos J, Sharman J, et al. A Phase 1/2 Study of the Selective Phosphatidylinositol 3-Kinase Delta(PI3Kd) Inhibitor, GS-1101 (CAL-101), with Ofatumumab in Patients with Previously Treated Chronic Lymphocytic Leukemia (CLL) [Poster 6518]. Paper presented at: 2012 ASCO Annual Meeting; June 1 –5, 2012, 2012; Chicago, Illinois, USA.

iNHL

Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by Idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014 Jan 22. [Epub ahead of print]

Flinn IW, Kahl BS, Leonard JP, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-δ, as therapy for previously treated indolent non-Hodgkin lymphoma. *Blood*, doi:10.1182/blood-2013-11-538546 Prepublished online March 10, 2014

Leonard JP, Wagner-Johnston ND, Coutre SE, et al. Tolerability and activity of combinations of the PI3Kδ inhibitor idelalisib (GS-1101) with rituximab and/or bendamustine are tolerable and highly active in patients with previously treated, indolent non-Hodgkin lymphoma (iNHL): Updated results from a phase I study [Presentation]. Paper presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4 2013; Chicago, Illinois.

Please do not hesitate to contact me if you have any questions related to this submission.

Sincerely,

Handwritten signature of Nancy Yao in cursive script.

Nancy Yao, M.D.