Submitted by:
Nancy Yao, MD
Senior Director, Medical Affairs-Oncology
Gilead Sciences, Inc
333 Lakeside Drive
Foster City, CA. 94404
650.522.5117
Nancy.yao@gilead.com

July 30, 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 as first line therapy for patients with Chronic Lymphocytic Leukemia (CLL) in the presence of 17p deletion and or TP53 mutation. This would be in addition to the recently submitted (7.23.2014) materials for the initial placement of idelalisib within the NCCN Guidelines.

Specific Changes: Recommendation for Idelalisib in combination with rituximab as first-line therapy for patients with CLL in the presence of 17p deletion and or TP53 mutation.

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.

EMA Clearance: Idelalisib has an EMA positive opinion (initial authorization) for the following indications:

Chronic Lymphocytic Leukemia
Zydelig is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.

Follicular B-cell Non-Hodgkin Lymphoma
Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

Rationale: On July 24, 2014 Gilead received an EMA positive opinion (initial authorization) for idelalisib in combination with rituximab for the treatment of relapsed CLL, first line treatment of CLL in the presence of 17p deletion or TP53 mutation and as monotherapy for FL that is refractory to two prior treatments. The approvals were based on the results of studies 312-116 (CLL) and 101-09 (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 17p deletion and or TP53 mutations, and un-mutated IGHV). A specific subset analysis from this study evaluated CLL patients with poor prognostic factors. Idelalisib + rituximab retained efficacy across all high risk subpopulations. Idelalisib + rituximab achieved 76.5% ORR, and PFS HR 0.13 in the highest risk patients who harbored both 17p deletion and TP53mutation, compared to 80.4% ORR, and PFS HR 0.17 in patients who had neither present. Patients with TP53mutation in the idelalisib + rituximab cohort had an ORR of 79.4%, and PFS HR 0.11 compared to 81.5% ORR, and PFS HR 0.15 for patients without TP53mutation. Patients with IGHV unmutated in the idelalisib + rituximab cohort had an ORR of 78.9% and PFS HR 0.13 compared to 88.2% ORR and PFS HR 0.25 for patients with IGHV mutation.

Idelalisib is being studied in an ongoing phase 2 study evaluating idelalisib in combination with rituximab in patient's ≥ 65 years of age with treatment-naïve CLL or SLL. Sixty four patients (CLL=59, SLL=5) with a median age of 71 years were included in the study. Thirty seven (37) patients (58%) had unmutated IGHV and 9 patients (14%) had 17p deletion and or TP53 mutation. Of the 64 patients, 12 (19%) achieved a CR, 50 (78%) had a PR, with an ORR of 97%. Among the 9 patients with 17p deletion and or TP53 mutation, the ORR was 100%; 3 patients achieved a CR and 6 patients achieved a PR. The PFS for all patients at 24 months was 93% and for patients with 17p deletion and or TP53 mutation the PFS at 24 months was 100%.

The EMA considered the benefit to risk balance to be favorable for the newly approved indications. This is consistent with conclusions that the safety and tolerability of idelalisib + rituximab in the cited studies was acceptable and generally consistent with the population of patients with advanced CLL who are receiving anti-CD20 antibody therapy.

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.

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.

European Medicines Agency. July 24, 2014. Summary of opinion (initial authorisation) Zydelig (idelalisib).

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

Sincerely,

Nancy Yao, M.D.