

Submitted by:

Krupa Parekh, Pharm.D.

Managed Care Medical Communications, Medical Affairs

Genentech, Inc.

1 DNA Way

South San Francisco, CA 94080

Phone: (973)-216-2891

Email: genentechmedinfo-d@gene.com

Date of request: May 20, 2017

NCCN Guidelines Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

On behalf of Genentech, Inc., I respectfully request the NCCN CLL/SLL Guideline Panel to consider the following key enclosed data for:

- **Rituximab/hyaluronidase for subcutaneous injection: CLL**
 - Assouline S, Bucchieri V, Delmer A, et al. Pharmacokinetics and safety of subcutaneous rituximab plus fludarabine and cyclophosphamide for patients with chronic lymphocytic leukaemia. *Br J Clin Pharmacol* 2015;80:1001-1009.
 - Assouline S, Bucchieri V, Delm0020er A, et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. *Lancet Haematol* 2016;3:e128-e138.

Specific Changes:

- For your updating purposes, please consider the efficacy and safety results from the SAWYER trial which was conducted to evaluate the use of rituximab/hyaluronidase for subcutaneous (SC) use in patients with CLL.

FDA Clearance:

- Rituximab/hyaluronidase for SC injection is a co-formulation of rituximab and recombinant human hyaluronidase (rHuPH20). Currently, it is not FDA-approved for use in patients with CLL. Genentech's Biologics License Application (BLA) for rituximab/hyaluronidase for SC injection was accepted by the Food and Drug Administration (FDA) with an action date of **June 26, 2017**.¹

Rationale:

We are aware that the NCCN Panel meeting for CLL/SLL is scheduled for **June 9, 2017** and are submitting the available published results of the SAWYER trial for your consideration.

SAWYER is a Phase 1b adaptive dose-finding (Stage 1) and dose-confirming (Stage 2), randomized, parallel-group, multicenter trial that was conducted to investigate the pharmacokinetics (PK), safety, and efficacy of rituximab/hyaluronidase for SC injection versus Rituxan[®] (rituximab for intravenous use [rituximab IV]) as induction therapy in combination with fludarabine and cyclophosphamide in first-line treatment of CLL.

Stage 1: Results from Stage 1 of the study indicated that a fixed dose of 1,600 mg rituximab/hyaluronidase for SC injection had comparable PK and safety profiles (with the exception of administration related reactions) to rituximab IV dosed at 500 mg/m² in patients with CLL. Thus, 1,600 mg rituximab SC was selected as the dose to be used in Stage 2 of the study.

Stage 2: The overall aim of Stage 2 was to confirm the PK non-inferiority of rituximab/hyaluronidase for SC injection at a fixed dose of 1,600 mg. Secondary endpoints included additional PK parameters, B-cell counts, immunogenicity, physician and nurse experience, and safety; efficacy endpoints were exploratory.

At Cycle 5, the adjusted geometric mean trough concentration ratio (SC:IV) was 1.53 (90% CI, 1.27-1.85); the lower limit of the 90% CI exceeded the predefined non-inferiority limit of 0.8 demonstrating non-inferiority of rituximab/hyaluronidase for SC injection to rituximab IV.

Grade ≥ 3 adverse events occurred in 59 of 85 patients in the rituximab/hyaluronidase for SC injection arm and in 63 of 89 patients in the rituximab IV arm. Serious adverse events occurred in 25 patients in the rituximab/hyaluronidase for SC injection arm and in 29 patients in the rituximab IV arm.

Administration-related reactions occurred in 37 patients in the rituximab/hyaluronidase for SC injection arm and in 40 patients in the rituximab IV arm; Grade 3-4 administration-related reactions were observed in 6 patients with in the rituximab/hyaluronidase for SC injection arm and 4 patients in the rituximab IV arm

Respectfully submitted,



Krupa Parekh, PharmD.

Supplemental References:

1. FDA Advisory Committee Unanimously Recommends Approval of Genentech's Subcutaneous Rituximab for Certain Blood Cancers [Press Release]. Basel, Switzerland; Roche. March 29, 2017, Accessed from: <https://www.gene.com/media/press-releases/14658/2017-03-29/fda-advisory-committee-unanimously-recom>

C#17-M0056