FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
July 11, 2017

DRAFT QUESTIONS

BLA 761060

Mylotarg (gemtuzumab ozogamicin)

Applicant: Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.

PROPOSED INDICATION: In combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia (AML).

Background

The first marketing application for Mylotarg (gemtuzumab ozogamicin) (GO) (NDA 021174) was discussed by ODAC on March 20, 2000. GO was granted accelerated approval on May 17, 2000, as a single agent for the treatment of patients with CD33-positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy. Myelosuppression and infusion-related reactions were identified as the major safety concerns at the time of approval. In the post-marketing period, fatal hepatotoxicity and veno-occlusive disease (VOD) were added as boxed warnings, highlighting an especially increased risk of VOD in patients who received GO either before or after hematopoietic stem cell transplantation (HSCT).

As the subpart H post-marketing requirement (PMR), Wyeth was required to confirm clinical benefit in a randomized controlled trial of GO plus daunorubicin and cytarabine (DA) versus DA alone as induction therapy in patients with de novo CD33-positive acute myeloid leukemia. Wyeth identified the SWOG study S0106 as the study to fulfill the PMR. S0106 was a randomized trial comparing DA with or without GO 6 mg/m^2 for treatment of patients $\leq$ 60 years old with newly-diagnosed AML. The primary endpoint was complete response (CR) rate post induction and disease-free survival (DFS) post consolidation. There were 637 patients randomized. The study showed no improvement in CR, DFS or OS (overall survival) with the addition of GO. There was a higher rate of fatal induction toxicities in the GO arm (5.8% vs 1.3%). FDA concluded that clinical benefit was not confirmed and that there was a potential safety issue due to the increase in early deaths. Wyeth voluntarily withdrew GO from marketing, and the NDA was formally withdrawn on October 25, 2010.

Wyeth has now submitted the results of ALFA-701 to support a new marketing application for Mylotarg for treatment of patients with newly-diagnosed AML.

DRAFT QUESTIONS (cont.)

Efficacy

ALFA-701 was a randomized trial comparing DA with or without GO 3 mg/m^2 days 1, 4 and 7 for induction and with or without GO 3 mg/m^2 day 1 for consolidation for treatment of patients 50-70 years old with newly-diagnosed AML. There were 271 patients randomized. The primary endpoint was event-free survival (EFS). Because FDA usually uses OS as the endpoint to confirm clinical benefit for treatment of AML, Wyeth performed analyses to determine if EFS was a surrogate of OS. The efficacy results are summarized as follows:

- In ALFA-0701, the addition of GO to DA resulted in a significant improvement in EFS in the primary analysis (hazard ratio (HR) 0.56; 95% CI 0.42, 0.76; p<0.001).

- In a trial-level analysis of 33 randomized studies in untreated patients with de novo AML, the trial-level weighted R^2 was only 0.46 (95% CI 0.23, 0.70). Note that an R^2 close to 1 would indicate a strong trial-level surrogacy.

- In the subgroup of 5 randomized GO studies for which patient-level data were available, the weighted R^2 through a copula model was 0.45 (95% CI 0.00, 1.00), and it was 0.61 (95% CI 0.20, 1.00) without application of a copula model.

- In ALFA-0701, the addition of GO to DA had no effect on OS (HR 0.81; 95% CI, 0.60, 1.09; p=0.16).

- A meta-analysis for OS in the subgroup of 5 randomized GO studies with patient-level data showed an HR of 0.91 (95% CR 0.84, 0.99) with an estimated 2.1 months increase in OS. FDA does not generally accept retrospective meta-analyses of OS as the primary evidence to establish clinical benefit.

Safety

- The safety analysis is limited by the retrospective nature of the collection of adverse events.

- For ALFA-0701
  - 30-day mortality was not significantly different between the GO + DA arm vs the DA arm (3.8% vs 2.2%). The disparity in 30-day mortality was lower than that reported for S0106 (5.8% vs 1.3%).

  - The adverse events that occurred more frequently with GO + DA vs DA were due to bleeding or infection, and such differences in the adverse event rates occurred during each phase of treatment (induction, consolidation 1 and consolidation 2).

  - VOD was reported for 6 (4.6%) patients treated with GO +DA, and 2 additional patients from the DA arm developed VOD after receiving GO as treatment for relapse.

- Hemorrhage events occurred more frequently with GO + DA than with DA during induction (87% vs 71%), consolidation 1 (60% vs 26%) and consolidation 2 (63% vs 43%).

- Platelet recovery was delayed in patients treated with GO + DA vs DA alone. Over all treatment phases, a delay in recovery to later than day 45 was reported for 20% of patients on GO+ DA vs 2% on DA alone. GO did not appear to impact time to recovery of neutrophils.

- The Individual Patient Data (IPD) meta-analysis showed a trend for lesser disparity in 30-day mortality, VOD, persistent Grade 3-4 thrombocytopenia and Grade 3-4 hemorrhage with decreasing GO dose.

- The additional data from the published literature was consistent with the clinical trial safety findings.

QUESTION

VOTE: Do the results of ALFA-0701 demonstrate a favorable risk:benefit for gemtuzumab ozogamicin 3 mg/m^2 days 1, 4 and 7 added to DA for patients with newly-diagnosed CD33-positive AML? Please explain the reasons for your vote.