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NCCN Guidelines Panel: Acute Myeloid Leukemia (AML)

Dear Ms. Gregory,

On behalf of Pfizer, Inc. I respectfully request the NCCN Acute Myeloid Leukemia (AML) Guideline Panel to review and consider the enclosed information on MYLOTARG™ (gemtuzumab ozogamicin) for the treatment of adult patients <60 years of age with newly diagnosed AML in NCCN Guidelines in Oncology® for AML Version 2.2019 and the associated Drugs and Biologics Compendium™.

- **Request for NCCN Guidelines Panel to review data for a specific indication(s)**
 - MYLOTARG (gemtuzumab ozogamicin) for patients with newly diagnosed CD33-positive AML who are <60 years of age and have favorable or intermediate-risk cytogenetics to receive standard-dose cytarabine 200mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² and MYLOTARG (gemtuzumab ozogamicin) 3mg/m² on day 1, based upon the MRC AML 15 trial. Please remove “up to one 4.5 mg vial” notation for Mylotarg for newly diagnosed CD33-positive AML who are <60 years of age and have favorable or intermediate-risk cytogenetics that is written in the current NCCN AML guidelines Version 2.2019
- **Specific changes recommended within the NCCN Guidelines (one sentence)**
 - Please update AML guidelines page AML-8, as well as relevant discussion sections, by deleting “(up to one 4.5 mg vial)” in connection with gemtuzumab ozogamicin dosing for patients less than 60 years old.
- **Statement of whether the submitted use is or is not FDA approved for that indication**
 - The use of a single 3 mg/m² dose of gemtuzumab ozogamicin on day 1 only (in combination with 7+3) is not the FDA approved dose for this indication ; the approved dose in combination with daunorubicin and cytarabine is 3 mg/m² (up to one 4.5 mg vial) of gemtuzumab ozogamicin

on days 1, 4 and 7, in adult patients (no restriction on age) with newly diagnosed CD33-positive AML.

- **Citation of literature support and complete articles supporting recommended change:**

- Burnett AK, Hills, RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML 15 trial. *J Clin Oncol* 2011;29:369-377
- Castaigne, S et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet* 2012;379:1508–1516
- Hills RK et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol* 2014;15:986-996
- MYLOTARG [prescribing information]. Philadelphia, PA: Pfizer Inc; 2018

Rationale:

The US Food and Drug Administration (FDA) approved Mylotarg in September 2017 based on the results of the ALFA-0701 study, which was a randomized, open-label, phase 3 study. Patients were randomized to receive a 3+7 induction course of intravenous daunorubicin (60 mg/m² on days 1 to 3) and intravenous cytarabine (200 mg/m² as continuous infusion for 7 days) alone or with intravenous gemtuzumab ozogamicin (3 mg/m² [maximum dose 5 mg] infused over 2 h on days 1, 4, and 7. Based upon the results of the ALFA-0701 study, the FDA approved indication for Mylotarg for newly-diagnosed, de novo CD33-positive AML (combination regimen) used for induction is 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin and cytarabine. In the ALFA-0701 protocol, the fractionated 3 mg/m² dose was specifically limited to 1 vial per administration regardless of BSA.

The NCCN Guidelines for AML first incorporated Mylotarg in the treatment algorithm for newly diagnosed AML on February 7, 2018 (Version 1.2018). The original recommendation included the ALFA-0701 regimen as an induction therapy option in 1) patients with newly diagnosed CD33-positive AML who are <60 years of age or 2) patients with newly diagnosed CD33-positive, de novo AML who are ≥60 years of age and do not harbor unfavorable cytogenetic or molecular abnormalities.

In the current version of the NCCN Guidelines for AML (Version 2.2019), the recommendation for patients with newly diagnosed CD33-positive AML who are <60 years of age is standard-dose cytarabine 200mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² and (gemtuzumab ozogamicin 3mg/m² (up to one 4.5 mg vial) on day 1. The reference for this recommendation is the MRC AML 15 trial. However, the “up to one 4.5.mg vial” limitation was not part of the MRC AML 15

protocol and the dose of gemtuzumab ozogamicin that patients received was based on their actual body surface area (BSA).

The MRC AML 15 trial was a randomized an open-label, Phase 3 trial, of 1,113 patients, predominantly younger than age 60 years, who were randomly assigned to receive a single dose of gemtuzumab ozogamicin (GO) (3 mg/m²), not limited to one 4.5 mg vial on day 1 of induction course 1 with one of the following three induction schedules: daunorubicin and cytarabine; cytarabine, daunorubicin, and etoposide; or fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin. In remission, 948 patients were randomly assigned to GO in course 3 in combination with amsacrine, cytarabine, and etoposide or high-dose cytarabine. The primary end points were response rate and survival.

The MRC AML 15 trial did not show an overall difference in response or survival in either induction or consolidation, between the study arms. However, a predefined analysis by cytogenetics showed highly significant interaction with induction GO (P = 0.001), with significant survival benefit for patients with favorable cytogenetics, no benefit for patients with poor-risk disease, and a trend for benefit in intermediate-risk patients. Further, as per the MRC AML 15 protocol, GO was given at 3mg/m² on day 1 of Course 1 based upon the patients' actual body surface area (BSA) and not limited to up to one 4.5 mg vial. The benefit risk profile of GO in combination with chemotherapy using a single dose at 3mg/m² limited to a 4.5mg vial was not evaluated or established in the AML15 trial.

At the prescribed dose of 3mg/m² (not limited to a 4.5mg vial) the MRC AML 15 investigators found no excess hematologic or nonhematologic toxicity. Liver toxicity was not significantly worse in the GO recipients, and they found no increase in liver toxicity overall or in patients who received transplantation within 120 days.

We appreciate the Panel's thorough consideration of the data supporting the use of MYLOTARG (gemtuzumab ozogamicin).

Sincere regards,

A handwritten signature in black ink that reads "Paul G. D'Amico". The signature is written in a cursive, flowing style with a large initial "P" and "D".

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