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NCCN Guidelines Panel: Acute Myeloid Leukemia (AML)

Dear Ms. McClure,

On behalf of Pfizer Oncology, 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 pediatric patients with newly diagnosed and relapsed/refractory AML in NCCN Guidelines in Oncology® for AML Version 4.2017 and the associated Drugs and Biologics Compendium™.

- **Request for NCCN Guidelines Panel to review data for a specific indication(s)**
 - MYLOTARG (gemtuzumab ozogamicin) combined with chemotherapy for newly diagnosed AML in pediatric patients or as a single-agent in pediatric patients with relapsed/refractory AML
- **Specific changes recommended within the NCCN Guidelines (one sentence)**
 - Please add practice guidelines for AML age ≤ 21 years and include gemtuzumab ozogamicin in combination with standard induction and intensification therapy as an option for pediatric patients with newly diagnosed AML; in the setting of relapsed/refractory disease, single-agent gemtuzumab ozogamicin should be included as a treatment option.
- **Statement of whether the submitted use is or is not FDA approved for that indication**
 - The submitted use in the newly diagnosed setting is not approved by the FDA while the submitted use in the relapsed/refractory setting is approved by the FDA for patients aged 2 years and older.
- **Citation of literature support and complete articles supporting recommended change:**
 - MYLOTARG [prescribing information]. Philadelphia, PA: Pfizer Inc; 2017.
 - Guest EM, Aplenc R, Sung L, et al. Gemtuzumab ozogamicin in infants with AML: results from the Children's Oncology Group trials AAML03P1 and AAML0531. *Blood*. 2017 Aug 17;130(7):943-945.
 - Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group Trial AAML0531. *J Clin Oncol*. 2014;32(27):3021-32.
 - Cooper TM, Franklin J, Gerbing RB, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia. *Cancer*. 2012;118(3):761-9.

The combination of gemtuzumab ozogamicin (GO) with intensive chemotherapy during induction and intensification therapy in pediatric patients (≥ 1 month and ≤ 21 years) with previously untreated AML was initially evaluated in AAML03P1, a pilot study sponsored by the Children's Oncology Group (COG). This single arm phase 2 study enrolled 350 children with previously untreated AML. Patients with a matched family donor received 3 courses of chemotherapy followed by hematopoietic stem cell transplantation (HSCT) while those without a match family donor received 5 courses of chemotherapy. GO 3 mg/m²/dose was administered on Day 6 of Course 1 (combined with ADE10: cytarabine on Days 1 to 10, daunorubicin on Days 1, 3, and 5, and etoposide

on Days 1 to 5) and Day 7 of Course 4 (combined with MA: mitoxantrone on Days 3 to 6 and cytarabine on Days 1 to 4). The primary outcome measures were remission status after induction I and II, overall survival (OS), event-free survival (EFS), disease-free survival (DFS), relapse risk, and treatment-related mortality (TRM). Among the 340 eligible patients, the complete remission rate was 83% after 1 course of induction and 87% after 2 courses of induction. TRM was 1.5% after GO containing induction course and 2.6% after the second induction course without GO. The 3-year EFS and OS rates were 53% and 66%, respectively. Toxicities observed in all courses of therapy were typical of AML chemotherapy regimens, with infection being the most common. VOD developed in 19 patients (5.6%). The authors concluded that combining GO with intensive chemotherapy was safe and feasible in this patient population. Results from this study were published by Cooper et al in *Cancer* in 2012.

COG followed AAML03P1 with AAML0531, a randomized, phase 3 study evaluating GO combined with standard five-course chemotherapy versus standard five-course chemotherapy alone in pediatric patients with previously untreated, de novo AML. Patients with a matched family donor received 3 courses of chemotherapy followed by HSCT while those without a match family donor received 5 courses of chemotherapy. GO was administered as described in the AAML03P1 study. The primary endpoints were OS and EFS from study entry. Secondary endpoints included remission rates, relapse risk, post-induction DFS, EFS, and OS censoring HSCT patients, TRM, and OS and EFS by risk group. A total of 1,022 evaluable patients were enrolled (n=511 in each treatment arm). GO significantly improved EFS (3 years: 53.1% vs 46.9%; HR 0.83; P = .04) but not OS (3 years: 69.4% vs 65.4%; HR 0.91; P = .39). The rate of remission was not improved, but post-hoc analyses showed a significant reduction in relapse risk (3 years: 32.8% vs 41.3%; HR 0.73; P = .006). There was a trend for improved DFS among GO-treated patients (3 years: 60.6% vs 54.7%; HR 0.82; P = .07). There was also a trend for increased post-remission toxic mortality with GO (3 years: 6.6% vs 4.1%; HR 1.69; P = .09), despite a lack of difference in overall toxicity incidence. Life threatening veno-occlusive disease (VOD) and all-grade VOD was similar between arms. Results from this study were published by Gamis et al in *J Clin Oncol* in 2014.

A more recent analysis from COG combined data from AAML03P1 and AAML0531 to evaluate the addition of GO to standard five-course chemotherapy versus standard five-course chemotherapy alone in infants younger than 1 year of age with previously untreated AML. GO 0.1 mg/kg was administered on Day 6 of Course 1 and Day 7 of Course 4. Data from 39 infants from AAML03P1 and 103 infants from AAML0531 were combined (n=64 no GO and n=78 with GO). The authors reported no statistically significant improvement in outcomes of infants but noted that the study was not powered to detect a statistically significant improvement in survival. There was a trend towards improved 5-year relapse risk and favorable hazard ratios for EFS and OS. Toxic death in this patient population did not increase with GO. There were no cases of VOD. Results from this study were published by Guest et al in *Blood* in 2017.

We appreciate the Panel's thorough consideration of the data supporting the use of MYLOTARG (gemtuzumab ozogamicin) in pediatric patients with newly diagnosed and relapsed/refractory AML.

Sincere regards,



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