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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 the enclosed information for inclusion of MYLOTARG™ (gemtuzumab ozogamicin) in combination with all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO) for the treatment of adult patients with newly diagnosed acute promyelocytic leukemia (APL) who have high risk disease in NCCN Guidelines in Oncology® for AML and the associated Drugs and Biologics Compendium™.

- **Request for NCCN Guidelines Panel to review data for a specific indication(s)**
 - The addition of MYLOTARG (gemtuzumab ozogamicin) in combination with ATRA and ATO for patients with newly diagnosed APL who have high risk disease
- **Specific changes recommended within the NCCN Guidelines (one sentence)**
 - Please update the following pages in the current AML guidelines: AML-2 and AML-4 as well as relevant discussion sections
- **Statement of whether the submitted use is or is not FDA approved for that indication**
 - The submitted use is not approved by the FDA for this indication.
- **Citation of literature support and complete articles supporting recommended change:**
 - Abaza, Yasmin, et al. "Long-term outcome of acute promyelocytic leukemia treated with all-*trans* retinoic acid, arsenic trioxide, and gemtuzumab." *Blood* 129.10 (2017): 1275-1283.
 - Ravandi, Farhad, et al. "Effective treatment of acute promyelocytic leukemia with all-*trans*-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin." *Journal of Clinical Oncology* 27.4 (2008): 504-510.
 - Burnett, Alan K., et al. "Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial." *The lancet oncology* 16.13 (2015): 1295-1305.

Rationale:

Ravandi and colleagues explored the potential of replacing conventional chemotherapy with a combination of ATRA plus ATO in patients with newly diagnosed APL. The study included 85 consecutive patients from two study cohorts treated from February 2002 to June 2007. In one cohort, 65 patients with APL were treated with a combination of all-*trans* retinoic acid (ATRA) 45mg/m² in two divided doses daily and arsenic trioxide (ATO) 0.15 mg/kg daily beginning on day 10 of ATRA therapy. The second cohort of 17 patients received the same doses of ATRA and ATO but both were started on day 1. In both cohorts, high risk patients (WBC $\geq 10 \times 10^9/L$) received gemtuzumab ozogamicin (GO) 9mg/m² on day 1. In the second cohort, low risk patients also received a dose of GO if their WBC increased to $> 30 \times 10^9/L$ during induction. Twenty-five patients with high risk disease received GO and 4 patients received GO for increasing WBC; one patient had a WBC of $11.3 \times 10^9/L$ but did not receive GO. Overall, 92% of patients achieved CR/CRi. In patients with high risk disease, the CR rate was 81%. Most severe adverse events were reported during induction and considered disease-related. Severe treatment-related events were predominantly grade 3 events and included ($\geq 2\%$): headache, renal failure, atrial arrhythmia, elevated liver enzymes, and cerebral infarct. The estimated 3 year survival rate in the overall population was 85%. Results from this analysis were published in *J Clin Oncol* in 2008.

The results of Ravandi et al 2009 were validated by Burnett and colleagues in a randomized phase 3 study comparing ATRA plus idarubicin with ATRA plus ATO in 235 patients with newly diagnosed APL. Patients were assigned to ATRA and idarubicin (n=119) or ATRA and ATO (n=116). In the ATRA plus ATO arm, high risk patients (WBC $>10 \times 10^9/L$) could receive an initial dose of GO 6 mg/m². The primary endpoint was quality of life; secondary endpoints included OS, RFS, EFS, and relapse rate. There were no differences between treatment arms for the primary endpoint of quality of life. EFS at 4 years was significantly better in the ATRA plus ATO arm versus the ATRA plus idarubicin arm (91% vs 70%; HR 0.35; p = 0.002). Significant benefit was apparent in the low risk patients though not apparent in the high risk patients despite near identical hazard ratios and no interaction with risk. OS at 4 years did not differ between treatment arms (93% vs 89%). In high risk patients, the 4 year OS rate was 87% vs 84%, respectively. Among the 30 high risk patients allocated to ATRA plus ATO, 28 also received GO (the other two high risk patients received anthracycline because GO was not available at the study site pharmacy); the 4-year OS rate in these patients was 89%. There was no increase in liver toxicities in patients who received GO nor any evidence of additional myelosuppression. Results from this study were published in the *Lancet Oncology* in 2015.

Abaza and colleagues published a long-term follow-up of the Ravandi et al 2008 study in *Blood* 2017. In this analysis, the authors included 187 patients with APL (53 high risk and 133 low risk) who were treated in 3 consecutive trials combining ATRA with ATO from July 2002 until May 2015. The two treatment regimens used were similar to those previously described in the Ravandi study, with high risk patients receiving a dose of GO 9 mg/m² or idarubicin (IDA) 12 mg/m² on day 1. IDA was allowed since there was a brief lack of availability of GO. Low risk patients in whom WBC count increased to $> 10 \times 10^9/L$ during the first 4 weeks of therapy also received a dose of GO or IDA. Among high risk patients, 45 (83%) received GO and 7 (13%) received IDA. One patient received both GO and IDA and one patient presenting with WBC $11.1 \times 10^9/L$ did not receive GO. 51 patients in the low risk group wound up receiving GO and 9 received IDA. The overall CR rate was 96% (CR rates for both low and high risk patients were similar at 96%). Induction mortality was 4% with only 7 relapses. Overall, the 5-year rate of event free, disease free, and overall survival was 85%, 96%, and 88% respectively. In patients with high risk disease, the 5-year rate of EFS, DFS, and OS was 81%, 89%, and 86%, respectively. The 5-year OS rate was similar among patients with high risk disease who received GO versus those who received

idarubicin (84% vs 100%). Most severe adverse events were reported during induction and considered disease-related. The most common ($\geq 5\%$) treatment-related grade 3/4 events were infections, QT prolongation, and hemorrhage. Grade 3/4 hepatotoxicity occurred in 14% of patients.

We appreciate the Panel's thorough consideration of the data for use of MYLOTARG (gemtuzumab ozogamicin) in combination with ATRA and ATO in adult patients with newly diagnosed, high risk APL.

Sincere regards,

A handwritten signature in black ink, appearing to read 'CH', with a long horizontal flourish extending to the right.

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