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NCCN Guidelines Panel: Acute Lymphoblastic Leukemia

Dear NCCN ALL Panel Members,

On behalf of Pfizer Oncology, I respectfully request the NCCN Guideline Panel for Acute Lymphoblastic Leukemia (ALL) to review the enclosed information for inclusion of BESPONSA (inotuzumab ozogamicin) for use in combination with low intensity chemotherapy (mini-hyper-CVD) as a therapy option for newly diagnosed older patients (≥60yrs) with Philadelphia Chromosome-Negative (Ph-) ALL and adult patients with Ph- Relapsed/Refractory(R/R) ALL.

Specific Changes Requested

1. Recommend the addition of Besponsa (inotuzumab ozogamizin) in combination with low intensity chemotherapy (mini-hyper-CVD) as a treatment option for older patients (≥60 years) with newly diagnosed Ph negative ALL.

2. Recommend the addition of Besponsa (inotuzumab ozogamizin) in combination with low intensity chemotherapy (mini-hyper-CVD) as a treatment option for adult patients with relapsed or refractory Ph negative ALL.

FDA Clearance: The submitted uses are not approved by the FDA.

Rationals:

1. Besponsa (inotuzumab ozogamizin) in combination with low intensity chemotherapy (mini-hyper-CVD) for older patients (≥60 yrs) with newly diagnosed Ph negative ALL.
    - Supporting evidence is from a single arm Phase II study among patients with a median age of 68 years (range, 60-81) newly diagnosed with Ph- ALL (n=52). Patients received cyclophosphamide (150 mg/m2 every 12 hours on Days 1 to 3) and dexamethasone (20 mg per day on Days 1 to 4 and 11 to 14); no anthracycline was administered. Vincristine (2 mg flat dose) was given on day 1 and 8. Even-numbered cycles included methotrexate (250 mg/m2 on Day 1) and cytarabine given 0.5 g/m2 given every 12 hours on Days 2 and 3. Cycles were administered every 4 weeks, as permitted by peripheral count recovery, for a total of 8 cycles. Inotuzumab was administered on Day 3 of each of the first 4 cycles.

- **Of the 48 untreated patients, 47 (98%) had a response, 41 (85%) of which were complete remission. The Minimal Residual Disease (MRD) negativity rate was noted in 36 (78%) of 46 patients who responded at the time of morphological response, but overall MRD was noted in 45 (96%) of 47 patients at any time within three cycles.**
- With a median follow-up of 29 months, **the 2-year progression-free survival and overall survival rates were 59% (95% CI 43-72) and 66% (95% CI 50-78), respectively. The median overall survival was not reached (95% CI 31.4 mos to not reached)**.
- Veno-Occlusive Disease (VOD) occurred in 4 patients (8%). The study found that compared to a historical matched older patient population treated with hyper-CVAD, inotuzumab with mini-hyper-CVD was associated with a significant improvement in 3-year survival (60% versus 33%; p<0.001).
- The treatment was well tolerated with mostly Grade 1 and 2 adverse events (AEs). 100% of patients in the study had hepatic AEs of any grade, including 33% that were Grade ≥3. VOD occurred in 4 patients (8%) after a median of 3 cycles. One case occurred post ASCT after receiving a conditioning regimen with fludarabine and busulfan, this patient subsequently died from multiple organ failure. After these occurences the protocol was amended to include ursodiol prophylaxis and the reduces inotuzumab dose, the 18 patients treated sense then have not developed VOD.

2. Besponsa (inotuzumab ozogamizin) in combination with low intensity chemotherapy (mini-hyper-CVD) for adult patients with relapsed or refractory Ph negative ALL.
    - Supporting evidence is from a single arm Phase II clinical trial among adult patients with R/R Ph- ALL (n=59). The median age of patients was 35 years (range, 18-87). Patients received cyclophosphamide (150 mg/m2 over 3 hours twice a day on Days 1 to 3) and dexamethasone (20 mg per day on Days 1 to 4 and 11 to 14); no anthracycline was administered. Vincristine (2 mg flat dose) was given on day 1 and 8. Intrathecal methotrexate 12 mg (6 mg via ommaya) on day 2 – cycles 1, 2, 3, and 4 and intrathecal cytarabine 100mg on Day 8 given every 12 hours on Days 2 and 3. Besponsa (inotzumab ozogamicin) was given on day 3 of the first 4 courses.
    - **The overall response rate was 78% and the complete response rate 59%. The overall MRD negativity rate among responders was 82%.** Forty four percent of p**atients proceeded to receive allogeneic stem cell transplantation.** The median follow up was 24 months, the median relapse free survival (RFS) was 8 months and the median overall survival (OS) was 11 months.
    - The treatment was well tolerated. Most AEs were Grade 1 and 2. Fifty six patients (95%) had hepatic adverse events, including Grade ≥3 in 12 patients (20%). In 9

patients (15%) VOD occurred after a median of 3 cycles. All 9 patients had received ASCT. Four of the patients with VOD received dual clofarabine and busulfan based conditioning.

The following references are submitted in support of the requested changes

1. Kantarjian et al., Inotuzumab Ozogamicin in Combination with low-Intensity Chemotherapy (mini-hyper-CVD) As Frontline Therapy for Older Patients with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Phase II Study. Lancet Oncol. 2018 Jan 15.

2. Jabbour et al., Salvage Chemoimmunotherapy with Inotuzumab Ozogamicin Combined with Mini-Hyper-CVD for Patients with Relapsed or Refractory Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Phase 2 Clinical Trial. *JAMA Oncology* (2017).

We appreciate the Panel's thorough consideration of the data for BESPONSA (inotuzumab ozogamicin) in combination with mini-hyper-CVD as a treatment option for older patients (≥60yrs) with newly diagnosed Ph negative ALL and adult patients with Ph negative r elapsed or refractory ALL.

Sincerely,

Fausto Loberiza, MD MS
US Medical Affairs
Pfizer Inc., Oncology Business Unit