Jazz Pharmaceuticals

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Submitted by
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NCCN Acute Myeloid Leukemia Panel

Re: Request for review of clinical data and recommendation for VYXEOS® in the NCCN Clinical Practice Guidelines in Oncology® - Acute Myeloid Leukemia (AML)

On behalf of Jazz Pharmaceuticals, I respectfully request the NCCN AML Panel to review the enclosed FDA approved label[1] and clinical studies[2-4] in support of VYXEOS® (daunorubicin and cytarabine) liposome for injection for the treatment of relapsed/refractory AML.

FDA Clearance: VYXEOS is a liposomal combination of daunorubicin, an anthracycline topoisomerase inhibitor, and cytarabine, a nucleoside metabolic inhibitor, that is indicated for the treatment of adults with newly-diagnosed therapy-related Acute Myeloid Leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).[1]

Suggested Changes: We respectfully ask the NCCN Panel to consider the following:

- **AML-F, "Therapy for Relapsed/Refractory Disease":**
  - Under "Aggressive therapy for appropriate patients":
    - add "Dual-drug liposomal encapsulation of daunorubicin and cytarabine[2-4]

Rationale:

Phase 2 randomized trial in relapsed/refractory disease - Patients with relapsed/refractory AML have a poor prognosis with low response rates and short median overall survival (OS), typically no greater than 9 months.[5] Dual-drug liposomal encapsulation of cytarabine and daunorubicin has been studied in a phase 2, randomized trial in the relapsed/refractory setting. Patients aged 18-65 years with AML in first relapse were randomized 2:1 to the dual-drug liposomal encapsulation (n=81) or investigators' choice of chemotherapy (n=45). Dual-drug liposomal encapsulation was administered by 90-minute infusion on days 1, 3, and 5 (first induction) and days 1 and 3 (second induction and consolidation). Investigators' choice of regimens in the trial were: mitoxantrone/etoposide/cytarabine (n=23); idarubicin/cytarabine (n=8); other cytarabine-based induction (n=11); cytarabine alone (n=1); mitoxantrone/etoposide (n=1). The primary endpoint of the study was survival at 1-year. Survival at 1-year was 36% with dual-drug liposomal encapsulation vs. 27% with control (P=0.33). Response rates were higher with dual-drug liposomal encapsulation (30 CR [37.0%] + 10 CRi [12.3%]) than with control (14 CR [31.8%] + 4 CRi [9.1%]). Statistical significant differences were not detected between treatment groups on survival at 1-year or median OS but showed numerical improvements with dual-drug liposomal encapsulation treatment. Median OS (95% CI) was 8.5 (5.9, 11.1) vs. 6.3 (3.7, 9.1) months (HR, 0.75 ; P=0.19), a 2-month numerical difference in survival with dual-drug liposomal encapsulation compared to control.[2]

The poor-risk strata, as defined by the European Prognostic Index, accounted for 68% of all patients (n=85), and the dual-drug liposomal encapsulation group demonstrated higher response rates (16 CR [28.6%] + 6 CRi [10.7%] vs. 6 CR [20.7%] + 2 CRi [6.9%]) and improved OS (95% CI) (6.6 [5.4, 10.2] vs. 4.2 [2.8, 5.7] months; HR, 0.55; P=0.02) over the control group in an exploratory analysis. In the dual-drug liposomal encapsulation arm, patients with poor-risk disease had a 28% (19%-46%) 1-year survival rate compared with 9% (0%-20%) in the control arm.[2]

Between the two treatment arms, the 60-day mortality rate was similar for the overall population (14.8% vs. 15.9%), but lower in the dual-drug liposomal encapsulation arm for poor-risk patients (16.1% vs. 24.1%). Grade 5 adverse events (AEs) for the overall relapsed/refractory patient population were similar between the two arms (23.5% vs. 20.5%).[2]

After persistent disease with 7 + 3 induction - A separate phase 2, randomized, multicenter, parallel-arm, open-label study that evaluated the efficacy and safety of dual-drug liposomal encapsulation (n = 85) compared with conventional 7 + 3 (cytarabine for 7 days plus daunorubicin for 3 days) (n = 41) regimen in newly diagnosed elderly patients with AML. In this phase 2 trial, patients with persistent AML after one or two induction courses with 7 + 3 were permitted to crossover and receive dual-drug liposomal encapsulation, based on the treating investigator's determination of a very low probability of response with 7+3 treatment. The decision was generally based on <50% reduction of bone marrow blasts compared with baseline. No crossover was permitted for nonresponding patients assigned to dual-drug liposomal encapsulation. A total of 10 patients in the 7 + 3 treatment arm that failed induction treatment (6 high-risk; 4 standard risk) crossed over and received dual-drug liposomal encapsulation. One patient received 2 induction courses, and 9 patients received 1 induction course. Of 10 patients, 4 patients responded (1 CR and 3 CRi), and all four patients remained alive greater than 12 months. Two of the CRi patients had high risk AML, and the 2 remaining patients (1 CR and 1 CRi) had standard risk AML. Five patients experienced grade 3-5 AEs, of which 2 were serious AEs and 1 leading to death. Due to limited number of patients, statistical analysis was not performed.[3]

Phase 1 dose-escalation study in relapsed/refractory disease - A separate phase 1 dose-escalation trial evaluated maximum-tolerated dose, dose-limiting toxicities, and pharmacokinetics of dual-drug liposomal encapsulation. Adult patients with advanced AML or acute lymphoblastic leukemia were eligible for the study. The results in patients with prior therapies showed that 30.4% (7/23 patients) achieved a CR or CR with incomplete platelet recovery (CRp) in the first salvage/primary refractory setting, 10% (1/10 patients) in the second salvage setting, and 20% (2/10 patients) in third or greater salvage setting. Seventy-two percent (31/43 patients) had received prior cytarabine/anthracycline therapy; of 31 patients, 25.6% (8 patients) achieved a CR following dual-drug liposomal encapsulation treatment. Due to limited number of patients, statistical analysis was not performed[4]

Dual-drug liposomal encapsulation of cytarabine and daunorubicin (VYXEOS) is approved by the FDA for the treatment of adults with newly diagnosed t-AML or AML-MRC. Vyxeos is not FDA approved for use in relapsed/refractory AML.[1]

Sincerely,

Francois di Trapani
Vice President Global Scientific Affairs, Medical Affairs

References (**enclosed**):

1. VYXEOS (cytarabine and daunorubicin) liposome for injection prescribing information. Jazz Pharmaceuticals, Inc.
2. Cortes JE, Goldberg SL, Feldman EJ et al. Phase II, multicenter, randomized trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. Cancer. 2015;121(2):234-242.
3. Lancet JE, Cortes JE, Hogge DE et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. Blood. 2014;123:3239-3246.
4. Feldman EJ, Lancet Je, Kolitz JE et al. First-in-man study of CPX-351: a liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. J Clin Oncol. 2011;29:979-985.
5. National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology Acute Myeloid Leukemia (Version 1.2018 - February 7, 2018). https://www.nccn.org. Accessed February 7, 2018.