

**Submitted by**

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**Request for review of additional clinical data 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 new clinical studies<sup>1,2</sup> in addition to existing data<sup>3,4</sup> in support of VYXEOS® (dual-drug liposomal encapsulation of cytarabine and daunorubicin) for the treatment of relapsed/refractory AML.

**Specific Changes:** Please consider the following based on new and previous study results:

- **AML-H, “Therapy for Relapsed/Refractory Disease”:**
  - Under “Aggressive therapy for appropriate patients”:
    - Add “Consider dual-drug liposomal encapsulation of daunorubicin and cytarabine for select patients”<sup>1-4</sup>

**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).<sup>5</sup>

**Rationale:** Patients with relapsed/refractory AML have a poor prognosis with low responses rates, short median overall survival (OS) typically no greater than 9 months and a lack of standard treatment.<sup>6</sup> A subgroup analysis from a randomized controlled trial, showed that dual-drug liposomal encapsulation of cytarabine and daunorubicin significantly improved response rate and survival in older, poor-risk patients compared with chemotherapy.<sup>3</sup> New data from 2 studies also showed significant activity in children, adolescents, and young adults with relapsed/refractory AML and the potential value of dual-drug liposomal encapsulation as an effective bridging treatment to HSCT.<sup>1,2</sup> Dual-drug liposomal encapsulation may be a reasonable option to consider for select patients in the relapsed/refractory setting.

**Supporting Literature in Relapsed/Refractory Disease:**

**New studies in young patients** - A phase 1 trial conducted by Cincinnati Children’s Hospital (CPX-MA-201) evaluated the safety and efficacy of dual-drug liposomal encapsulation of cytarabine and daunorubicin in young patients.<sup>1</sup> A total of 23 AML patients aged ≥1 and ≤30 years who were refractory to 2 induction attempts were included in the study. Of the 21 evaluable patients, 8 (38%) achieved a CR or CR with incomplete platelet recovery (CRi). Eleven of the treated patients who showed a response in the marrow went on to allogeneic HSCT (48%); therefore supporting dual-drug liposomal encapsulation as an option for effective bridge to allogeneic HSCT for patients with relapsed/refractory AML. Of note, 2 patients experienced treatment failure due to the development of central nervous system disease, without detectable leukemia in the marrow. Fever with neutropenia was observed in 89% of patients, but there were no cases of severe mucositis or acute cardiac injury.<sup>1</sup> Another phase 1/2 study (COG, AAML1421) evaluated the efficacy of dual-drug liposomal encapsulation of cytarabine and daunorubicin in 38 patients aged >1 and ≤21 years with relapsed AML.<sup>2</sup> The response rate was determined after up to 2 cycles of therapy (Cycle1: dual-drug liposomal encapsulation of cytarabine and daunorubicin, cycle 2: fludarabine, cytarabine, G-CSF). The CR + CRi rate was 68.3% and overall response rate was

81.1%. Seventy percent of the responses occurred after cycle 1. Twenty one of 25 patients with CR/CRi had no detectable residual disease (84%) by flow cytometry. Among the responders, 79% (23/29) went on to receive HSCT, 78% (18/23) had no detectable residual disease prior to HSCT. The most common Grade 3 or higher toxicities included fever/neutropenia (45%), infection (47%), and rash (40%).<sup>2</sup>

**Evidence in older patients** - Dual-drug liposomal encapsulation of cytarabine and daunorubicin has been evaluated in 2 studies in older adults with relapsed/refractory AML.<sup>3,4</sup> In a phase 2 randomized study, 125 patients aged 18-65 years with AML in first relapse were randomized 2:1 to dual-drug liposomal encapsulation or investigators' choice of chemotherapy. In the overall group, CR + CRi rates were numerically higher with dual-drug liposomal encapsulation (49.3%) than with control (40.9%). 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. Survival at 1-year in the overall group was 36% with dual-drug liposomal encapsulation and 27% with control (P=0.33). 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). The poor-risk strata accounted for 68% of all patients (n=85) and dual drug liposomal encapsulation demonstrated higher CR + CRi rates (39.3% vs. 27.6%) and improved OS (6.6 vs. 4.2 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. Grade 5 adverse events for the overall patient population were similar between the two arms (23.5% vs. 20.5%).<sup>3</sup>

Results of this randomized study are consistent with an earlier phase 1 study where CR was observed both in elderly patients ≥60 years and in patients younger than 60 years with relapsed/refractory AML.<sup>4</sup>

In summary, 4 clinical studies in different age groups have demonstrated activity and safety of dual-drug liposomal encapsulation of cytarabine and daunorubicin in patients with relapsed/refractory AML. Inclusion in this setting can expand the treatment options for a population of patients with poor prognosis.

Sincerely,



Francois Di Trapani  
Vice President Global Scientific Affairs

**References (enclosed):**

1. Absalon MJ, Breese EH, Lee LH et al. A Phase I/pilot study of CPX-351 [daunorubicin and cytarabine liposome for injection (Vyxeos®)] for children, adolescents and young adults with recurrent or refractory acute leukemia. Oral Presentation at ASH 2018. Abstract 336.
2. Cooper TM, Absalon MJ, Alonzo TA, et al. AAML 1421, a phase 1/2 study of CPX-351 followed by fludarabine, cytarabine, and G-CSF (FLAG) for children with relapsed acute myeloid leukemia (AML): A report from the Children's Oncology Group. Abstract accepted as an oral presentation for the 2019 ASCO Annual Meeting.  
**\*ASCO abstract embargo lifts at 5 pm ET on May 15, 2019.**
3. 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.
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. VYXEOS (cytarabine and daunorubicin) liposome for injection prescribing information. Jazz Pharmaceuticals, Inc.
6. National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. V2.2019. <https://www.nccn.org>. Accessed April 18, 2019.