Jazz Pharmaceuticals

www.JazzPharmaceuticals.com

Submitted by
Francois Di Trapani, Vice President Global Scientific Affairs
Company/Organization: Jazz Pharmaceuticals
Address: 3170 Porter Drive
Palo Alto, CA 94304
Phone: 650-496-2759
Email: francois.ditrapani@jazzpharma.com

Date of request: November 5th, 2018

**NCCN Acute Myeloid Leukemia (AML) Panel**
**Re: Request for clarification of VYXEOS® recommendations in the NCCN AML Guidelines**

On behalf of Jazz Pharmaceuticals, I respectfully request the NCCN AML Panel to review the following observations and suggested changes regarding VYXEOS® (dual-drug liposomal cytarabine and daunorubicin):

**Observation 1**: Results of our Wave 2 AML Chart Study[1] revealed that a significant fraction of clinicians are using other regimens as second induction (43%) or consolidation (62%) after VYXEOS first induction. This treatment approach is not supported by the phase 3 randomized controlled registrational study in which VYXEOS was used consistently through all treatment phases.[2,3] This observation of mixed regimens also occurs in APL which is currently addressed by footnote g in the APL algorithm of the NCCN guideline. Similar NCCN guidance will be valuable for AML treatment.

Suggested change:

- We respectfully suggest adding a similar footnote as **APL's footnote g** to the AML algorithm (**AML-9, AML-13** for re-induction, **AML-11, AML-14** for consolidation): "*To achieve the expected results, one needs to use the regimen consistently through all treatment phases and not mix induction from one treatment approach with consolidation from another.*"

**Observation 2**: Currently, VYXEOS is the only category 1, FDA-approved option for induction in patients ≥60y with unfavorable-risk AML based on randomized phase 3 study evidence; however, this is not reflected in the order of listing.

Suggested Change:

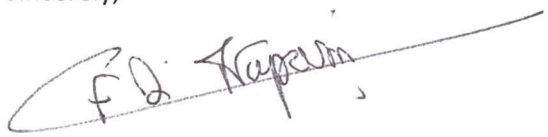
- We respectfully suggest moving VYXEOS (dual-drug liposomal cytarabine and daunorubicin) from the last option to the first option in **AML-12 (AML ≥60y, Candidate for intensive remission induction therapy, unfavorable cytogenetic/molecular markers/Antecedent hematologic disorder/Therapy-related AML)**

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).[4]

Summary of Evidence Supporting Suggested Changes:

Dual-drug liposomal encapsulation of cytarabine and daunorubicin (VYXEOS) is the first nano-scale liposome co-formulation to receive an FDA indication for adults with AML.[4] The pivotal, phase 3, randomized, open-label study enrolled 309 patients with newly-diagnosed secondary/high-risk AML.[2] Patients in the VYXEOS arm received up to 2 inductions and up to 2 consolidations with VYXEOS and patients in the control arm received conventional standard-dose cytarabine and daunorubicin (7+3 for first induction, 5+2 for second induction and consolidation). Mix regimen was not allowed in the study protocol. VYXEOS significantly improved overall survival (HR, 0.69; 1-sided *P*=0.005; median OS, 9.56 vs. 5.95 months), and VYXEOS demonstrated significantly higher overall remission rates (CR + CRi) compared with control (47.7% vs 33.3%; two-sided *P* = .016) and CR rate (37.3% vs 25.6%; two-sided *P* = .040).[2,4] A post-hoc analysis showed that for patients who received consolidation, those in the VYXEOS arm (n = 49) had greater median survival than those in the control arm (n = 32) (25.4 vs. 8.5 months; HR, 0.44; 95% CI, 0.25-0.77).[3] Grade 3-5 adverse events were similar between the two groups.[2]

Sincerely,



Francois Di Trapani
Vice President Global Scientific Affairs, Medical Affairs

References (**enclosed**):


1. Wave 2 AML Chart Study. Jazz Market Research. Feb/Mar 2018.
2. Lancet JE, et al. CPX-351 (cytarabine:daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol. 2018;36(26):2684-2692.
3. Kolitz JE, et al. Outcomes in older patients with newly diagnosed, high-risk/secondary acute myeloid leukemia (sAML) who received consolidation in a phase 3 study of CPX-351 versus conventional 7+3/5+2 cytarabine and daunorubicin. Poster presented at the 6th annual Meeting of the Society of Hematologic Oncology (SOHO); September 12-15, 2018; Houston, Texas. Poster AML-275.
4. VYXEOS (daunorubicin and cytarabine) liposome for injection prescribing information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.