Jazz Pharmaceuticals www.JazzPharmaceuticals.com

Submitted by
Francois Di Trapani, Vice President Global Scientific Affairs
Company/Organization: Jazz Pharmaceuticals
Address: 3180 Porter Drive
Palo Alto, CA 94304
Phone: 650.496.27.59
Email: francois.ditrapani@jazzpharma.com

Date of request: 08/07/2017

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[2-6] in support of VYXEOS™ (daunorubicin and cytarabine) liposome for injection for the treatment of 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-11, AML ≥60 y, under "Treatment Induction":**
  - For "De novo AML without unfavorable cytogenetics/molecular markers/no antecedent hematologic disorder/no therapy-related AML":
    add "Dual-drug liposomal encapsulation of daunorubicin and cytarabine*"[2]
  - For "unfavorable cytogenetic/molecular markers/antecedent hematologic disorder/therapy-related AML":
    add "Dual-drug liposomal encapsulation of daunorubicin and cytarabine (preferred)*"[1,3-5]
    (supported by category 1 clinical evidence[3])
- **AML-7, Age <60 y, under "Treatment Induction":**
  - add "Dual-drug liposomal encapsulation of daunorubicin and cytarabine *"[1]
- **AML-8 and AML-12, "After standard-dose cytarabine":**
  - Add corresponding re-induction therapy for "dual-drug liposomal encapsulation of daunorubicin and cytarabine *"[1]
- **AML-10 and AML-13, "Post-remission therapy":**
- Add corresponding consolidation therapy for "dual-drug liposomal encapsulation of daunorubicin and cytarabine *"[1]
- **AML-F, "Therapy for Relapsed/Refractory Disease":**
  - Under "Aggressive therapy for appropriate patients":
    add "Dual-drug liposomal encapsulation of daunorubicin and cytarabine *"[6]
- *Please note the following indicated dosage for VYXEOS:
  - Induction: 44 mg/100 mg per m^2 via intravenous infusion over 90 minutes on days 1, 3, and 5 and on days 1 and 3 for subsequent cycles of induction, if needed;
    consolidation: 29 mg/65 mg per m^2 via intravenous infusion over 90 minutes on days 1 and 3

Rationale for Induction Therapy:
Phase 3, randomized study - Dual-drug liposomal encapsulation of daunorubicin and cytarabine (VYXEOS) is the first nano-scale liposome co-formulation to receive an FDA indication for adults with AML.[1] The pivotal, phase 3,

randomized, open-label study enrolled 309 patients aged 60-75 years with untreated high-risk AML.[3] Patients with the following AML subtypes were included in the study: therapy-related AML (t-AML), myelodysplastic syndrome AML (MDS AML), and chronic myelomonocytic leukemia AML (CMMoL AML) with documented history of MDS or CMMoL prior to transformation to AML, and de novo AML with karyotype changes characteristic of myelodysplasia per WHO 2008 criteria. Patients were randomized 1:1 to dual-drug liposomal encapsulation of daunorubicin and cytarabine (44mg/100 mg per m^2, days 1, 3, 5) or 7+3 (cytarabine 100 mg/m^2/day x 7 days, daunorubicin 60 mg/m^2 days 1, 2, 3) induction therapy. Endpoints included overall survival (OS), primary, and complete remission (CR/CRi), secondary. After a minimum follow-up of 13.7 months, the dual-drug liposomal encapsulation resulted in superior overall survival (HR, 0.69; *P*=0.005 (two-sided); median OS, 9.56 vs. 5.95 months) and CR+CRi (47.7% vs. 33.3%; *P*=0.016 [two-sided]). The 30-day and 60-day mortality rate favored the dual-drug liposomal encapsulation (30-day: 6% vs. 11%; 60-day: 13.7% vs. 21.2%). Grade 3-5 non-hematologic adverse events (AEs) occurring ≥ 5% were similar between the two groups, except pneumonia (20% vs 15%) and bacteremia (10% vs 2%) were numerically higher in the dual drug liposomal encapsulation group compared with 7 + 3 group, respectively. Also, median time to recovery of absolute neutrophil count (ANC) ≥ 500/µL and platelets ≥ 50,000/µL were longer in the dual-drug liposomal encapsulation group than 7 + 3 group. A total of 52 patients in the dual-drug liposomal encapsulation arm (34%) received HSCT compared with 39 patients treated with 7+3 (25%) (*P*=0.049; 1-sided).[3]

In a posthoc analysis, following allogeneic hematopoietic cell transplantation (HCT), patients in the dual-drug liposomal encapsulation arm demonstrated improved OS compared to standard 7+3 (HR 0.46, *P*=0.009 (1-sided)). Another subgroup analysis focusing on age stratification[5] demonstrated that dual-drug liposomal encapsulation of daunorubicin and cytarabine had significantly higher median OS than standard 7 + 3 for both age groups of 60-69 (9.63 vs. 6.87 mo; HR, 0.68; 95% CI, 0.49-0.95) and 70-75 (8.87 vs. 5.62 mo; HR, 0.55; 95% CI, 0.36-0.84). Additionally, more patients in the age 70-75 group received an allogeneic HCT compared with the 7 + 3 arm (28.1% vs. 11.1%; OR, 3.12; 95% CI, 1.12-8.72). In a sub-group analysis of patients who were positive for FLT3 mutation (n=22 for VYXEOS, n=20 for 7+3), the median survival in the dual-drug liposomal encapsulation arm was 10.25 months compared with 4.60 months for patients treated with 7+3 (*P*=0.093; HR, 0.57).[7]

Phase 2, randomized study – In a phase 2, randomized study, 126 patients with newly diagnosed AML were randomized 2:1 to first-line dual-drug liposomal encapsulation of daunorubicin and cytarabine or 7 + 3.[2] The study group included 61% patients at high risk (age 70-75, secondary AML, complex karyotype) and 39% at standard risk (age 60-69, de novo AML). Overall, dual-drug liposomal encapsulation resulted in higher response rates (66.7% vs. 51.2%) that met pre-specified criteria (*P*<0.1). There was a trend towards higher median OS (14.7 vs. 12.9 mo; *P*=0.61) and EFS (6.5 vs. 2.0 mo; *P*=0.36) with the dual-drug liposomal encapsulation. A planned analysis of the secondary AML subgroup demonstrated a statistically significant improvement of response (57.6% vs. 31.6%; *P*=0.06), EFS (HR, 0.59; *P*=0.08), and OS (HR, 0.46; *P*=0.01). There was no increase in infection-related deaths (3.5% vs 7.3%). Mortality rates at 30 and 60 days were 3.5% vs 7.3% and 4.7% vs 14.6% in the dual-drug liposomal encapsulation and 7+3 arm, respectively.

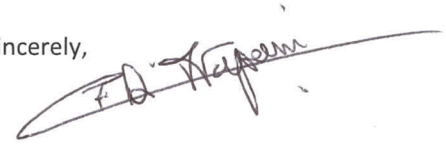
Rationale for Relapsed/Refractory Therapy:

Phase 2, randomized study - Dual-drug liposomal encapsulation of daunorubicin and cytarabine has also been studied in a phase 2, randomized trial in the relapse/refractory setting.[6] Patients aged 18-65 with AML in first relapse (n=125) were randomized 2:1 to the dual-drug liposomal encapsulation or investigators' choice of chemotherapy. Investigators' choice in most patients consisted of cytarabine and anthracycline, which were usually administered with additional agents, most frequently etoposide or gemtuzumab ozogamicin. Overall, there was a trend towards higher CR+CRi (49% vs. 41%), EFS (4.0 vs. 1.4 mo; *P*=0.08), and OS (8.5 vs. 6.3 mo; HR, 0.75; *P*=0.19) with the dual-drug liposomal encapsulation compared with control, however, the primary endpoint of 1-year survival did not show a statistically significant difference (36% dual-drug liposomal encapsulation group; 27% control group). The poor-risk strata accounted for 68% of all patients (n=85), and the dual-drug liposomal encapsulation group demonstrated higher CR+CRi (39% vs. 28%) and significantly improved OS (6.6 vs. 4.2 mo; HR, 0.55; *P*=0.02) over the control group. Survival at 12 months was 28% (19%-46%) in the dual-drug liposomal

encapsulation group and 9% (0%-20%) for the control group. The 60-day mortality rate was similar overall (14.8% vs. 15.9%) and lower in the dual-drug liposomal encapsulation arm for poor-risk patients (16.1% vs. 24.1%).

Dual-drug liposomal encapsulation (VYXEOS) is approved by the FDA for the treatment of adults with newly diagnosed t-AML or AML-MRC.[1] Prior to the approval, it received Breakthrough Therapy designation by the FDA in May 2016 for the treatment of adults with t-AML or AML-MRC. Overall, dual-drug liposomal encapsulation of daunorubicin and cytarabine significantly improved OS and response with a trend toward reduction in 30, 60-day mortality in a phase 3, randomized trial of older AML patients with t-AML or AML-MRC. Grade 3-5 adverse events were equal (92% vs. 91%) and were similar in frequency and severity in both arms.[3] This was consistent with an earlier phase 2, randomized study that showed higher overall response rates with the dual-drug liposomal encapsulation in older patients with high risk or standard risk AML.[2] In a phase 2 randomized trial, benefits of the dual-drug liposomal encapsulation were also observed in the relapse/refractory setting, an area with limited therapeutic options.[6]

Sincerely,



Francois di Trapani
Vice President Global Scientific Affairs, Medical Affairs
T: 650-496-2759

References (**enclosed**):

1. VYXEOS™ (daunorubicin and cytarabine) liposome for injection prescribing information. Jazz Pharmaceuticals, Inc.
2. Lancet JE, 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(21): 3239-3246.
3. Lancet JE, et al. Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. J Clin Oncol. 2016;34 (suppl):abstract 7000.
4. Lancet JE, et al. Survival following allogeneic hematopoietic cell transplantation in older high-risk acute myeloid leukemia patients initially treated with CPX-351 liposome injection versus standard cytarabine and daunorubicin: subgroup analysis of a large phase III trial. Blood. 2016;128(22): Abstract 906.
5. Medeiros BC, et al. Analysis of efficacy by age for patients aged 60–75 with untreated secondary acute myeloid leukemia (AML) treated with CPX-351 liposome injection versus conventional cytarabine and daunorubicin in a phase III trial. Blood. 2016;128(22): Abstract 902.
6. Cortes JE, 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):234-42.
7. Lancet JE, et al. CPX-351 Treatment of previously untreated older patients with high risk AML markedly increases the response rate over 7 + 3 in patients with FLT3 mutations. Presented at: European Hematology Association 21st Congress. June 9-12, 2016; Copenhagen, Denmark. Abstract S502.