

For adults with secondary AML (sAML) facing a poor prognosis and unfavorable outcomes...



Chemotherapy and HSCT provide an opportunity for prolonged survival^{1,2}

In a large, randomized, active-controlled Phase 3 trial, VYXEOS (CPX-351) was shown to provide benefits to adults with newly-diagnosed sAML subtypes t-AML or AML-MRC who were candidates for chemotherapy³

Superior overall survival vs 7+3^a

A greater opportunity to achieve CR vs 7+3

A better chance to reach HSCT vs 7+3

Liposomal daunorubicin and cytarabine (VYXEOS) is the **ONLY Category 1 recommendation^b in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®])** for induction in adult patients 60 years of age or older with therapy-related AML or antecedent MDS/CMML or cytogenetic changes consistent with MDS (AML-MRC)⁴

INDICATION

VYXEOS 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).

IMPORTANT SAFETY INFORMATION

WARNING: DO NOT INTERCHANGE WITH OTHER DAUNORUBICIN AND/OR CYTARABINE-CONTAINING PRODUCTS

VYXEOS has different dosage recommendations than daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors.

Please see additional Important Safety Information on pages 7 and 8 and **full Prescribing Information**, including **BOXED Warning**.

^aCytarabine 100 mg/m² and daunorubicin 60 mg/m².

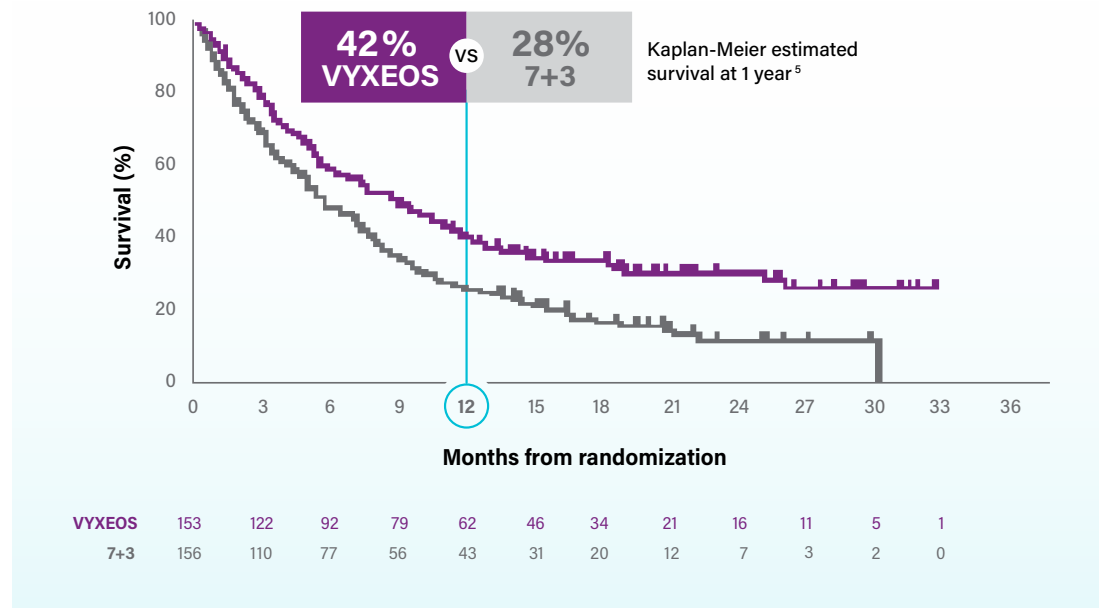
^bCategory 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.⁴

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

AML=acute myeloid leukemia; AML-MRC=AML with myelodysplasia-related changes; CMML=chronic myelomonocytic leukemia; CR=complete remission; HSCT=hematopoietic stem cell transplant; MDS=myelodysplastic syndromes; NCCN=National Comprehensive Cancer Network; t-AML=therapy-related AML.

VYXEOS demonstrated superior OS vs 7+3, reducing the risk of death by 31%^a in sAML patients facing a poor prognosis (primary endpoint)³

Kaplan-Meier curve for overall survival, ITT population³



Study Design³

The Phase 3 study was a randomized, multicenter, open-label, active-controlled superiority study of VYXEOS versus cytarabine and daunorubicin (7+3) in patients 60 to 75 years of age with newly-diagnosed t-AML or AML-MRC. There were 153 patients randomized to VYXEOS and 156 patients randomized to the 7+3 arm. Twenty percent had t-AML, 54% had AML with an antecedent hematological disorder, and 25% had de novo AML with MDS-related cytogenetic abnormalities. Efficacy was established on the basis of overall survival from the date of randomization to death from any cause.

VYXEOS 44 mg/100 mg per m² (daunorubicin/cytarabine) was given intravenously on Days 1, 3, and 5 for first induction and on Days 1 and 3 for those needing a second induction. For consolidation, the VYXEOS dose was 29 mg/65 mg per m² (daunorubicin/cytarabine) on Days 1 and 3. In the 7+3 arm, first induction was cytarabine 100 mg/m²/day on Days 1-7 by continuous infusion + daunorubicin 60 mg/m²/day on Days 1-3. For second induction and consolidation, cytarabine was dosed on Days 1-5 and daunorubicin on Days 1 and 2. Patients could receive up to 2 cycles of induction and 2 cycles of consolidation in each arm. Subsequent induction was recommended for patients who did not achieve a response and was mandatory for patients achieving >50% reduction in percent blasts.

Hazard ratio =0.69 (0.52, 0.90)	Median survival (95% CI) VYXEOS: 9.6 months (6.6, 11.9) 7+3: 5.9 months (5.0, 7.8)
P value =0.005	

^aHazard ratio was adjusted for age and AML subtype.

IMPORTANT SAFETY INFORMATION

Contraindications

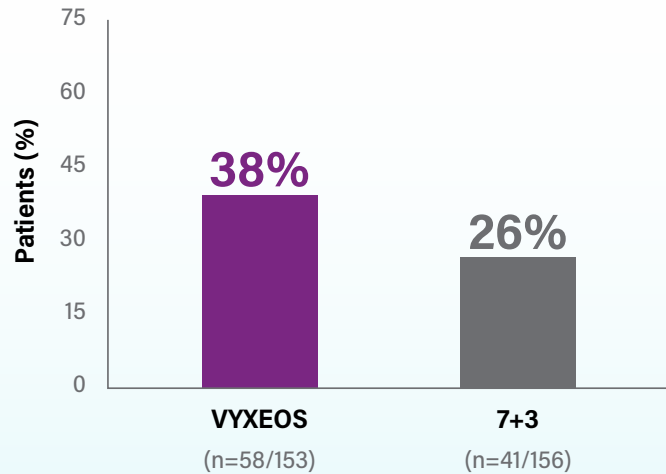
VYXEOS is contraindicated in patients with a history of serious hypersensitivity reactions to cytarabine, daunorubicin, or any component of the formulation.

Please see additional Important Safety Information on pages 7 and 8 and full Prescribing Information, including BOXED Warning.



VYXEOS demonstrated a statistically significant improvement in CR vs 7+3³

Percentage of patients who achieved complete remission³



P value=0.036

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage

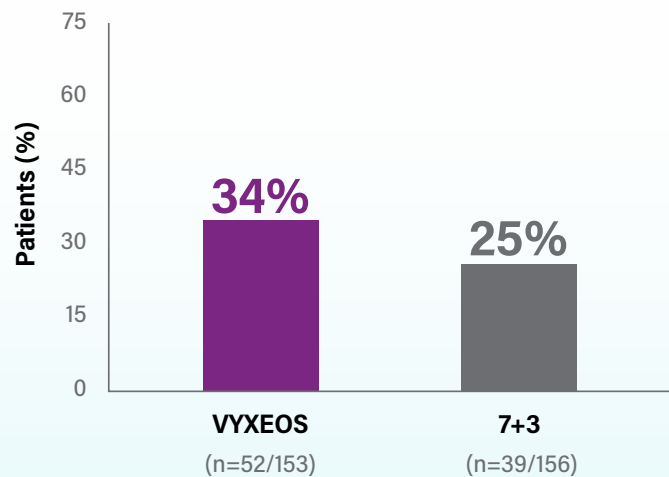
Serious or fatal hemorrhage events, including fatal CNS hemorrhages, associated with prolonged thrombocytopenia, have occurred with VYXEOS. The overall incidence (grade 1-5) of hemorrhagic events was 74% in the VYXEOS arm and 56% in the control arm. The most frequently reported hemorrhagic event was epistaxis (36% in VYXEOS arm and 18% in control arm). Grade 3 or greater events occurred in 12% of VYXEOS-treated patients and in 8% of patients in the control arm. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and in 0.7% of patients in the control arm. Monitor blood counts regularly and administer platelet transfusion support as required.

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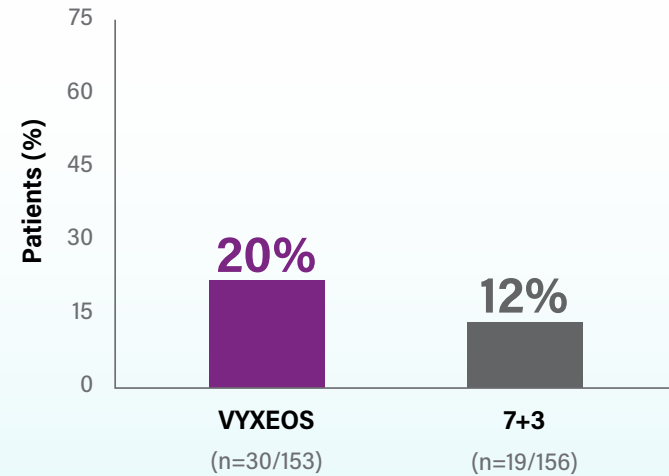
Vyxeos[®]
(daunorubicin and cytarabine) ^{44 mg/100 mg}
liposome for injection per vial

More patients received HSCT following treatment with VYXEOS vs 7+3³

Overall rate of HSCT^{3,a}



Rate of HSCT during first CR^{3,6}



^aInduction failure, first CR, or as salvage after relapse.

IMPORTANT SAFETY INFORMATION

Cardiotoxicity

VYXEOS contains daunorubicin, which has a known risk of cardiotoxicity. This risk may be increased in patients with prior anthracycline therapy, preexisting cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs. Assess cardiac function prior to VYXEOS treatment and repeat prior to consolidation and as clinically required. Discontinue VYXEOS in patients with impaired cardiac function unless the benefit of initiating or continuing treatment outweighs the risk. VYXEOS is not recommended in patients with cardiac function that is less than normal.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m² have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m²) in patients who received radiation therapy to the mediastinum. Calculate the lifetime cumulative anthracycline exposure prior to each cycle of VYXEOS. VYXEOS is not recommended in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit.

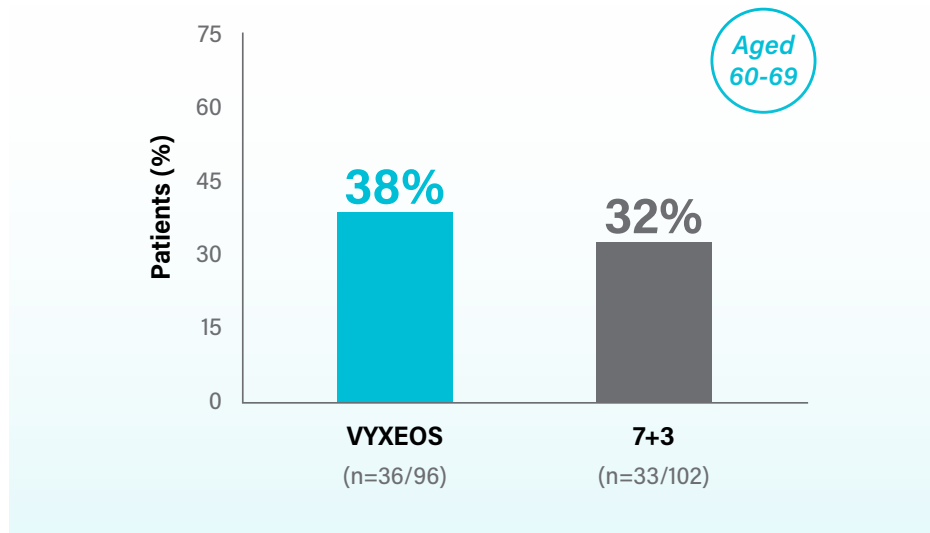
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Vyxeos[®]
(daunorubicin and cytarabine) ^{44 mg/100 mg}
liposome for injection

More VYXEOS patients received HSCT compared to 7+3 in both age subgroups⁷

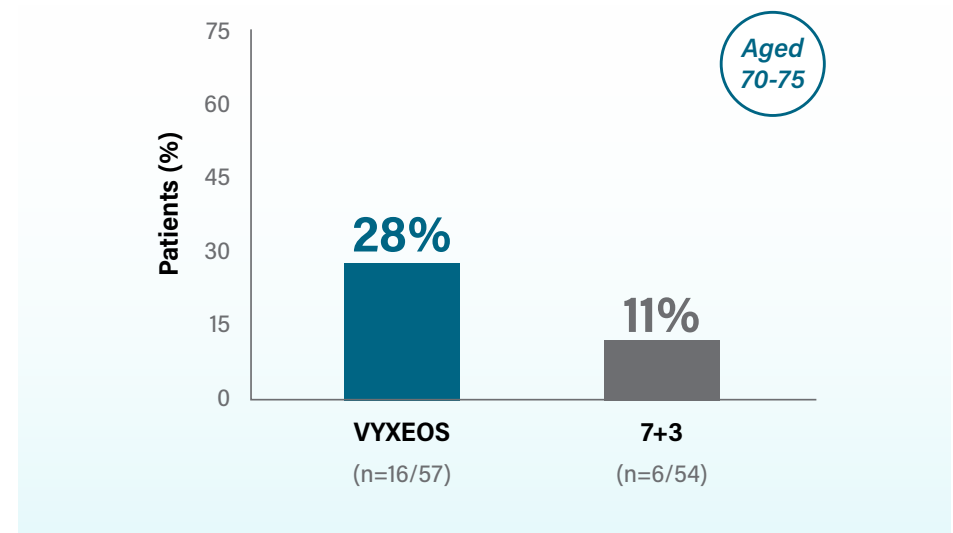
Outcomes in a prespecified exploratory subgroup analysis of transplant rate by age in the Phase 3 trial⁷

Transplant rate—aged 60-69^{7a}



^aData presented are for the subgroup of patients aged 60-69 years in the ITT population.

Transplant rate—aged 70-75^{7b}



^bData presented are for the subgroup of patients aged 70-75 years in the ITT population.

Limitations of subanalysis⁷

- Results should be interpreted with caution, as this is an exploratory analysis of a specific subgroup
- This analysis was limited by the small patient number and that no statistical analysis was conducted on rate of HSCT by age group

IMPORTANT SAFETY INFORMATION

Hypersensitivity Reactions

Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, interrupt or slow the rate of infusion with VYXEOS and manage symptoms. If a severe or life-threatening hypersensitivity reaction occurs, discontinue VYXEOS permanently, treat the symptoms, and monitor until symptoms resolve.

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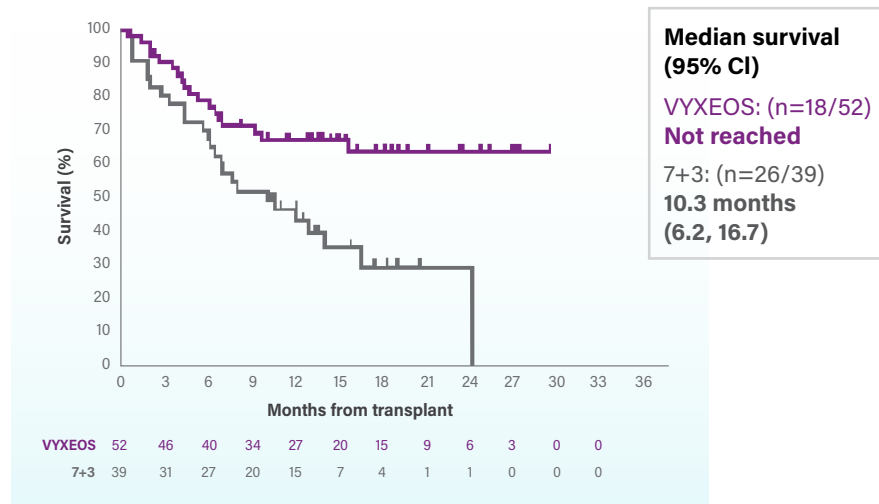
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Exploratory post hoc analyses of OS following HSCT in the Phase 3 trial

These subgroup analyses were exploratory and not powered to determine statistical significance. No efficacy conclusions about OS following HSCT can be drawn from these analyses

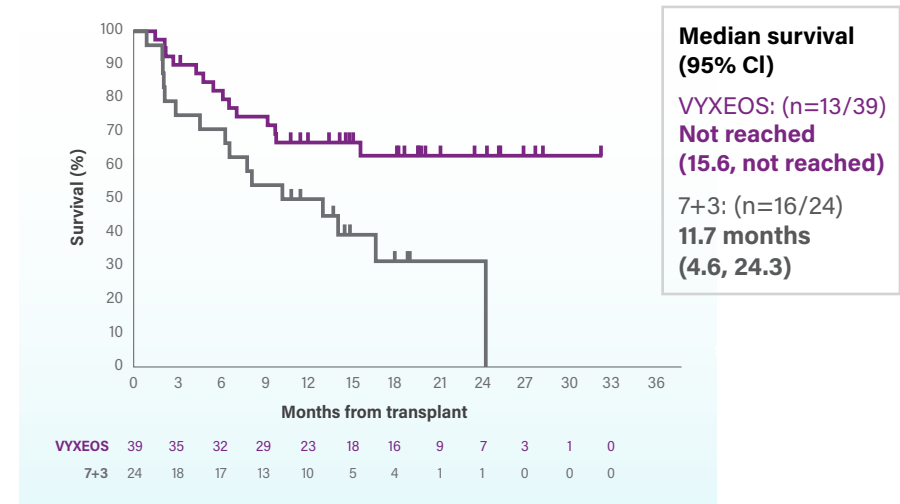
Kaplan-Meier curve for OS landmarked from time of transplant, ITT population^{5,a}

Analysis 1



Kaplan-Meier curve for OS landmarked from time of transplant in patients in CR/CRi at time of HSCT⁸

Analysis 2



Limitations of subanalyses

- Results should be interpreted with caution, as these analyses were not prespecified and were conducted in small nonrandomized subgroups (Analysis 1, n=91; Analysis 2, n=63)^{5,8,9}
- The treatment effect of these nonrandomized subgroups is possibly confounded by unbalanced baseline characteristics
 - In Analysis 1, a higher proportion of patients proceeding to HSCT in the VYXEOS arm (75%) were in CR/CRi as compared with the 7+3 arm (62%)⁸
 - To address this limitation, Analysis 2 evaluated only those patients in each treatment arm who were in CR/CRi at the time they received HSCT⁹

IMPORTANT SAFETY INFORMATION

Copper Overload

VYXEOS contains copper. Consult with a hepatologist and nephrologist with expertise in managing acute copper toxicity in patients with Wilson's disease treated with VYXEOS. Monitor total serum copper, serum non-ceruloplasmin-bound copper, 24-hour urine copper levels, and serial neuropsychological examinations during VYXEOS treatment in patients with Wilson's disease or other copper-related metabolic disorders. Use only if the benefits outweigh the risks. Discontinue in patients with signs or symptoms of acute copper toxicity.

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^aLancet JE, et al. CPX-351 (cytarabine and 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. Reprinted with permission. © 2018 American Society of Clinical Oncology. All rights reserved.

Important Safety Information

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Tissue Necrosis

Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer VYXEOS by the intravenous route only. Do not administer by intramuscular or subcutaneous route.

Please see additional Important Safety Information on next page and full Prescribing Information, including BOXED Warning.

Vyxeos[®]
(daunorubicin and cytarabine) 44 mg/100 mg
liposome for injection

For adults with newly-diagnosed **secondary AML subtypes t-AML or AML-MRC** facing a poor prognosis¹

VYXEOS (CPX-351) was shown to deliver superior overall survival and a better chance to reach HSCT vs 7+3 in a large, randomized, active-controlled Phase 3 trial³

Median survival of 9.6 months with VYXEOS vs 5.9 months with 7+3 ($P=0.005$) (primary endpoint)³

- VYXEOS reduced the risk of death by 31%^a in sAML patients facing a poor prognosis^{1,3}
- Kaplan-Meier estimated survival at 1 year was 42% for those treated with VYXEOS compared to 28% for those treated with 7+3⁵

38% of patients treated with VYXEOS achieved CR vs 26% of those treated with 7+3 ($P=0.036$)³

Overall rate of HSCT^b was 34% for patients treated with VYXEOS vs 25% for those treated with 7+3³

Reported adverse reactions were generally consistent with the known safety profile of cytarabine and daunorubicin therapy³

^aHazard ratio was adjusted for age and AML subtype.

^bInduction failure, first CR, or as salvage after relapse.

IMPORTANT SAFETY INFORMATION, continued

Embryo-Fetal Toxicity

VYXEOS can cause embryo-fetal harm when administered to a pregnant woman. Patients should avoid becoming pregnant while taking VYXEOS. If VYXEOS is used during pregnancy or if the patient becomes pregnant while taking VYXEOS, apprise the patient of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of VYXEOS.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 25\%$) were hemorrhagic events (74%), febrile neutropenia (70%), rash (56%), edema (55%), nausea (49%), mucositis (48%), diarrhea (48%), constipation (42%), musculoskeletal pain (43%), fatigue (39%), abdominal pain (36%), dyspnea (36%), headache (35%), cough (35%), decreased appetite (33%), arrhythmia (31%), pneumonia (31%), bacteremia (29%), chills (27%), sleep disorders (26%), and vomiting (25%).

Please see additional Important Safety Information on preceding page and full Prescribing Information, including BOXED Warning.

References: 1. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. *J Clin Oncol*. 2015;33(31):3641-3649. 2. Wang, ES. Treating acute myeloid leukemia in older adults. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):14-20. 3. VYXEOS [package insert]. Palo Alto, CA: Jazz Pharmaceuticals. 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Acute Myeloid Leukemia V.2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed March 8, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. 5. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and 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. 6. Lin TL, Medeiros BC, Uy GL, et al. Outcomes by number of induction cycles with CPX-351 vs 7+3 chemotherapy in older adults with newly diagnosed high-risk/secondary acute myeloid leukemia (sAML). Poster presented at: American Society of Clinical Oncology Annual Meeting; June 1-5, 2018; Chicago, IL. 7. Lancet JE, Uy GL, Cortes JE, et al. Analysis of survival after allogeneic transplantation by age strata for patients treated with CPX-351 liposome for injection versus cytarabine and daunorubicin 7+3 in patients aged 60-75 years with untreated high-risk acute myeloid leukemia. Poster presented at: 43rd Annual Meeting of the European Society for Blood and Marrow Transplantation; March 26-29, 2017; Marseille, France. 8. Data on file. VYX-2019-019. Palo Alto, CA: Jazz Pharmaceuticals. 9. Data on file. VYX-2019-018. Palo Alto, CA: Jazz Pharmaceuticals.