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 chemotherapy\(^3\)

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\(^c\)) 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.

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\(^a\)Cytarabine 100 mg/m\(^2\) and daunorubicin 60 mg/m\(^2\).
\(^b\)Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.\(^4\)

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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.
**Study Design**

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 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.

**Kaplan-Meier curve for overall survival, ITT population**

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

**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.

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VYXEOS demonstrated a statistically significant improvement in CR vs 7+3\textsuperscript{3}

**Percentage of patients who achieved complete remission\textsuperscript{3}**

- **VYXEOS** (n=58/153): 38%
- **7+3** (n=41/156): 26%

*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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More patients received HSCT following treatment with VYXEOS vs 7+3

**Overall rate of HSCT**

- **VYXEOS** (n=39/156) - 34%
- **7+3** (n=52/153) - 25%

**Rate of HSCT during first CR**

- **VYXEOS** (n=30/153) - 20%
- **7+3** (n=19/156) - 12%

*Induction 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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More VYXEOS patients received HSCT compared to 7+3 in both age subgroups\textsuperscript{7}

Outcomes in a prespecified exploratory subgroup analysis of transplant rate by age in the Phase 3 trial\textsuperscript{7}

**Transplant rate—aged 60-69\textsuperscript{a}**

<table>
<thead>
<tr>
<th></th>
<th>VYXEOS (n=36/96)</th>
<th>7+3 (n=33/102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>38%</td>
<td>32%</td>
</tr>
</tbody>
</table>

**Transplant rate—aged 70-75\textsuperscript{b}**

<table>
<thead>
<tr>
<th></th>
<th>VYXEOS (n=16/57)</th>
<th>7+3 (n=6/54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>28%</td>
<td>11%</td>
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\textsuperscript{a}Data presented are for the subgroup of patients aged 60-69 years in the ITT population.

\textsuperscript{b}Data presented are for the subgroup of patients aged 70-75 years in the ITT population.

**Limitations of subanalysis\textsuperscript{7}**

- 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

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**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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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

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)\textsuperscript{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%)\textsuperscript{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 HSCT\textsuperscript{9}

**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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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.

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

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 trial

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

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

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

Overall rate of HSCT was 34% for patients treated with VYXEOS vs 25% for those treated with 7+3

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

References:
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