Vyxeos®
(daunorubicin and cytarabine) 44 mg/100 mg per vial
liposome for injection

VYXEOS Clinical Overview

Learn how VYXEOS delivers more than 7+3 for patients with sAML: significantly longer OS, better remission rates, and improved opportunity for HSCT vs 7+3[1-3,a]

HSCT=hematopoietic stem-cell transplantation; MOA=mechanism of action; OS=overall survival; sAML=secondary acute myeloid leukemia.

[a]Results seen in Phase 3 study.[1-3]

INDICATION

VYXEOS is indicated for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older.

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.

Contraindications

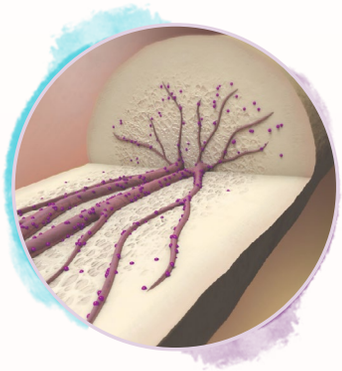
VYXEOS is contraindicated in patients with a history of serious hypersensitivity reactions to cytarabine, daunorubicin, or any component of the formulation.

Please see Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

MECHANISM OF ACTION

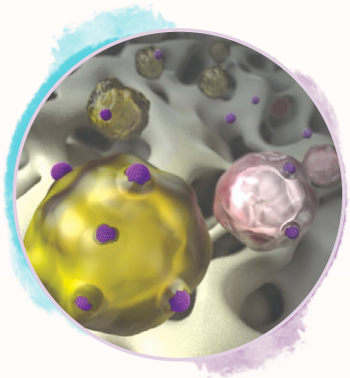
Synergistic combination for controlled delivery

VYXEOS was developed to persist in the bone marrow, leading to prolonged and controlled levels of daunorubicin and cytarabine that reach leukemia cells. VYXEOS is a combination liposome that coordinates the pharmacokinetics of 2 drugs to provide delivery at a synergistic 1:5 molar ratio.[1,4,a]



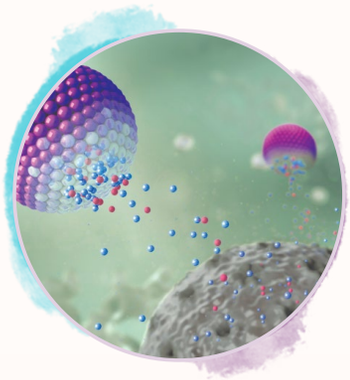
1 Delivery to the bone marrow

VYXEOS liposomes penetrate and persist in the bone marrow.[1,a]



2 Greater leukemia cell uptake and killing of leukemic cells

The synergistic 1:5 molar ratio of daunorubicin and cytarabine has demonstrated increased activity vs free drug in vitro and in murine models, thereby enhancing the killing of leukemia cells.[1,4]



3 Prolonged exposure

VYXEOS is released into the intracellular environment and has a longer half-life than traditional daunorubicin and cytarabine, which results in greater drug exposure within the plasma and bone marrow than traditional chemotherapy.[1,5]

[a]Based on animal studies; clinical relevance unknown.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

STUDY DESIGN

VYXEOS is the only FDA-approved treatment for sAML demonstrating superior OS[a] in a Phase 3 study[2,6,b]

The Phase 3 study was a multicenter, open-label, active-controlled, randomized (1:1) trial of VYXEOS vs 7+3 in 309 patients (aged 60-75 years) with newly diagnosed sAML[1,2]

VYXEOS (n=153)
(daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome given via IV infusion

VYXEOS
(daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome given via IV infusion

First induction (required)	Second induction (if needed)	First consolidation (if needed)	Second consolidation (if needed)
Days 1, 3, & 5	Days 1 & 3	Days 1 & 3	Days 1 & 3

7+3 (n=156)
(cytarabine 100 mg/m^2/day by continuous infusion and daunorubicin 60 mg/m^2/day)

First induction (required)	Second induction (if needed)	First consolidation (if needed)	Second consolidation (if needed)
Cytarabine: Days 1-7 Daunorubicin: Days 1-3	Cytarabine: Days 1-5 Daunorubicin: Days 1 & 2	Cytarabine: Days 1-5 Daunorubicin: Days 1 & 2	Cytarabine: Days 1-5 Daunorubicin: Days 1 & 2

All patients in the Phase 3 study faced a poor prognosis[1,3]

Diagnosed with therapy-related AML

Diagnosed with de novo AML-MDS

Diagnosed with AML-MRC

AML=acute myeloid leukemia; FDA=US Food and Drug Administration; IV=intravenous; MDS=myelodysplastic syndromes; MRC=myelodysplasia-related changes.

[a]Vs 7+3: cytarabine 100 mg/m^2 and daunorubicin 60 mg/m^2.[2]

[b]Evaluating the largest sAML population assessed in clinical studies of FDA-approved AML therapies.[6]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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.

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STUDY DESIGN

VYXEOS is the only FDA-approved treatment for sAML demonstrating superior OS[a] in a Phase 3 study[2,6,b]

All patients in the Phase 3 study had difficult-to-treat sAML[2]

Baseline patient and disease characteristics[2,7]		VYXEOS (n=153) n (%)	7+3 (n=156) n (%)
Male/female		94/59 (61/39)	96/60 (62/38)
Median age (range)		68 (60, 75)	68 (60, 75)
ECOG	PS 0	37 (24)	45 (29)
	PS 1	101 (66)	89 (57)
	PS 2	15 (10)	22 (14)
All patients with prior HMA exposure		62 (41)	71 (46)
Number with cytogenetic risk by National Comprehensive Cancer Network® (NCCN®)		143	146
Cytogenetic risk	Favorable	7 (5)	5 (3)
	Intermediate	64 (45)	58 (40)
	Unfavorable	72 (50)	83 (57)
Genetic mutations	FLT3[c]	22 (14)	21 (14)
	NPM1	13 (9)	12 (8)
	CEBPA	12 (8)	5 (3)

CONTINUE

CEBPA=CCAAT/enhancer-binding protein-alpha; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FLT3=FMS-like tyrosine kinase 3; HMA=hypomethylating agent; NPM1=nucleophosmin-1.

[a]Vs 7+3: cytarabine 100 mg/m^2 and daunorubicin 60 mg/m^2.[2]

[b]Evaluating the largest sAML population assessed in clinical studies of FDA-approved AML therapies.[6]

[c]In the 5-year analysis, 22/138 patients (16%) in the VYXEOS arm and 21/141 patients (15%) in the 7+3 arm had an FLT3 mutation.[3]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Cardiotoxicity (cont'd)

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m^2 have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m^2) 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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Key study details[1-3,8]:

- Primary endpoint: OS
- Median follow-up: 20.7 months
- VYXEOS was administered as 90-minute infusions
- Second induction was highly recommended for patients who did not achieve a response and was mandatory for patients achieving >50% reduction in percent blasts
- Postremission therapy with HSCT was permitted either in place of or after consolidation chemotherapy
- In the Phase 3 study, a bone marrow assessment following induction was done between Days 14 and 21
- A prospectively planned OS analysis of the ITT population was conducted based on the final 5-year follow-up results from the Phase 3 study. Exploratory post hoc subgroup analyses were also conducted

Eligibility criteria[3]:

- Previously untreated and aged 60-75 years
- Able to tolerate intensive therapy
- ECOG PS 0-2
- Adequate renal, liver, and cardiac function

ITT=intent-to-treat.

[a]Vs 7+3: cytarabine 100 mg/m^2 and daunorubicin 60 mg/m^2.[2]

[b]Evaluating the largest sAML population assessed in clinical studies of FDA-approved AML therapies.[6]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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.

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.

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

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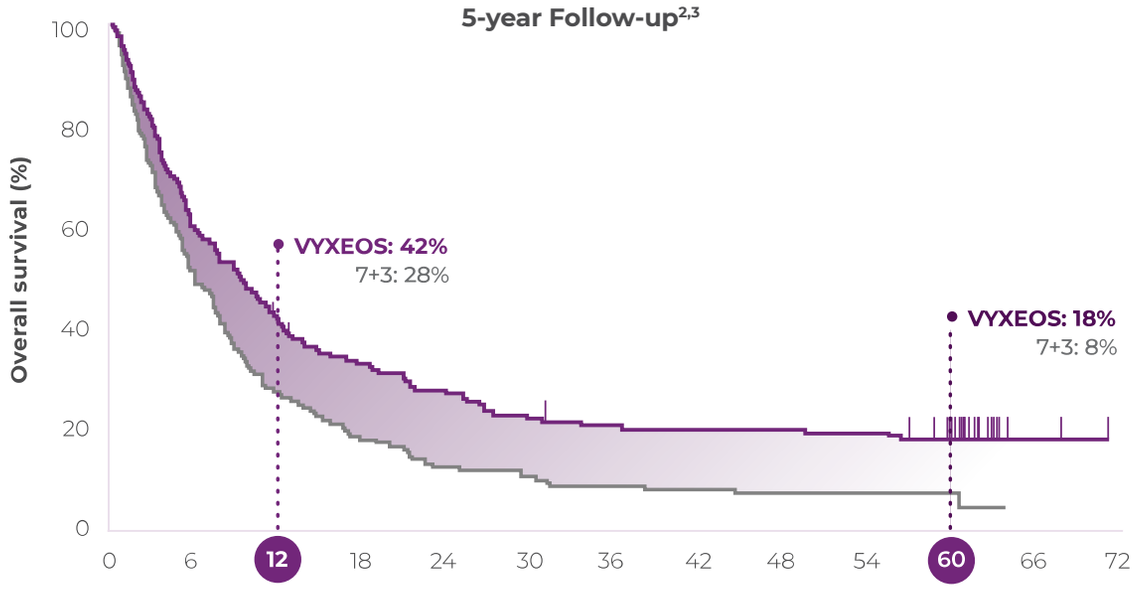
EFFICACY

The only choice for more than double the 5-year OS vs 7+3[3,a]

Median OS (primary analysis) of 9.6 months with VYXEOS vs 5.9 months with 7+3, reducing the risk of death by 31% (HR=0.69 [95% CI: 0.52, 0.90], *P*=0.005 [*P* value is 2 sided])[1]



Number at risk

VYXEOS	**153**	**92**	**62**	**49**	**40**	**33**	**30**	**29**	**29**	**28**	**22**	**2**	**0**
7+3	156	77	43	28	20	17	14	13	12	12	5	0	0

This prospectively planned OS analysis of the ITT population was conducted based on the final 5-year follow-up results from the Phase 3 study.[3]

Reprinted from *Lancet Haematol*, volume 8, issue 7, Lancet JE et al, CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial, pages e481-e491, copyright 2021, with permission from Elsevier.

HR=hazard ratio; KM=Kaplan-Meier.

[a]Based on KM estimates.[3]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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.

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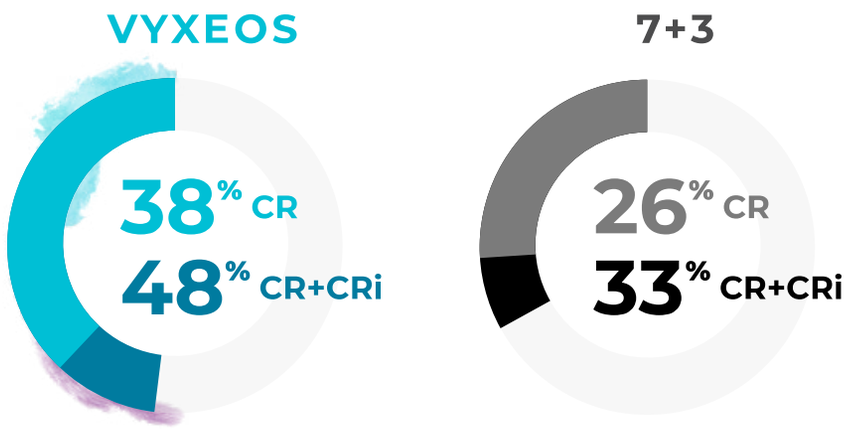
EFFICACY

Give your patients the best chance at remission[1,2]

In the Phase 3 study, almost half of patients with sAML treated with VYXEOS achieved CR+CRi

Percentage of patients with sAML who achieved CR and CR+CRi



Nearly 50% of patients treated with VYXEOS achieved overall remission (CR+CRi).

CR, n/N
VYXEOS: 58/153
7+3: 41/156
2-sided: *P*=0.036

CR+CRi, n/N
VYXEOS: 73/153
7+3: 52/156
2-sided: *P*=0.016

CR=complete remission; CRi=complete remission with incomplete count recovery.

IMPORTANT SAFETY INFORMATION (cont'd)

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥25%) are 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%).

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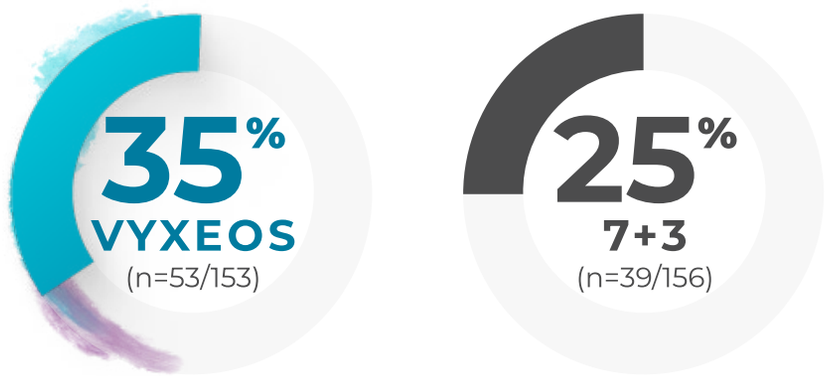
EFFICACY

When transplant is the goal, VYXEOS helps more patients reach HSCT[3]

Data from the Phase 3 study showed that more patients with sAML reached HSCT with VYXEOS vs 7+3[3]

Overall rate of HSCT[3,a]



The foundation of sAML treatment is intensive chemotherapy, with the ultimate goal of achieving remission and reaching HSCT[9,10]

[a]First CR, induction, failure, or as salvage after relapse.[1]

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Hemorrhage

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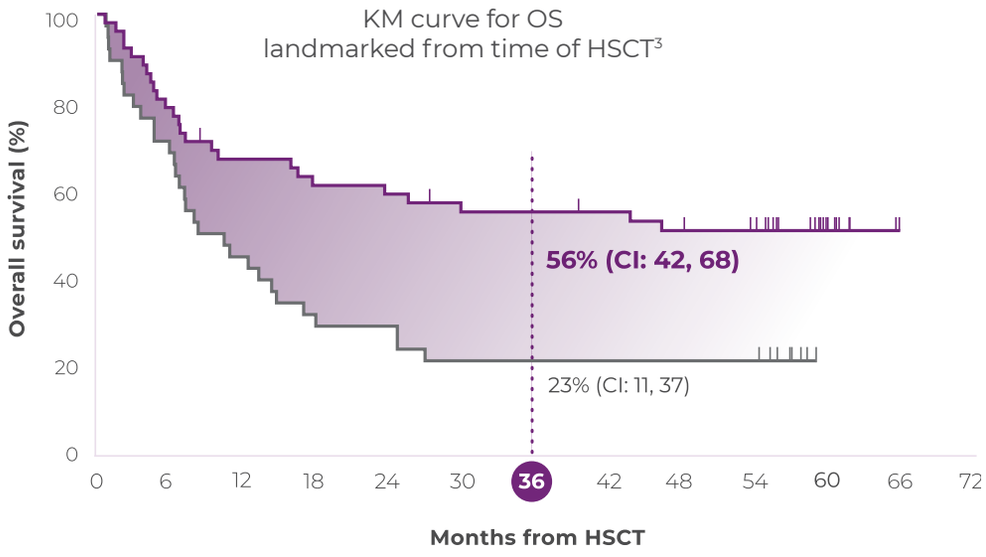
EXPLORATORY POST HOC ANALYSIS

Starting with VYXEOS can lead to prolonged survival after HSCT[3]

More than double the 3-year OS[a] post HSCT for patients treated with VYXEOS (56%) vs 7+3 (23%)



Number at risk

VYXEOS	**53**	**42**	**35**	**32**	**31**	**28**	**28**	**27**	**24**	**21**	**6**	**0**	**0**
7+3	39	27	18	12	12	9	9	9	9	8	0	0	0

MEDIAN OS (95% CI):

VYXEOS:
Not reached
(16.2, NR)(n=23/53)

7+3:
10.3 months
(6.2, 16.7)(n=30/39)

5-year KM estimates from date of HSCT were not available, as the follow-up time from date of HSCT was less than 5 years

CONTINUE

Reprinted from *Lancet Haematol*, volume 8, issue 7, Lancet JE et al, CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial, pages e481-e491, copyright 2021, with permission from Elsevier.

[a]Based on KM estimates.

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EXPLORATORY POST HOC ANALYSIS

Starting with VYXEOS can lead to prolonged survival after HSCT

- A second KM analysis of OS from time of HSCT in patients who achieved CR/CRi continued to show superior survival with VYXEOS, with OS >50% at 3 years[8]
  - KM-estimated OS at 36 months is 58% for VYXEOS (95% CI: 41, 71) vs 29% with 7+3 (95% CI: 13, 48)

Limitations of subanalyses[3,8]

- These exploratory post hoc subgroup analyses were not powered to determine statistical significance. No efficacy conclusions about OS following HSCT (Analysis 1) or OS following HSCT after CR or CRi (Analysis 2) can be drawn from these analyses
- Results should be interpreted with caution, as these analyses were not prespecified and were conducted in small, nonrandomized subgroups (Analysis 1, n=92; Analysis 2, n=65)
- The treatment effect of this nonrandomized subgroup was possibly confounded by unbalanced baseline characteristics
  - 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%)
  - 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

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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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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SAFETY

Comparable safety to 7+3

The safety profile of VYXEOS in the Phase 3 study was found to be comparable to 7+3. The types of adverse reactions, proportions of patients who experienced them, and severity of events were similar between treatment arms.[2]

Common adverse reactions (≥20% incidence in the VYXEOS arm) during the induction phase[1]

Adverse Reaction	All Grades[a]		Grades 3 to 5[a]	
	VYXEOS (n=153) n (%)	7+3 (n=151) n (%)	VYXEOS (n=153) n (%)	7+3 (n=151) n (%)
Hemorrhage	107 (70)	74 (49)	15 (10)	9 (6)
Febrile neutropenia	104 (68)	103 (68)	101 (66)	102 (68)
Rash	82 (54)	55 (36)	8 (5)	2 (1)
Edema	78 (51)	90 (60)	2 (2)	5 (3)
Nausea	72 (47)	79 (52)	1 (1)	1 (1)
Diarrhea/colitis	69 (45)	100 (66)	4 (3)	10 (7)
Mucositis	67 (44)	69 (46)	2 (1)	7 (5)
Constipation	61 (40)	57 (38)	0	0
Musculoskeletal pain	58 (38)	52 (34)	5 (3)	4 (3)
Abdominal pain	51 (33)	45 (30)	3 (2)	3 (2)
Cough	51 (33)	34 (23)	0	1 (1)
Headache	51 (33)	36 (24)	2 (1)	1 (1)
Dyspnea	49 (32)	51 (34)	17 (11)	15 (10)
Fatigue	49 (32)	58 (38)	8 (5)	8 (5)
Arrhythmia	46 (30)	41 (27)	10 (7)	7 (5)

CONTINUE

[a]Adverse reactions were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Embryo-Fetal Toxicity

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Adverse Reaction	All Grades[a]		Grades 3 to 5[a]	
	VYXEOS (n=153) n (%)	7+3 (n=151) n (%)	VYXEOS (n=153) n (%)	7+3 (n=151) n (%)
Decreased appetite	44 (29)	57 (38)	2 (1)	5 (3)
Pneumonia (excluding fungal)	39 (26)	35 (23)	30 (20)	26 (17)
Sleep disorders	38 (25)	42 (28)	2 (1)	1 (1)
Bacteremia (excluding sepsis)	37 (24)	37 (25)	35 (23)	31 (21)
Vomiting	37 (24)	33 (22)	0	0
Chills	35 (23)	38 (25)	0	0
Hypotension	30 (20)	32 (21)	7 (5)	1 (1)
Non-conduction cardiotoxicity	31 (20)	27 (18)	13 (9)	15 (10)

Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and 0.7% in the control arm (7+3).[1]

Other adverse reactions that occurred in ≥10% of patients in the VYXEOS arm included dizziness, fungal infection, hypertension, hypoxia, upper respiratory infections (excluding fungal), chest pain, pyrexia, catheter/device/injection site reaction, delirium, pleural effusion, anxiety, pruritus, sepsis (excluding fungal), hemorrhoids, petechiae, renal insufficiency, transfusion reactions, and visual impairment (except bleeding).[1]

The safety population included all patients in the VYXEOS cohort and 151 patients from the 7+3 cohort (5 patients withdrew consent before the receipt of treatment).[2]

CNS=central nervous system.

[a]Adverse reactions were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

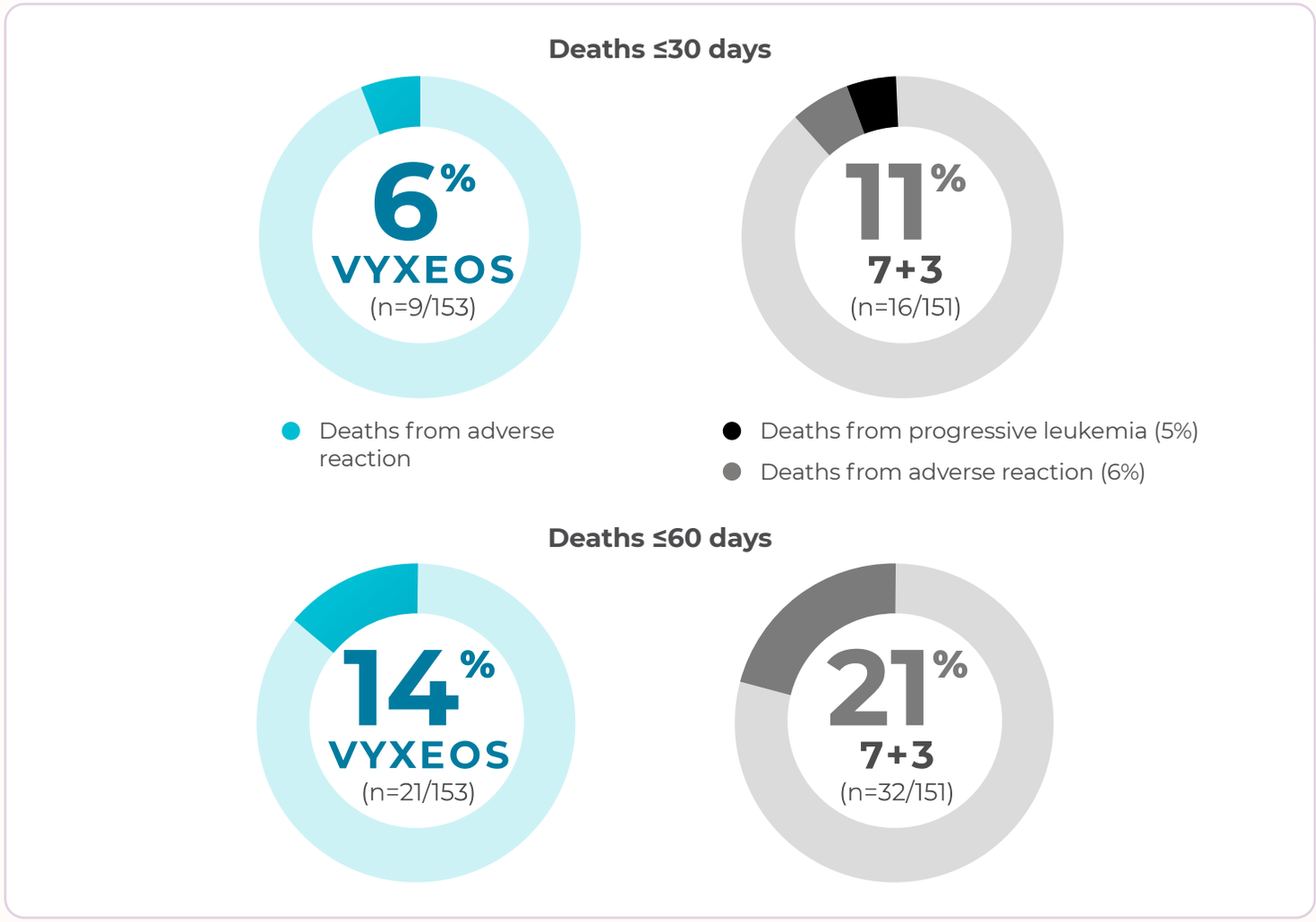
MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥25%) are 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%).

SAFETY

VYXEOS was associated with lower 30- and 60-day mortality rates compared with 7+3[1]

30- and 60-day overall all-cause mortality in patients with sAML aged 60-75 years (safety population)



- 9 patients each in the VYXEOS arm (6%) and control arm (6%) had a fatal adverse reaction on treatment or within 30 days of treatment that was not in the setting of progressive disease
- 8 patients in the control arm (5%) died within 30 days of treatment due to progressive leukemia
- Fatal adverse reactions in the VYXEOS arm included infection, CNS hemorrhage, and respiratory failure

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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RETHINK THE POTENTIAL OF YOUR PATIENTS WITH sAML

The Best Chance at a Cure[1,3]

VYXEOS delivers on key treatment milestones better than 7+3, with significantly longer OS, better remission rates, and improved opportunity for HSCT.[1-3]

- **Longer median OS with VYXEOS** (9.6 months) than 7+3 (5.9 months; HR=0.69 [95% CI: 0.52, 0.90], *P*=0.005)[1]
- **More than double the OS at 5 years** with VYXEOS (18%) vs 7+3 (8%)[3,a]
- The **only** sAML treatment with a 56% 3-year OS rate post HSCT[1,3,a]
- **Comparable** safety profile with 7+3[2]
- VYXEOS gives patients a **finite treatment duration**, giving them additional flexibility between induction and consolidation[1]

VYXEOS is indicated for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older.[1]

Visit **VYXEOSPro.com** to learn about how VYXEOS can deliver on a broad range of clinical milestones that may extend the survival of your patients with sAML.

[a]Based on KM estimates.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

Please see Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

Important Safety Information

INDICATION

VYXEOS is indicated for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older.

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.

Contraindications

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

Warnings and Precautions

Hemorrhage

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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/m^2 have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m^2) 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.

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.

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.

Tissue Necrosis

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

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

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 ≥25%) are 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 full Prescribing Information, including BOXED Warning.

References: 1. VYXEOS [package insert]. Palo Alto, CA: Jazz Pharmaceuticals. **2.** 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. **3.** Lancet JE, Uy GL, Newell LF, et al. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol*. 2021;8(7):e481-e491. **4.** Mayer LD, Tardi P, Louie AC. CPX-351: a nanoscale liposomal co-formulation of daunorubicin and cytarabine with unique biodistribution and tumor cell uptake properties. *Int J Nanomedicine*. 2019;14:3819-3830. **5.** 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(8):979-985. **6.** Data on File (VYX-2022-047). Jazz Pharmaceuticals, Inc. **7.** Data on File (REF-18624). Jazz Pharmaceuticals, Inc. **8.** Supplement to: Lancet JE, Uy GL, Newell LF, et al. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol*. 2021;8(7):e481-e491. **9.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia Version 3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed June 17, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. 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. **10.** Lalayanni C, Gavriilaki E, Athanasiadou A, et al. Secondary acute myeloid leukemia (sAML): similarly dismal outcomes of AML after an antecedent hematologic disorder and therapy related AML. *Clin Lymphoma Myeloma Leuk*. 2022;22(4):e233-e240.