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

5-YEAR OS DATA

A STRONG START FOR SUPERIOR SURVIVAL[1,2]

VYXEOS demonstrated superior efficacy with longer overall survival compared to traditional chemotherapy[a] and provided an improved opportunity for transplant[1]

NCCN

Liposomal daunorubicin and cytarabine (VYXEOS) is the ONLY treatment recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for induction in patients ≥60 years of age with therapy-related AML or antecedent MDS/CMML or AML-MRC (Category 1)[3,b]

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.

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 24 and 25 and full Prescribing Information, including BOXED Warning.

[a]7+3: cytarabine 100 mg/m^2 and daunorubicin 60 mg/m^2.[1]

[b]Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[3]

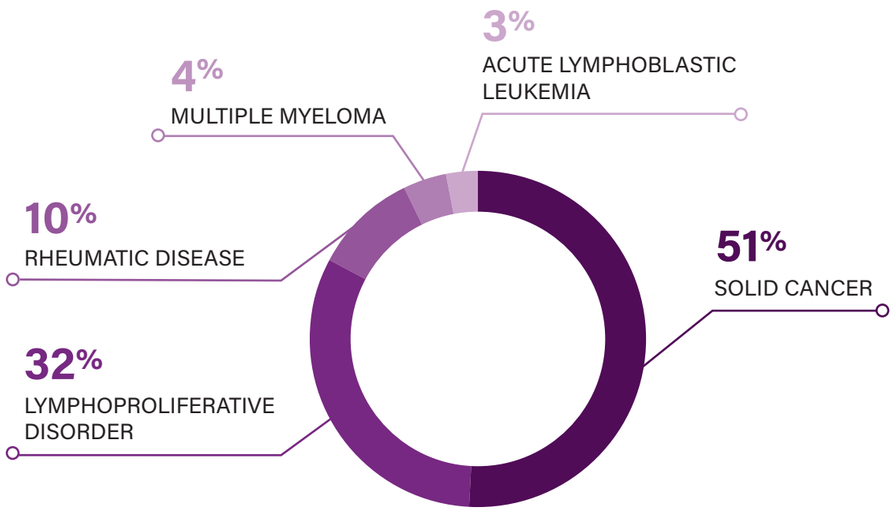
AML=acute myeloid leukemia; AML-MRC=AML with myelodysplasia-related changes; CMML=chronic myelomonocytic leukemia; MDS=myelodysplastic syndromes; NCCN=National Comprehensive Cancer Network; OS=overall survival.

Approximately 30% of all AML cases are made up of secondary AML subtypes t-AML and AML-MRC[4,5]

t-AML: ~4% to 10% of all AML cases[4,5]

WHO defines t-AML as AML that arises from treatment with cytotoxic therapy or ionizing radiotherapy for an unrelated disease or prior cancer[6,7]

Prior malignancies associated with t-AML[8,a]



If your patient presents with a history of any of these malignancies, determine if they have been treated with a cytotoxic therapy or radiotherapy, as this may point to t-AML[6,7]

[a]Distribution of previous disease in 203 patients with t-AML regardless of treatment intent. Data from a national, population-based study of 3055 patients diagnosed with AML from 2000 to 2013 in Denmark.[8]

t-AML=therapy-related AML; WHO=World Health Organization.

AML-MRC: ~25% of all AML cases[4]

WHO defines AML-MRC as ≥20% blasts in the peripheral blood or bone marrow and ANY of the following[7,9]:

MDS

PREVIOUSLY DOCUMENTED MDS OR MDS/MPN

OR

Non-MDS

MYELODYSPLASIA-RELATED CYTOGENETIC ABNORMALITIES[a-c]

OR

DYSPLASIA PRESENT IN ≥50% OF CELLS IN AT LEAST 2 MYELOID CELL LINES, UNLESS AN *NPM1* MUTATION OR BIALLELIC MUTATION OF *CEBPA* IS PRESENT

Among the most common genetic abnormalities found in the unfavorable cytogenetic risk group in AML are -7/del(7q) and -5/del(5q)[10,11]

IMPORTANT SAFETY INFORMATION

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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[a]Complex karyotype: 3 or more abnormalities.[7]

[b]Unbalanced abnormalities: -7/del(7q), del(5q)/t(5q), i(17q)/t(17p), -13/del(13q), del(11q), del(12p)/t(12p), idic(X)(q13).[7]

[c]Balanced abnormalities: t(11;16)(q23.3;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23.3), t(5;12)(q32;p13.2), t(5;7)(q32;q11.2), t(5;17)(q32;p13.2), t(5;10)(q32;q21.2), t(3;5)(q25.3;q35.1).[7]

MPN=myeloproliferative neoplasms.

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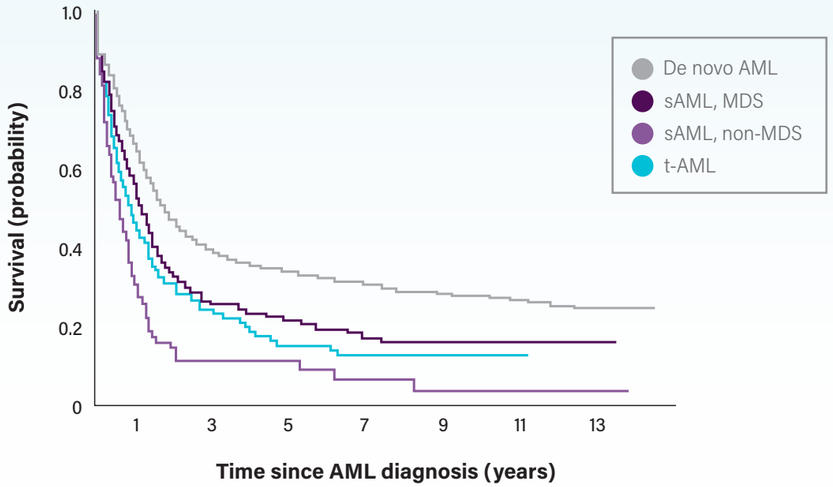
Historically, there have been challenges in treating sAML[8]

sAML subtypes t-AML and AML-MRC are associated with a poor prognosis[8]



Granfeldt Østgård LS, 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. Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved.

It is critical to identify sAML prior to treatment[8]

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/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.

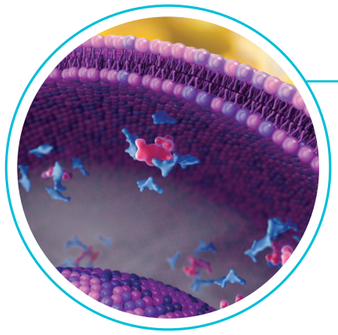
Please see additional Important Safety Information on pages 24 and 25 and full Prescribing Information, including BOXED Warning.

sAML=secondary AML.

Synergistic combination for potent delivery[1,12]

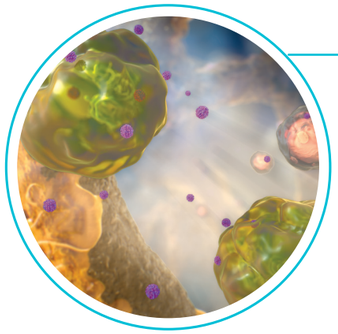
VYXEOS (CPX-351) is a unique combination liposome, engineered to deliver 2 established therapies at a synergistic ratio[1,12]

Based on animal studies[a]...



INCREASED ACTIVITY VS FREE DRUG

The synergistic 1:5 molar ratio of daunorubicin and cytarabine has been shown to enhance the killing of leukemia cells in vitro and in murine models[1]

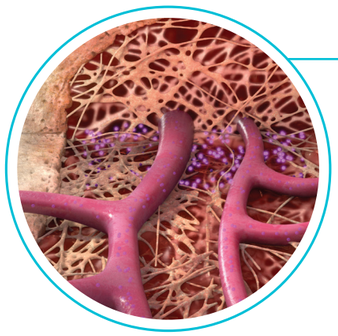


GREATER LEUKEMIA CELL UPTAKE

VYXEOS liposomes enter the bone marrow and are preferentially taken up by leukemia cells to a greater extent than by normal bone marrow cells in a murine model[1,13]

- Their unique composition allows the negatively charged VYXEOS liposomes to interact with receptors that are overexpressed by leukemic cells compared to the expression by normal bone marrow cells[13,14]

Based on pharmacokinetic Phase 1 trial data...



PROLONGED DELIVERY

The longer half-life of VYXEOS resulted in greater drug exposure within the plasma and bone marrow than traditional chemotherapy[1,15]

- Estimated median half-life of daunorubicin was 32 hours with VYXEOS vs 19 hours as free drug[1,16]
- Estimated median half-life of cytarabine was 40 hours with VYXEOS vs approximately 1 to 3 hours as free drug[1,17]

[a]The clinical relevance of this is unknown.

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The FDA approval of VYXEOS (CPX-351) was based on data from a large, pivotal Phase 3 study[2]

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

VYXEOS (N=153)

Daunorubicin 44 mg/cytarabine 100 mg per m^2 IV infusion

First induction
Days 1, 3, & 5

Second induction
(if needed)
Days 1 & 3

Daunorubicin 29 mg/cytarabine 65 mg per m^2 IV infusion

First consolidation
Days 1 & 3

Second consolidation
(if needed)
Days 1 & 3

Follow-up

7+3 (N=156)

Cytarabine 100 mg/m^2/day continuous IV infusion
Daunorubicin 60 mg/m^2/day

First induction
Cytarabine: Days 1-7
Daunorubicin: Days 1-3

Second induction
(if needed)
Cytarabine: Days 1-5
Daunorubicin: Days 1 & 2

First consolidation
Cytarabine: Days 1-5
Daunorubicin: Days 1 & 2

Second consolidation
(if needed)
Cytarabine: Days 1-5
Daunorubicin: Days 1 & 2

Follow-up

Key eligibility[2,18,19]
- Previously untreated
- Aged 60-75
- Able to tolerate intensive therapy
- ECOG PS 0-2

Primary endpoint[1]
- Overall survival (OS)[a]

- VYXEOS was administered as 90-minute intravenous infusions[1]
- Second induction was highly recommended for patients who did not achieve a response and was mandatory for patients achieving >50% reduction in percent blasts[1]
- Postremission therapy with HSCT was permitted either in place of or after consolidation chemotherapy[1]
- In the Phase 3 trial, a bone marrow assessment following induction was done between Days 14 and 21[20]
- A preplanned overall survival analysis was conducted based on the final 5-year follow-up results from the Phase 3 trial[18]

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.

Please see additional Important Safety Information on pages 24 and 25 and full Prescribing Information, including BOXED Warning.

[a]Overall survival was defined as date of randomization to death from any cause.[1]

ECOG=Eastern Cooperative Oncology Group; FDA=Food and Drug Administration; HSCT=hematopoietic stem cell transplant; IV=intravenous; PS=performance status.

sAML patient characteristics in the Phase 3 study

All patients in the Phase 3 study had difficult-to-treat sAML[1,2]

Patients with documented history[1,2]

Therapy-related AML	AML-MRC AML with an antecedent hematological disorder
20%	54%

Undocumented history[1,2]

AML-MRC De novo AML with MDS-related cytogenetic abnormalities[a]
25%

[a]De novo AML with MDS-related cytogenetic abnormalities was defined as patients having cytogenetic abnormalities characteristic of myelodysplasia based on 2008 WHO criteria.[2,9]

Baseline patient and disease characteristics[1,2,21]		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[b]		62 (41)	71 (46)
Number with cytogenetic risk by NCCN		143	146
Cytogenetic risk	Favorable	7 (5)	5 (3)
	Intermediate	64 (45)	58 (40)
	Unfavorable	72 (50)	83 (57)
Genetic mutations	*FLT3*	22 (14)	21 (14)
	NPM1	13 (9)	12 (8)
	CEBPA	12 (8)	5 (3)

41% of patients treated with VYXEOS had prior HMA exposure[2]

NCCN

For patients >60 years old with AML, NCCN Guidelines® recommend selecting a treatment option based on patient performance status, comorbid conditions, and adverse features such as subtype rather than chronologic age alone[3]

[b]Includes patients in the prespecified randomization strata of antecedent MDS with prior HMA exposure as well as patients in other strata (eg, t-AML, antecedent CMML) who had previously received HMAs.[2]

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HMA=hypomethylating agent.

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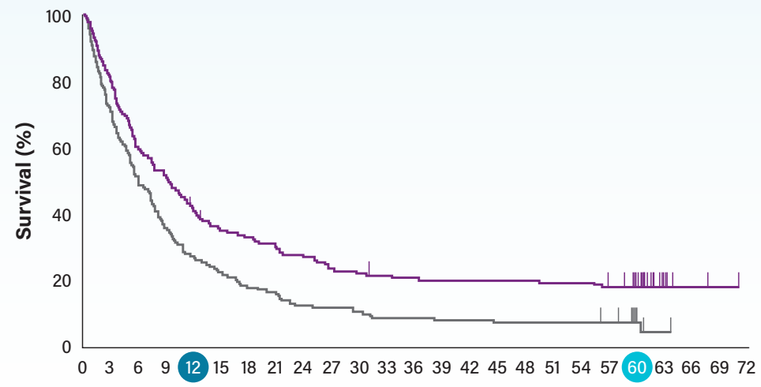
Overall survival more than doubled at 5 years with VYXEOS (18%) vs 7+3 (8%) based on KM estimates[1,18]

Median overall survival (primary endpoint) of 9.6 months with VYXEOS vs 5.9 months with 7+3 (HR=0.69 [0.52, 0.90], *P*=0.005[a])[1]

With median follow-up of 60 months, the improvement in OS was maintained with a stable hazard ratio[18]

5-YEAR FOLLOW-UP

Kaplan-Meier curve for overall survival, ITT population[18]



VYXEOS	153	122	92	79	62	52	49	45	40	35	33	31	30	29	29	29	29	28	28	26	22	6	2	1	0
7+3	156	110	77	56	43	35	28	25	20	19	17	14	14	13	13	12	12	12	12	11	5	1	0	0	0

1-YEAR
KM-estimated survival[2]

VYXEOS: 42%
7+3: 28%

5-YEAR
KM-estimated survival[18]

VYXEOS: 18%
7+3: 8%

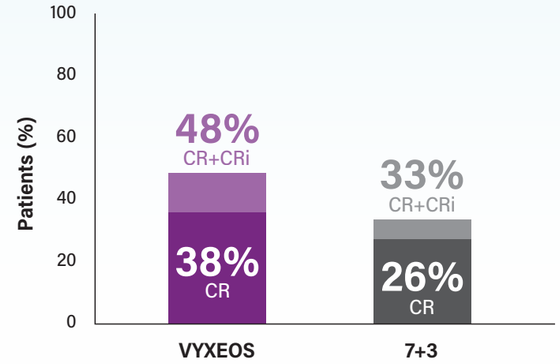
[a]*P* value is 2-sided.[1]

HR=hazard ratio; ITT=intent to treat; KM=Kaplan-Meier.

Strive for higher remission rates in sAML with VYXEOS[1,2]

Almost half of sAML patients treated with VYXEOS achieved CR+CRi[2]

Percentage of sAML patients who achieved CR and CR+CRi[1,2]



CR, n/N:	CR+CRi, n/N:
VYXEOS: 58/153 | 7+3: 41/156	VYXEOS: 73/153 | 7+3: 52/156
P=0.036[a]	*P*=0.016[a]

[a]*P* value is 2-sided.[1]

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

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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Exploratory post hoc analysis of patients who achieved CR or CRi and did not undergo transplant in the Phase 3 trial[22,a]

MEDIAN OS FOR NON-HSCT
PATIENTS WHO ACHIEVED CR[22]

19.2 months vs 8.4 months

VYXEOS (n=27) | 7+3 (n=21)

MEDIAN OS FOR NON-HSCT
PATIENTS WHO ACHIEVED CR+CRi[22]

14.7 months vs 7.6 months

VYXEOS (n=33) | 7+3 (n=28)

Limitations of subanalysis[22]

- This subgroup analysis was exploratory and not powered to determine statistical significance. No efficacy conclusions about OS following CR or CRi can be drawn from this analysis
- Results should be interpreted with caution, as this analysis was not prespecified and was conducted in a small, nonrandomized subgroup (n=61)[22]
- The treatment effect of this nonrandomized subgroup was possibly confounded by unbalanced baseline characteristics

IMPORTANT SAFETY INFORMATION

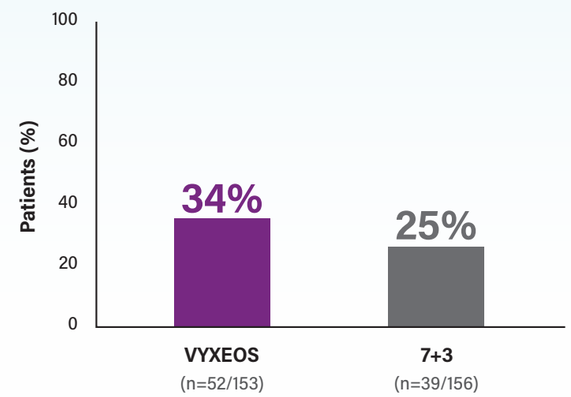
Tissue Necrosis
Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer VYXEOS by the intravenous route only. Do not administer by intramuscular or subcutaneous route.

Please see additional Important Safety Information on pages 24 and 25 and full Prescribing Information, including BOXED Warning.

[a]Based on primary analysis of median follow-up of 20.7 months.[2]

For sAML patients whose treatment goals align with transplant, start with VYXEOS[1]

Overall rate of HSCT[1,18,a,b]



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

[b]At 5-year follow-up, HSCT had been received by 53/153 (35%) and 39/156 (25%) patients in the VYXEOS and 7+3 arms, respectively.[18]

A greater proportion of patients who achieved first CR with VYXEOS subsequently underwent HSCT[23]

RATE OF HSCT **DURING FIRST CR[1,2,23,c]**

20% VYXEOS vs 12% 7+3

(n=30/153) (n=19/156)

[c]First CR after 1 or 2 induction cycles.[23]

The goal of chemotherapy is to eliminate as many leukemia cells from the body as possible to achieve remission,[3,24] and low leukemic burden impacts outcomes of HSCT[25]

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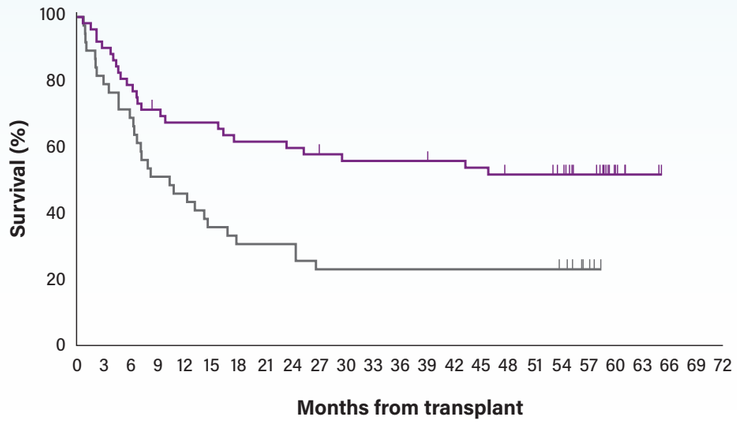
Exploratory post hoc analyses of 5-year OS in patients who received HSCT in the Phase 3 trial[18]

5-YEAR FOLLOW-UP

ANALYSIS 1

Kaplan-Meier curve for overall survival landmarked from time of transplant, **ITT population**[18]



VYXEOS	53	48	42	37	35	35	32	32	31	29	28	28	28	27	27	26	24	24	21	15	6	2	0	0	0
7+3	39	31	27	20	18	14	12	12	12	9	9	9	9	9	9	9	9	8	2	0	0	0	0	0	0

MEDIAN SURVIVAL (95% CI)

VYXEOS: **Not reached** (n=25/53)	7+3: 10.3 months (6.2, 16.7) (n=30/39)

Limitations of subanalysis[18]

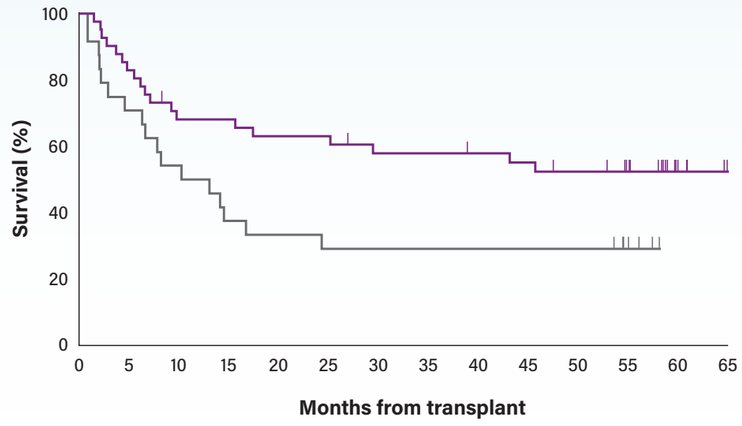
- This subgroup analysis was exploratory and not powered to determine statistical significance. No efficacy conclusions about OS following HSCT can be drawn from this analysis
- Results should be interpreted with caution, as this analysis was not prespecified and was conducted in a small, nonrandomized subgroup (n=92)[18]
- 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 (77%) were in CR/CRi as compared with the 7+3 arm (62%)[18]
  - To address this limitation, Analysis 2 (right) evaluated only those patients in each treatment arm who were in CR/CRi at the time they received HSCT[18]

CI=confidence interval.

5-YEAR FOLLOW-UP

ANALYSIS 2

Kaplan-Meier curve for overall survival landmarked from time of transplant **in patients who achieved CR or CRi**[18]



VYXEOS	41	34	27	27	25	25	22	22	21	20	18	13	6	0
7+3	24	17	13	9	8	7	7	7	7	7	7	5	0	0

MEDIAN SURVIVAL (95% CI)

VYXEOS: **Not reached** (n=19/41)	7+3: 11.7 months (4.6, 24.3) (n=17/24)

Limitations of subanalysis[18]

- This subgroup analysis was exploratory and not powered to determine statistical significance. No efficacy conclusions about OS following HSCT after CR or CRi can be drawn from this analysis
- Results should be interpreted with caution, as this analysis was not prespecified and was conducted in a small, nonrandomized subgroup (n=65)[18]
- The treatment effect of this nonrandomized subgroup was possibly confounded by unbalanced baseline characteristics

IMPORTANT SAFETY INFORMATION

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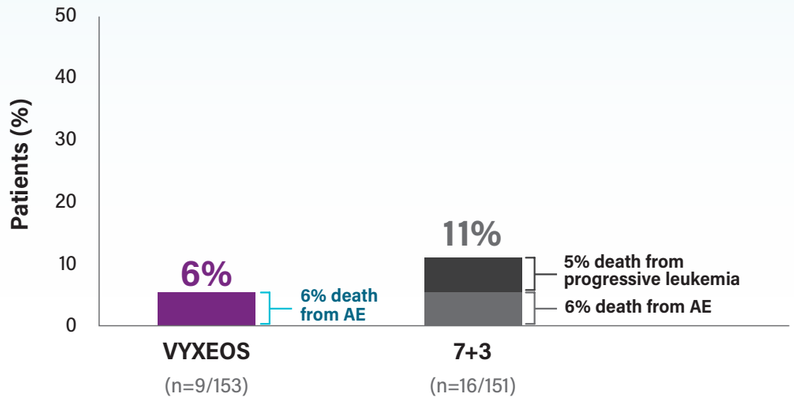
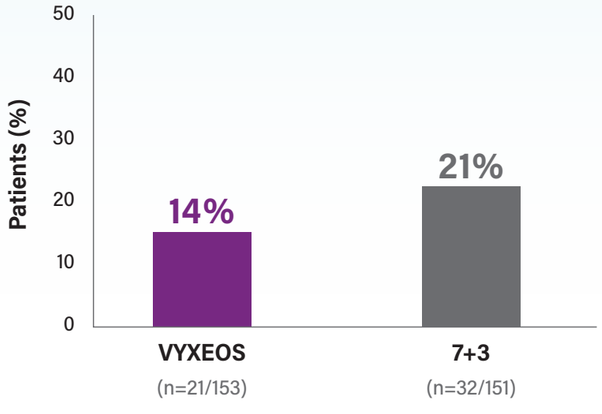
VYXEOS was associated with lower 30- and 60-day mortality rates compared to 7+3[1]

30-DAY
overall all-cause mortality in patients aged 60-75 (safety population[a])[1]



60-DAY
overall all-cause mortality in patients aged 60-75 (safety population[a])[1]



- 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[1]
- 8 patients in the control arm (5%) died within 30 days of treatment due to progressive leukemia[1]
- Fatal adverse reactions in the VYXEOS arm included infection, CNS hemorrhage, and respiratory failure[1]

[a]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]

AE=adverse event; CNS=central nervous system.

Safety profile in the Phase 3 trial consistent with 7+3[1]

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[1]

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)
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)

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

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]

Please see additional Important Safety Information on pages 24 and 25 and full Prescribing Information, including BOXED Warning.

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

VYXEOS is a fixed course of therapy that allows patients time off sAML treatment[1,a,b]

FIRST INDUCTION	1	2	3	4	5	6	7
Days 1, 3, and 5 Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 **90-min infusions**							

Administer first consolidation cycle 5 to 8 weeks after the start of the last induction[1]

CONSOLIDATION	1	2	3	4	5	6	7
Days 1 and 3 Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 **90-min infusions**							

The majority of patients received induction with VYXEOS in an inpatient setting during the Phase 3 trial[26]

51% of patients received consolidation with VYXEOS in an outpatient setting during the Phase 3 trial[27]

Second induction (if needed)[1]

Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome on Days 1 and 3

- In patients not achieving a response, start 2 to 5 weeks after first induction

Second consolidation (if needed)[1]

Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 liposome on Days 1 and 3

- 5 to 8 weeks after the start of first consolidation in patients who do not show disease progression or unacceptable toxicity

Dosing considerations

- Prior to initiating each cycle, calculate the prior cumulative anthracycline exposure for the patient[1]
- Assess cardiac function, complete blood counts, and liver and renal function before each consolidation cycle[1]
- Do not start consolidation until the absolute neutrophil count (ANC) recovers to greater than 0.5 Gi/L and the platelet count recovers to greater than 50 Gi/L in the absence of unacceptable toxicity[1]

[a]Patients may receive up to 2 cycles of induction and up to 2 cycles of consolidation.[1]

[b]All infusions administered intravenously.[1]

Factors to consider for outpatient administration with VYXEOS[a-c]

PATIENT FACTORS

1 Deemed stable by medical team[28-31]

- ECOG PS 0-1 and no significant comorbidities such as kidney or cardiopulmonary diseases or active uncontrolled infections

2 Capable of self-care activities[28,30]

- Ability to consistently attend all scheduled visits and participate in self-care activities such as taking temperature

3 In close proximity to their infusion center[28,30]

- Ability to consistently attend all scheduled visits for treatment and monitoring

INSTITUTIONAL FACTORS

1 Timely access to supportive care that may include[28,30]

- Blood and platelet transfusion support
- Prophylactic antimicrobial implementation

2 A multidisciplinary team that can[28,30]

- Coordinate and manage expectations for outpatient care with the patient
- Assess and evaluate lab results
- Monitor symptoms, side effects, and/or signs of toxicity

3 Inpatient access that allows for[28]

- Unplanned admission due to urgent adverse events

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥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 pages 24 and 25 and full Prescribing Information, including BOXED Warning.

[a]In the Phase 3 trial, site of induction and consolidation administration—inpatient vs outpatient—was not defined. The decision was left to the discretion of the investigators according to the standard practices of their institution.[26,27]

[b]Most patients in the Phase 3 trial received induction in an inpatient setting.[26]

[c]Outpatient administration may decrease the number of days a patient needs to be hospitalized for treatment.[27]

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Institutions have evaluated administering VYXEOS in the outpatient setting[32,33]

Two small, postapproval, single-institution studies assessed the feasibility of adult patients receiving VYXEOS induction in the inpatient/outpatient (IPOP) setting[32,33,a]

Treatment in the IPOP setting enables appropriate patients to receive induction in an outpatient setting with inpatient admission scheduled or as needed for continued monitoring and subsequent treatment[32,33]

IPOP-eligible patients who received VYXEOS infusions in an outpatient setting were closely monitored[32,33]

- In a study by Kubal et al, patients were excluded for IPOP if they had increased risk for tumor lysis including white count >50K, increased creatine and uric acid, active cardiopulmonary symptoms, ECOG PS >2, or lacked a caregiver or were unable to reside within 60 minutes of the treating facility[32]
  - Patients were evaluated each day with CMP and uric acid and phosphorus measures. Planned admission occurred on Day 6 for continued care[32]
- In another study, by Deutsch et al, patients were excluded if they had signs or symptoms of active infection or cardiopulmonary disease, were at risk for tumor lysis syndrome, had ECOG PS >2, or did not have an appropriate caregiver or transportation to the cancer center[33]
  - Patients were monitored at least every other day until count recovery and admitted for continued care if complications occurred[33]

[a]Most patients in the Phase 3 trial received induction in an inpatient setting.[26]

Study information

In a small, single-center pilot study by Kubal et al, 22 patients received a full induction course of VYXEOS. Of these, 64% (n=14; median age 69) received induction in an IPOP setting, and 93% of those patients (n=13) were admitted for continued care on Day 6, as planned. One patient was admitted on Day 2 of induction.[32]

In a small, single-center pilot study by Deutsch et al, 12 patients received a full induction course of VYXEOS, with 58% (n=7; median age 72) receiving induction in an IPOP setting. Of these patients, 86% (n=6) were eventually admitted for continued care; all admissions were due to infection complications. One patient was admitted prior to completing the third induction dose.[33]

CMP=comprehensive metabolic panel.

One institution's experience with VYXEOS administration in the outpatient setting[30]

Real-world experience from one institution's implementation of VYXEOS administration in the outpatient setting[30]

Patient factors for outpatient treatment[30]

- No active, uncontrolled infections
- Ability to travel to
  - Infusion center during the first week of therapy for infusions and supportive care
  - Infusion center twice per week after initial induction for continued monitoring
  - A cancer center close to home to help with transfusion support if infusion center is too distant

Institutional factors to conduct outpatient treatment[30]

- Access to advanced practice providers (APPs)
- Multidisciplinary team trained in transfusion support, symptom management, and transfer of patients to the inpatient setting

There is no planned day of admission; however, when treating patients with VYXEOS, it is not uncommon for a patient to experience fevers. When fever persists, inpatient admission allows further observation and intervention[30]

Successful implementation of an outpatient approach requires that patients have quick, easy access to providers.[30]

- Treating hematologist

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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A case study: patient presentation

Elizabeth | 67 years old | retired

- ECOG PS 1
- Was diagnosed with lower-risk MDS (IPSS low) 2 years ago and has been under observation since then
- Received 3 blood transfusions since diagnosis
- Contacts her hematologist after 3 consecutive days of severe fatigue, shortness of breath, and chest pain
- Married; husband is also retired
- Lives a short drive from hospital

LAB RESULTS

	CBC results	Reference range[34,35]
WBC	4.1 x 10^9/L	4.5-11 x 10^9/L
ANC	1.4 x 10^9/L	2.0-8.25 x 10^9/L
Hb	8.5 g/dL	12-16 g/dL
Hct	20%	36%-47%
RBC	1.9 x 10^{12}/L	4.2-5.9 x 10^{12}/L
MCV	115 fL	80-100 fL
PLT	55 x 10^9/L	150–350 x 10^9/L

ANALYSIS AND FINDINGS

Aspirate smear

45% blasts with multilineage dysplasia (MLD)

Bone marrow biopsy

50% blasts

Flow cytometry

46% myeloblasts

Cytogenetics and PCR molecular findings: results pending

DIAGNOSIS

Based on her medical history and test results, ***Elizabeth is diagnosed with AML-MRC***

Based on her condition and practical considerations, Elizabeth is deemed a candidate for outpatient induction

PATIENT CONSIDERATIONS

- Elizabeth lives within 30 minutes of hospital and has a reliable caregiver who will provide transportation for appointments as needed
- Elizabeth has consistently attended all scheduled appointments with her hematologist and has clearly communicated symptoms she has experienced

PRACTICE CONSIDERATIONS

- Practice has multidisciplinary support staff needed to coordinate outpatient care with the patient, assess and evaluate lab results, and monitor symptoms, side effects, and/or signs of toxicity
- Practice has access to supportive care, including blood and platelet transfusion support
- Practice has inpatient access in case unplanned admission is required due to urgent adverse event(s)

CBC=complete blood count; Hb=hemoglobin; Hct=hematocrit; IPSS=International Prognostic Scoring System; MCV=mean corpuscular volume; PCR=polymerase chain reaction; PLT=platelet; RBC=red blood cell; WBC=white blood cell.

VYXEOS reimbursement and support

J code issued for VYXEOS

Permanent, product-specific HCPCS J code for VYXEOS		
J9153	**Dosage**	**Billing**
	Injection, liposomal, 1 mg daunorubicin and 2.27 mg cytarabine	units per dose: 1
		units per vial: 44

JazzCares™
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Call the support hotline 1-855-5VYXEOS (1-855-589-9367), Monday through Friday between 8 AM and 8 PM ET to speak with a representative

[a]Insurance coverage and plans may vary. The JazzCares program provides general information only and is not a guarantee of any coverage or reimbursement outcome. All treatment decisions rest solely with the treating physician or qualified healthcare professional.

You can also request to be contacted by an Access and Reimbursement Manager (ARM) to assist you with additional reimbursement-related questions.

HCPCS=Healthcare Common Procedure Coding System.

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VYXEOS distribution partners

Specialty Distributors

VYXEOS (daunorubicin and cytarabine) is available for purchase from the authorized **Specialty Distributors** listed below. Verify that your facility has an account with their Specialty Distributor before ordering. If not, they should contact their Specialty Distributor. The facility should also contact their Specialty Distributor with questions regarding product returns.

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VYXEOS is now partnering with certain group purchasing organizations (GPOs)

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- Onmark GPO (McKesson Specialty Health)
- Unity GPO (The US Oncology Network/McKesson Specialty Health)
- VitalSource (Cardinal Health)

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Important Safety Information

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.

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
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.

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.

Warnings and Precautions, continued

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.

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%) 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 full Prescribing Information, including BOXED Warning.

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VYXEOS HAS PROVEN EFFICACY BENEFITS
in newly-diagnosed sAML subtypes t-AML or AML-MRC[1,2]

Overall survival more than doubled at 5 years with VYXEOS (18%) vs 7+3 (8%) based on KM estimates[1,18]

- Median overall survival (primary endpoint) of 9.6 months with VYXEOS vs 5.9 months with 7+3 (HR=0.69 [0.52, 0.90], *P*=0.005[a])[1]
  - Higher rates of CR and CR+CRi with VYXEOS (38%; 48%) vs 7+3 (26%; 33%)[1,2]
  - More patients received HSCT[b] with VYXEOS (34%) vs 7+3 (25%)[1,18]
- With median follow-up of 60 months, the improvement in OS was maintained with a stable hazard ratio[18]

Dosing designed with patients in mind[1,26]

- Fixed dosing regimen
- Allows patients time off sAML treatment
- Outpatient opportunity for appropriate patients, based on assessment of patient and institutional factors
- 90-minute infusions

Reported adverse reactions were generally consistent with the known safety profile of cytarabine and daunorubicin therapy[1,2]

The most common adverse reactions (incidence ≥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%)[1,36]

INDICATION

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[a]*P* value is 2-sided.[1]

[b]At 5-year follow-up, HSCT had been received by 53/153 (35%) and 39/156 (25%) patients in the VYXEOS and 7+3 arms, respectively.[18]