Clinical Cancer Research

FDA Approval Summary: (Daunorubicin and Cytarabine) Liposome for Injection for the Treatment of Adults with High-Risk Acute Myeloid Leukemia

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Abstract

On August 3, 2017, the FDA granted regular approval to Vyxeos (also known as CPX-351; Jazz Pharmaceuticals), a liposomal formulation of daunorubicin and cytarabine in a fixed combination, for the treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC). Approval was based on data from Study CLTR0310-301, a randomized, multicenter, open-label, active-controlled trial comparing Vyxeos with a standard combination of daunorubicin and cytarabine ("7+3") in 309 patients 60–75 years of age with newly diagnosed t-AML or AML-MRC. Because of elemental copper concerns with the Vyxeos formulation, patients with Wilson disease were excluded from the study. Vyxeos demonstrated an improvement in overall survival (HR 0.69; 95% confidence interval, 0.52–0.90; $P = 0.005$) with an estimated median overall survival of 9.6 months compared with 5.9 months for the "7+3" control arm. The toxicity profile of Vyxeos was similar to that seen with standard "7+3" with the exception of more prolonged neutropenia and thrombocytopenia on the Vyxeos arm. Because the pharmacology of Vyxeos differs from that of other formulations of daunorubicin and cytarabine, labeling includes a warning against interchanging formulations during treatment. This is the first FDA-approved treatment specifically for patients with t-AML or AML-MRC.

Introduction

Approximately 10% of patients with acute myeloid leukemia (AML) have disease that occurs after chemotherapy or radiation for an unrelated disease, known as therapy-related acute myeloid leukemia (t-AML). Another 20% have AML with an antecedent hematologic disorder, most commonly myelodysplastic syndrome (MDS), or with cytogenetic changes characteristic of MDS. According to World Health Organization (WHO) 2016 criteria, the latter two categories are combined into the "AML-MRC" designation. This includes cases of AML that evolve from MDS or a myeloproliferative neoplasm (MDS/MPN), AML that has established MDS-related cytogenetic abnormalities, with the exception of del(9q), or AML with associated dysplasia in $\geq$50% of cells in $\geq$2 myeloid lineages (in the absence of favorable *NPM1* or biallelic *CEBPA* mutations; ref. 1).

The limited literature around t-AML or AML-MRC uses the older nomenclature of secondary AML, referring only to patients with t-AML or antecedent hematologic disorders. In 2001, the WHO classification of myeloid neoplasms introduced the category of "AML with multilineage dysplasia (MLD)," comprising patients with a prior history of MDS or MDS/MPNs and *de novo* AML presenting with MLD (2). In 2008 and 2016, this was renamed AML-MRC, and refined to include also AML with MDS-related cytogenetic abnormalities, as well as specify that isolated MLD would only be included in the absence of *NPM1* or biallelic *CEBPA* mutations. Isolated MLD accounts for a small minority of these cases, and overall the category represents a population with a poor prognosis even in the setting of *de novo* AML (3–6). While the categories are somewhat heterogeneous, older patients with t-AML and AML-MRC have an expected median overall survival (OS) as low as 6–7 months (7) and have historically been excluded from the many trials using new therapeutic agents.

Combination chemotherapy regimens with or without hematopoietic stem cell transplantation (HSCT) are the mainstay of therapy for patients with most AML subtypes. Patients who can tolerate intensive therapy typically receive induction chemotherapy, commonly the "7+3" regimen which results in complete response (CR) rates of 60%–70% and 2-year OS of approximately 50% in patients <60 years of age (8). Older patients (age $\geq$ 60)

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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have lower expected CR rates of approximately 50% and 2-year OS of approximately 20% (9); patients with t-AML and AML with antecedent hematologic disorders have expected CR rates in the 24%–51% range (7, 10).

No new therapies with confirmed clinical benefit were approved by the FDA through 2016 for the treatment of AML since the "7+3" regimen was shown to be effective in the early 1970 (11). In 2017, the FDA approved three therapies for specific AML subtypes in certain populations, midostaurin, gemtuzumab ozogamicin, and enasidenib; none have been studied in patients with newly diagnosed t-AML and AML-MRC. There remains a clear need for new treatments for patients with AML in these poor-risk subgroups. Herein, we summarize the review for the FDA approval of Vyxeos (Jazz Pharmaceuticals).

Vyxeos Drug Product

Vyxeos is a liposomal formulation of a fixed molar ratio (1:5) combination of the antineoplastic drugs daunorubicin and cytarabine. The liposome membrane is composed of distearoyl phosphatidylcholine, distearoyl phosphatidylglycerol, and cholesterol in a 7:2:1 molar ratio. After cellular internalization, the liposomes undergo degradation, releasing cytarabine and daunorubicin intracellularly to induce DNA damage resulting in cell death. When reconstituted for infusion, Vyxeos contains 5 mg/mL copper gluconate, of which 14% is elemental copper.

Preclinical Rationale

In vitro studies demonstrated that the 1:5 fixed molar ratio combination of daunorubicin and cytarabine resulted in synergistic *in vitro* cytotoxicity in the majority (8/15, 53%) of cancer cell lines evaluated. Studies in mice and rats confirmed that CPX-351 was distributed to the bone marrow. After entering bone marrow cells, the intracellular concentrations of daunorubicin and cytarabine were transiently maintained near the optimal 1:5 ratio. Retention in the bone marrow increased exposure (as measured by the area under the concentration–time curve) to both daunorubicin and cytarabine, and correlated with improved *in vivo* antitumor activity in mouse models.

Clinical Pharmacology

The total plasma concentrations (i.e., encapsulated plus unencapsulated drug) of daunorubicin and cytarabine administered as Vyxeos were investigated in adult patients. The clearance (CL), volume of distribution (V_d), and terminal half-life ($t_{1/2}$) for daunorubicin and cytarabine were nearly similar, because >99% of the daunorubicin and cytarabine in the circulation remains within the liposomes. Vyxeos exhibited a prolonged $t_{1/2}$ [coefficient of variation (CV%) of 31.5 hour (28.5%) for daunorubicin and 40.4 hour (24.2%) for cytarabine], markedly different from that of nonliposomal formulations (12, 13). Time-dependent kinetics or major departures from dose proportionality over the range of 1.3 mg/3 mg/m^2 (daunorubicin/cytarabine) to 59 mg/134 mg/m^2 were not observed.

Cytarabine is excreted primarily in the urine. Around 40% increase in exposures of daunorubicin and cytarabine and greater grade 3–5, serious and fatal treatment-emergent adverse events were observed in patients with moderate renal impairment compared with those with normal renal function; however, no dose adjustment is recommended, because the observed exposure difference was not clinically meaningful based on exposure–response relationship for safety. A dedicated clinical trial (NCT03555955) is ongoing to evaluate the effect of severe renal impairment and to reassess the effect of moderate renal impairment on the safety and pharmacokinetics of daunorubicin and cytarabine when administered as Vyxeos.

Daunorubicin is primarily eliminated by the hepatobiliary system. Varying bilirubins at any level $\leq$3 mg/dL had no clinically meaningful effect on the exposure of daunorubicin or cytarabine or the safety profile when administered as Vyxeos; therefore, no dose adjustment is recommended. No additional studies were recommended to further understand the effect of hepatic impairment on the safety or pharmacokinetics, as intensive chemotherapy with standard dose daunorubicin and/or cytarabine is not commonly administered to patients with severe hepatic impairment.

The population pharmacokinetics analysis suggested that body surface area (BSA) was a significant allometric factor on CL and V_d of daunorubicin and cytarabine, which supported the BSA-based dosing regimen. Other patient demographics (e.g., age, sex, body weight, body mass index, and white blood cell count) were not found to have a clinically meaningful influence on the pharmacokinetics of daunorubicin or cytarabine after adjusting dose by BSA.

Clinical Trial Design

As stated in the prescribing information for Vyxeos (14), the pivotal Study CLTR0310-301 (Study 301, NCT01696084) was a randomized, multicenter, open-label, active-control trial comparing Vyxeos with standard "7+3" in patients 60–75 years old with newly diagnosed t-AML, AML with antecedent MDS or CMML, or *de novo* AML with karyotypic changes characteristic of MDS per WHO 2008 criteria. Patients were randomized 1:1 and stratified by age and AML subtype.

Vyxeos was given intravenously at a dose of (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome on days 1, 3, and 5 for the first induction and on days 1 and 3 for the second induction if needed. For consolidation, the dose was (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome on days 1 and 3. In the "7+3" arm, first induction consisted of cytarabine 100 mg/m^2/day on days 1–7 by continuous infusion and daunorubicin 60 mg/m^2/day on days 1–3; for second induction and consolidation cycles, cytarabine 100 mg/m^2/day was given on days 1–5 and daunorubicin 60 mg/m^2/day on days 1–2. A second induction was highly recommended for patients not achieving a response and was mandatory for patients achieving >50% reduction in percent blasts. Postremission therapy with HSCT was permitted in place of or after consolidation chemotherapy. Patients on both arms with $\geq$500 mg/m^2 prior cumulative anthracycline exposure could receive an alternate regimen of intermediate dose cytarabine (1.5 g/m^2 twice a day on days 1, 3, and 5), as could those with a >10% decrease in left ventricular ejection fraction to <50% during the study. Treatment consisted of up to two cycles of induction and two cycles of consolidation in each arm.

The primary endpoint of the trial was OS, measured from the date of randomization to death from any cause. Patients were to be followed for up to 5 years. With an accrual target of 300 subjects and an assumed median OS of 6.3 months with "7+3", the study with 236 deaths had 93.7% power and a one-sided

significance level alpha of 0.025 to detect a HR of 0.635 in OS. Randomization and the OS analysis were stratified by patient age (60–69 vs. 70–75) and AML subtype (t-AML vs. AML with antecedent MDS with prior treatment with hypomethylating agents vs. AML with antecedent MDS without prior treatment with hypomethylating agents vs. *de novo* AML with MDS karyotype vs. AML with antecedent CMML). CR was the first alpha-controlled key secondary endpoint of the trial.

Results

Efficacy

Study 301 enrolled 309 patients, with 153 randomized to Vyxeos and 156 randomized to the control arm. The demographic and baseline disease characteristics were generally balanced between the arms (Table 1). All patients on the Vyxeos arm and 97% of those on the control arm received at least one cycle of induction, and 32% on the Vyxeos arm and 21% on the control arm received at least one cycle of consolidation. The rate of HSCT in first CR was 20% in the Vyxeos arm and 12% in the control arm.

The OS efficacy analysis results are shown in Fig. 1. The observed median OS in the Vyxeos arm was 9.6 months [95% confidence interval (CI), 6.6–11.9] compared with 5.9 months (95% CI, 5–7.8) in the control arm, with a HR of 0.69 (95% CI, 0.52–0.90) and a two-sided stratified long-rank $P = 0.005$, demonstrating a survival benefit with Vyxeos treatment. In a sensitivity analysis, a trend for improved OS was maintained when OS was censored at HSCT, although the difference did not reach nominal significance. CR was achieved by 38% of patients on the Vyxeos arm and 26% of those on the control arm, providing supportive evidence for the treatment effect of Vyxeos. The treatment effect on OS was consistent across the subgroups that were stratification factors, including for t-AML (HR 0.48; 95% CI, 0.26–0.86), and for AML-MRC (HR 0.70; 95% CI, 0.52–0.93).

Table 1. Demographic characteristics of the intention-to-treat population in Study CLTR0310-301

	Vyxeos (*N* = 153)	**7+3 (*N* = 156)**
Sex		
Male	94 (61.4)	96 (61.5)
Female	59 (38.6)	60 (38.5)
Age		
Mean years (SD)	67.8 (4.2)	67.7 (4.1)
Median (years)	68.0	68.0
Min, max (years)	60, 75	60, 75
Age group		
<65 years	39 (25.5)	41 (26.3)
≥65 years	114 (74.5)	115 (73.7)
60–64 years	39 (26)	41 (26)
65–69 years	57 (37)	61 (39)
70–75 years	57 (37)	54 (35)
ECOG PS		
0	37 (24)	45 (29)
1	101 (66)	89 (57)
2	15 (10)	22 (14)
Race		
White	128 (83.7)	139 (89.1)
Black or African American	7 (4.6)	6 (3.9)
Asian	6 (3.9)	2 (1.3)
American Indian or Alaska Native	1 (0.7)	0
Multiple	0	1 (0.6)
Other	11 (7.2)	8 (5.1)
Ethnicity		
Hispanic or Latino	7 (4.6)	7 (4.5)
Not Hispanic or Latino	146 (95.4)	149 (95.5)
Region		
United States	144 (94.1)	147 (94.2)
Canada	9 (5.9)	9 (5.8)
AML type		
AML-MRC	123 (80.4)	123 (78.8)
t-AML	30 (19.6)	33 (21.2)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety

The primary data supporting safety for the proposed indication came from Study 301. On the Vyxeos arm, 42% of patients received one cycle of therapy, 39% received two cycles, 17% received three cycles, and only 3 patients (2%) received the maximum four cycles of therapy. Adverse reactions (AR) with Vyxeos were mostly similar to those seen with standard "7+3"; a summary of ARs by arm during the induction phase is presented in Table 2.

In comparison with "7+3", patients on the Vyxeos arm had fewer deaths due to adverse events (14% vs. 15%), lower day-30 (6% vs. 11%) and day-60 (14% vs. 21%) all-cause mortality, and fewer deaths within 30 days of the last dose of treatment (10% vs. 17%). The most common fatal ARs within 30 days of the last dose of Vyxeos were central nervous system hemorrhage, infection, and respiratory failure. The most common AR leading to Vyxeos discontinuation was cytopenia, either isolated thrombocytopenia or both neutropenia and thrombocytopenia. Arrhythmias and nonconduction cardiotoxicities, known ARs associated with anthracycline therapy, occurred at similar rates on each arm (30% and 27%, and 20% and 18%, respectively).

Hemorrhagic events occurred in the Vyxeos arm at a higher rate than on the control arm (74% and 56%), including grade ≥3 events (12% and 8%) and fatal central nervous system hemorrhages not in the setting of progressive disease (2% and 0.7%). These were associated with prolonged severe thrombocytopenia, which, in addition to prolonged severe neutropenia, were also seen at higher rates in the Vyxeos arm (Supplementary Table S2).

Copper levels were assessed at baseline, on induction days 5 and 14, after the last induction dose and at day 150; if elevated, they were monitored monthly until 1 year from randomization or documentation of return to normal. Median copper levels on the Vyxeos arm were >5 times baseline on day 5. In 87% of patients, these returned to baseline by day 14; in all patients tested on day 150, levels returned to baseline.

Supporting safety data from Study CLTR0308-204 (NCT00788892) comparing Vyxeos with "7+3" in patients 60–76 years of age with newly diagnosed AML, and from Study CLTR0308-205 (NCT00822094) comparing Vyxeos with investigator's choice in patients 18–60 years of age with AML in first relapse, were similar to those in Study 301. In comparison with younger patients, ARs more common by ≥10% in patients ≥65 years of age included hemorrhage (77% vs. 59%), febrile neutropenia (69% vs. 59%), edema (61% vs. 46%), diarrhea (55% vs. 44%), dyspnea (41% vs. 32%), cough (41% vs. 27%), hypoxia (23% vs. 11%), and pulmonary edema (11% vs. 1%).

Regulatory Insights

Study 301 provides the first evidence for benefit of a treatment for t-AML and AML-MRC, showing improved OS with Vyxeos in comparison with "7+3". OS is the endpoint

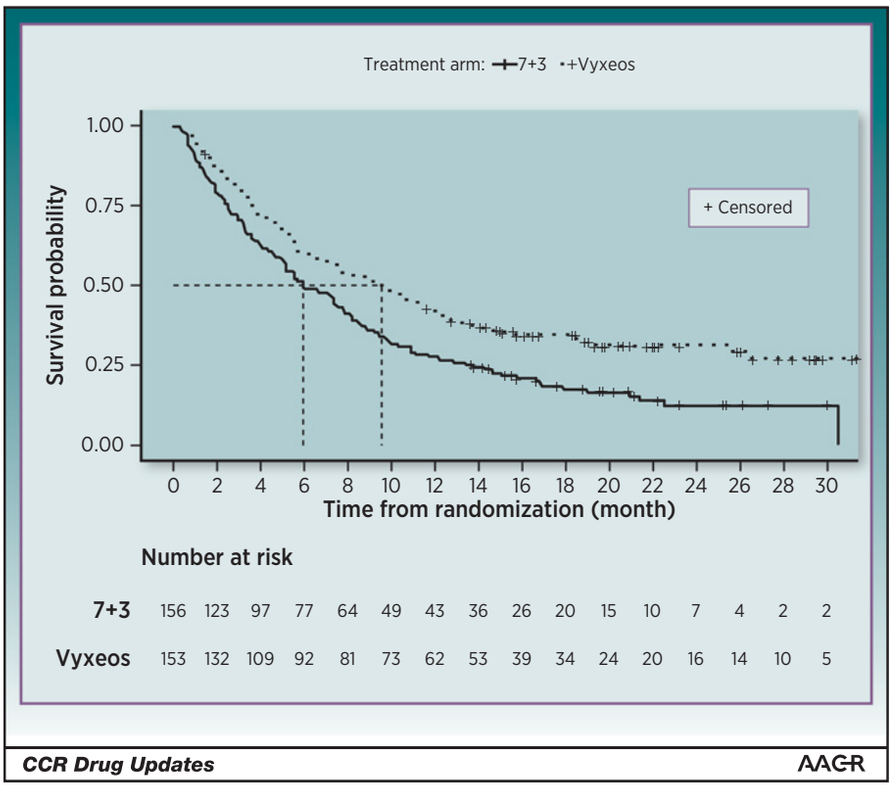

Figure 1.
OS in the intention-to-treat population in Study CLTR0310-301. The HR (95% CI) was 0.69 (0.52–0.90) based on a Cox proportional hazards model comparing the hazard functions associated with treatment groups. The two-sided $P = 0.005$ based on a stratified log-rank test.

generally accepted by the FDA as evidence of clinical benefit for traditional approval of agents for the treatment of AML. The FDA has accepted event-free survival, a reflection of durable CR, as clinical benefit for patients with newly diagnosed AML (15) when the OS endpoint is confounded by other factors. However, OS remains a rational endpoint for studies where treatments have low CR rates, short survivals, few effective salvage therapies for patients who relapse, and/or a substantial risk that would be offset only by a survival benefit. Because these are all relevant to patients with t-AML and AML-MRC, OS was considered the appropriate endpoint for Study 301. The higher rate of HSCT (34%) in the Vyxeos arm compared with the control arm (25%) introduces potential bias into the primary analysis of OS, because HSCT is a potentially curative therapy for patients with AML. The sensitivity analysis censoring patients at HSCT, and the increased CR rates in the Vyxeos arm, provide supportive evidence for the treatment effect of Vyxeos on OS on Study 301.

Although the inclusion criteria for Study 301 included only patients with t-AML or with a history of MDS, CMML or cytogenetic changes associated with MDS per WHO 2008 criteria, the clinical and biologic similarity of the three subgroups in the AML-MRC category allowed for the indication to include the entire AML-MRC population.

Although Study 301 was limited to patients $\geq$60 years old, the biology of t-AML and AML-MRC are fairly consistent across the adult population, so efficacy was extrapolated to younger adult patients with these disorders. Because safety analyses of the recommended dose showed no major issues in adults <60 years old, it is reasonable to conclude that the benefit-risk assessment favors approval of Vyxeos for treatment of adults with t-AML or AML-MRC.

The safety profile of Vyxeos is similar to that of "7+3"; the major exceptions are the acute copper load and prolonged cytopenias. The maximum theoretical copper exposure would be 106 mg/m^2 using the recommended dosing regimen for Vyxeos; for patients with Wilson disease, copper loads of these magnitudes could theoretically cause fulminant hepatotoxicity. A warning regarding these risks for patients with Wilson disease was therefore included in the prescribing information. Cytopenias are expected with myelosuppressive chemotherapy, but the incidence of prolonged severe thrombocytopenia with Vyxeos exceeded that for "7+3" and was associated with increased bleeding events. Hence, there is a warning regarding the increased risk of serious or fatal bleeding in patients treated with Vyxeos.

The cardiotoxicity associated with anthracyclines in general, seen on both arms on Study 301, warranted close monitoring of cumulative anthracycline doses before and during Vyxeos treatment and is described in a warning. Because the active pharmaceutical ingredients of Vyxeos are available commercially in nonliposomal and liposomal formulations, and the potential for interchangeability between different formulations could have life-threatening consequences, a boxed warning regarding these differences was included in the prescribing information.

The FDA identified several safety issues for which data were incomplete at the time of approval. These included the incidence and nature of ARs related to infusion of Vyxeos, and whether dose adjustments are needed in patients with

Table 2. Common ARs during the induction phase in Study CLTR0310-301

	All grades[b]		Grade ≥3	
AR[a]	Vyxeos N = 153	7+3 N = 151	Vyxeos N = 153	7+3 N = 151
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 (1)	5 (3)
Nausea	72 (47)	79 (52)	1 (0.7)	1 (0.7)
Diarrhea/colitis	69 (45)	100 (66)	4 (3)	10 (7)
Mucositis	67 (44)	69 (46)	2 (1)	7 (5)
Constipation	61 (40)	57 (38)	—	
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)	—	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 (24)	35 (23)	31 (21)
Vomiting	37 (24)	33 (22)	—	
Chills	35 (23)	38 (25)	—	
Hypotension	30 (20)	32 (21)	7 (5)	1 (1)
Nonconduction cardiotoxicity	31 (20)	27 (18)	13 (9)	15 (10)
Dizziness	27 (18)	26 (17)	1 (0.7)	—
Fungal infection	27 (18)	19 (13)	11 (7)	9 (6)
Hypertension	28 (18)	22 (15)	15 (10)	8 (5)
Hypoxia	28(18)	31 (21)	19 (12)	23 (15)
URTI (excluding fungal)	28 (18)	19 (13)	4 (3)	1 (1)
Chest pain	26 (17)	22 (15)	5 (3)	—
Pyrexia	26 (17)	23 (15)	1 (0.7)	2 (1)
Catheter-device-injection site reaction	24 (16)	15 (10)	—	—
Delirium	24 (16)	33 (22)	4 (3)	9 (6)
Pleural effusion	24 (16)	25 (17)	3 (2)	2 (1)
Anxiety	21 (14)	16 (11)	—	
Pruritis	23 (15)	14 (9)	—	
Sepsis (excluding fungal)	17 (11)	20 (13)	n/a[c]	
Haemorrhoids	16 (11)	12 (8)	—	
Petechiae	17 (11)	17 (11)	—	
Renal insufficiency	17 (11)	17 (11)	7 (5)	7 (5)
Transfusion reaction	16 (11)	16 (11)	3 (2)	1 (0.7)
Visual impairment (except bleeding)	16 (11)	8 (5)	—	—

Abbreviation: URTI, upper respiratory tract infection.
[a]Includes grouped terms (see Supplementary Table S1).
[b]Limited to ARs in ≥10% in the Vyxeos arm.
[c]All sepsis is grade 4 per Common Terminology Criteria for Adverse Events.

moderate or severe renal impairment. Given the survival benefit of Vyxeos and a safety profile comparable with "7+3" demonstrated using the eligibility criteria, monitoring and dose modifications within the parameters of Study 301, it was concluded that these issues could be addressed in postmarketing studies, allowing for approval and use in patients with instructions for safe use as described in labeling.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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