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AML

VOD

Abstract 2845

Treatment with CPX-351 Induces Deep Responses and TP53 Mutation Clearance in Patients with t-AML and AML MRC, Including Younger Patients and Those with Pre-Existing MPNs: A Real-World Experience

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Background: Patients with secondary acute myeloid leukemia (sAML) have poor outcomes compared to those with de novo AML. In 2017, liposomal daunorubicin and cytarabine (CPX-351) was FDA approved for the treatment of adults with newly diagnosed AML with myelodysplasia-related change (AML-MRC) or therapy-related AML (t-AML). In its landmark trial, CPX-351 has displayed significant improvement in overall survival (OS) compared to conventional 7+3 in patients 60–75 years of age with sAML. Gaps remain in the literature regarding the clinical use of CPX-351 in context of the FDA approved label. Here we evaluate real-world outcomes with disease response and molecular monitoring in patients treated with CPX-351.

Methods: Adults who received CPX-351 between September 2017 and December 2019 were identified. The primary endpoint was overall response rate (ORR), defined by complete remission (CR) and CR with incomplete hematologic recovery (CRi) according to the Revised IWG criteria. Additional outcomes of interest included molecular minimal residual disease (MRD) status post induction as measured by next-generation sequencing (NGS), ORR in patients with baseline TP53, and progression-free survival (PFS) in patients with CR/CRi, with and without MRD after induction. Mutations associated with clonal hematopoiesis (TET2, ASXL1, DNMT3A) were excluded from analysis of molecular MRD.

Results: Fifty-four patients were identified with baseline characteristics as shown in **Table 1**. Overall, the study population was elderly with the median age of 64 [IQR: 60–68], and 13 patients were younger than 60 years old. Six patients developed AML in the setting of a pre-existing myeloproliferative neoplasm (MPN). The most common indication for treatment with CPX-351 was antecedent MDS (42.6%), followed by de novo AML with MDS karyotype (24.1%), therapy-related AML (13%), and antecedent MPN (11.1%). NGS was performed prior to treatment with CPX-351 in all but one patient, and 88.7% had at least one molecular marker that is not identified as one of the mutations associated with clonal hematopoiesis. Most commonly identified molecular markers were TP53 (16/53, 30.2%), RUNX1 (10/53, 18.9%), SRSF2 (8/53, 15.1%), NRAS (7/53, 13.2%), and IDH2 and JAK2 (6/53, 11.3%, each).

Most patients were hospitalized until hematologic recovery. However, 5 patients received induction in the outpatient setting, and an additional 6 patients were discharged early before hematologic recovery. Among the patients who were discharged early or underwent outpatient induction, 81.8% (9/11) were admitted for a complication. There were no deaths associated with outpatient induction. Overall, 46 patients (85.2%) experienced febrile neutropenia and 17 patients (31.5%) had bacteremia. Thirty-day and 60-day mortality were 9.3% and 14.8%, respectively.

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The ORR was 54%, and the response rates observed in patients who were younger vs older than 60 years were similar (41.7% vs. 57.9%, p=0.508). In patients who achieved a remission after induction, 56% (14/25) were MRD positive by NGS. Among those who had TP53 mutation at baseline, 14 were available for response assessment after induction. The ORR in this subgroup was 57% (8/14) and all but 3 (63%) were MRD negative by NGS. Consolidation with allogeneic transplant was performed in 18 patients (33%).

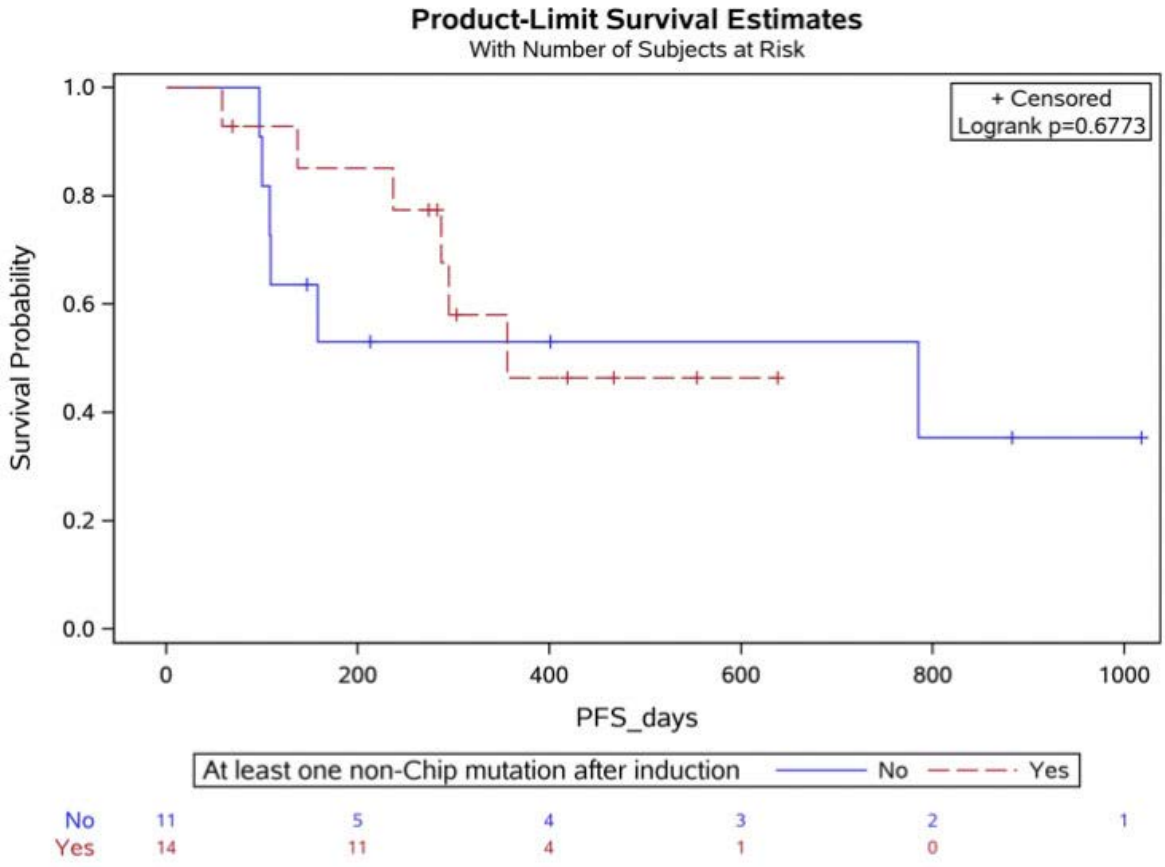
Median OS was 10.4 mos. Median OS was similar for patients older or younger than 60 years (p=0.76). For patients achieving a CR/CRi, median OS had not been reached at the time of analysis but was significantly improved compared to those with refractory disease (6.1 mos, p=0.0007). Median OS or PFS did not differ significantly (p=0.68) based on MRD negativity (**Figure 1**).

Conclusion: This analysis demonstrates comparable response rates to the landmark trial (54% in our analysis vs. 47.7%). Outpatient induction and/or early discharge was safe and feasible in appropriately selected patients. While this analysis is limited by the small sample size, CPX-351 appeared effective in populations that were not included in the published randomized studies, such as patients below the age of 60 years old and those with antecedent MPN. Remission rates and MRD clearance was high among TP53 mutants. A considerable number of patients who achieved a remission remained MRD positive by NGS, but this did not impact PFS. Future studies should evaluate the impact of molecular MRD and allele frequency to further guide treatment.

Table 1. Baseline characteristics

Variable	**N=54, n (%)**
Median Age, y, (IQR)	64 (60,68)
Male	35 (64.8)
Race/Ethnicity	
• White	40 (74.1)
• Black	5 (9.3)
• Asian	1 (1.9)
• Other	8 (14.8)
Indication for CPX-351	
• Antecedent MDS	23 (42.6)
• De Novo AML with MDS karyotype	13 (24.1)
• Therapy-related AML	7 (13)
• Antecedent MPN	6 (11.1)
• Antecedent CMML	3 (5.6)
• Other	2 (3.7)
Prior Allogeneic Hematopoietic Stem Cell Transplant	5 (9.3)
Mutations Prior to Treatment with CPX-351	
• TP53	16/53 (30.2)
• RUNX1	10/53 (18.9)
• SRSF2	8/53 (15.1)
• NRAS	7/53 (13.2)
• IDH2	6/53 (11.3)
• JAK2	6/53 (11.3)

Figure 1. PFS for patients in remission, with and without a detectable mutation after induction



Disclosures: Koprivnikar: *Alexion:* Speakers Bureau; *BMS:* Speakers Bureau; *Novartis:* Speakers Bureau; *Amgen:* Speakers Bureau. **McCloskey:** *Takeda:* Consultancy, Honoraria, Speakers Bureau; *Novartis:* Speakers Bureau; *Abbvie:* Speakers Bureau; *Amgen:* Consultancy, Speakers Bureau; *BMS:* Consultancy, Honoraria, Speakers Bureau; *Jazz:* Consultancy, Honoraria, Speakers Bureau.

Abstract 635

Five-Year Final Results of a Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed High-Risk/Secondary Acute Myeloid Leukemia (AML): Outcomes By Age Subgroup and Among Responders

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Introduction: CPX-351 (Vyxeos®; daunorubicin and cytarabine liposome for injection) is a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar drug ratio. In a pivotal, randomized phase 3 study (NCT01696084) in patients aged 60 to 75 y with newly diagnosed high-risk/secondary AML, after a median follow-up of 20.7 mo, induction followed by consolidation with CPX-351 significantly improved median overall survival (OS) versus conventional 7+3, with a comparable safety profile. This primary endpoint analysis of the study helped to support the approval of CPX-351 by the US FDA and EMA for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes. Here, we report the prospectively planned, final 5-y follow-up results from this phase 3 study, including outcomes by age subgroup.

Methods: Patients were randomized 1:1 to receive 1 to 2 induction cycles of CPX-351 (100 units/m^2 [cytarabine 100 mg/m^2 + daunorubicin 44 mg/m^2] as a 90-min infusion on Days 1, 3, and 5 [2nd induction: Days 1 and 3]) or 7+3 (cytarabine 100 mg/m^2/d continuously for 7 d + daunorubicin 60 mg/m^2 on Days 1 to 3 [2nd induction: 5+2]). Patients achieving complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 consolidation cycles. Patients could receive hematopoietic cell transplantation (HCT) at the physician's discretion. Patients were followed until death or up to 5 y after randomization. Subgroup analyses were conducted in patients who achieved CR or CRi and in those aged 60 to 69 y and 70 to 75 y.

Results: In total, 309 patients were randomized to CPX-351 (n=153) or 7+3 (n=156). The Kaplan-Meier–estimated survival rates were higher for CPX-351 versus 7+3 at 3 y (21% vs 9%) and 5 y (18% vs 8%). Among patients who died, the most common primary cause of death was progressive leukemia in both arms (CPX-351: 56%; 7+3: 53%). After a reverse Kaplan-Meier–estimated median follow-up of 60.65 mo (10th to 90th percentile: 58.22, 63.90), improved median OS with CPX-351 versus 7+3 was maintained (9.33 vs 5.95 mo; HR=0.70 [95% CI: 0.55, 0.91]; **Figure 1**), with an HR that was very stable and consistent with the prior primary endpoint analysis (9.56 vs 5.95 mo; HR=0.69 [95% CI: 0.52, 0.90]). Median OS for the CPX-351 arm differed from that reported for the primary endpoint analysis due to a patient death reported after the cutoff date for that analysis.

When analyzed by age subgroup, improved median OS with CPX-351 versus 7+3 was also maintained in patients aged 60 to 69 y (9.59 vs 6.87 mo; HR=0.73 [95% CI: 0.54, 0.99]; **Figure 2A**) and in those aged 70 to 75 y (8.87 vs 5.62 mo; HR=0.52 [95% CI: 0.34, 0.77]; **Figure 2B**).

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HCT was received by 53 (35%) and 39 (25%) patients in the CPX-351 and 7+3 arms, respectively. Among patients who underwent HCT, the Kaplan-Meier–estimated survival rate landmarked from the date of HCT was higher for CPX-351 versus 7+3 at 3 y (56% vs 23%), and median OS landmarked from the date of HCT was not reached for CPX-351 versus 10.25 mo for 7+3 (HR=0.51 [95% CI: 0.28, 0.90]; **Figure 3**).

CR or CRi was achieved by 73 (48%) and 52 (33%) patients in the CPX-351 and 7+3 arms, respectively. Among patients who achieved CR or CRi, the Kaplan-Meier–estimated survival rate was higher for CPX-351 versus 7+3 at 3 y (36% vs 23%) and at 5 y (30% vs 19%), and median OS was longer with CPX-351 versus 7+3 (21.72 vs 10.41 mo; HR=0.59 [95% CI: 0.39, 0.88]). Additionally, 41/73 (56%) patients in the CPX-351 arm and 24/52 (46%) in the 7+3 arm who achieved CR or CRi proceeded to HCT; in these patients, median OS landmarked from the date of HCT was not reached for CPX-351 versus 11.65 mo for 7+3 (HR=0.50 [95% CI: 0.26, 0.97]).

Conclusions: After 5 y of follow-up, improved OS with CPX-351 versus conventional 7+3 chemotherapy was maintained in this phase 3 study in the overall study population regardless of patient age, in those who underwent HCT, and among patients who achieved CR or CRi. The longer OS with CPX-351 versus 7+3 in patients who underwent HCT and in those who achieved CR or CRi suggests potentially deeper responses may be achieved with CPX-351. These data support prior evidence that CPX-351 has the ability to produce or contribute to long-term remission and survival in older patients with newly diagnosed high-risk/secondary AML.

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Figure 1. OS in the Overall Study Population

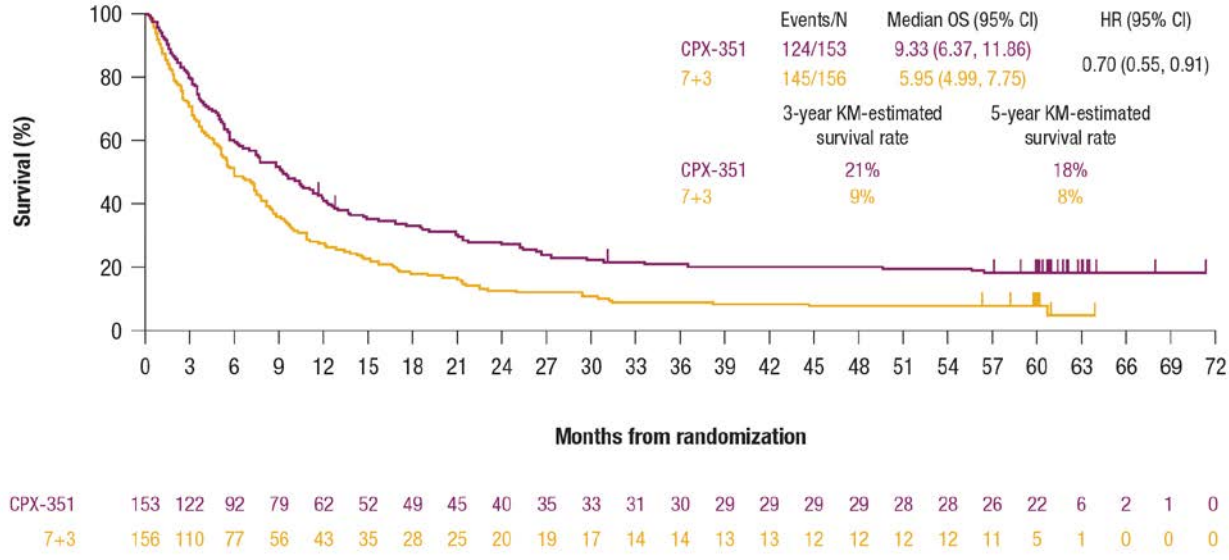


Figure 2. Os by Age Subgroup

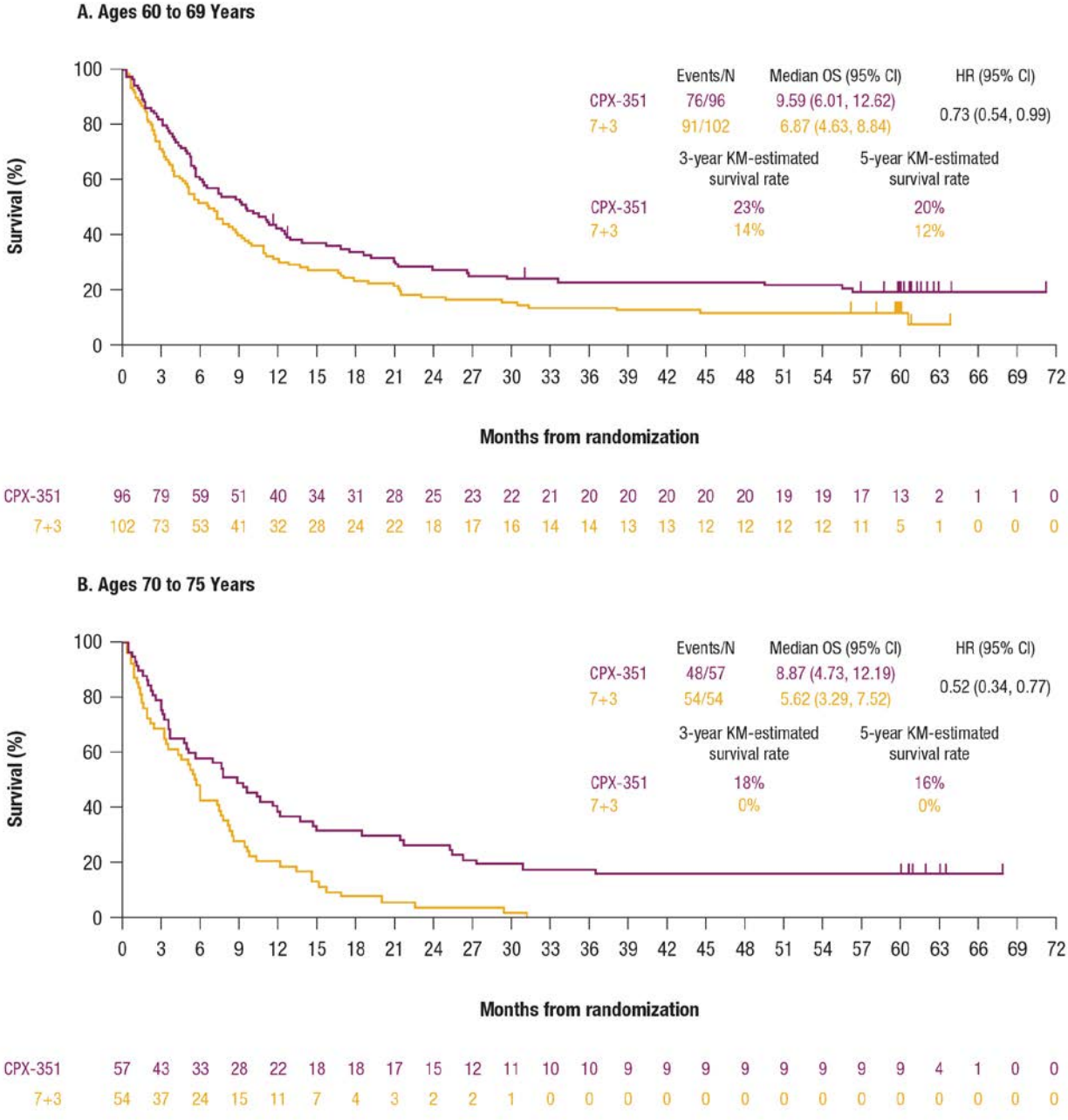
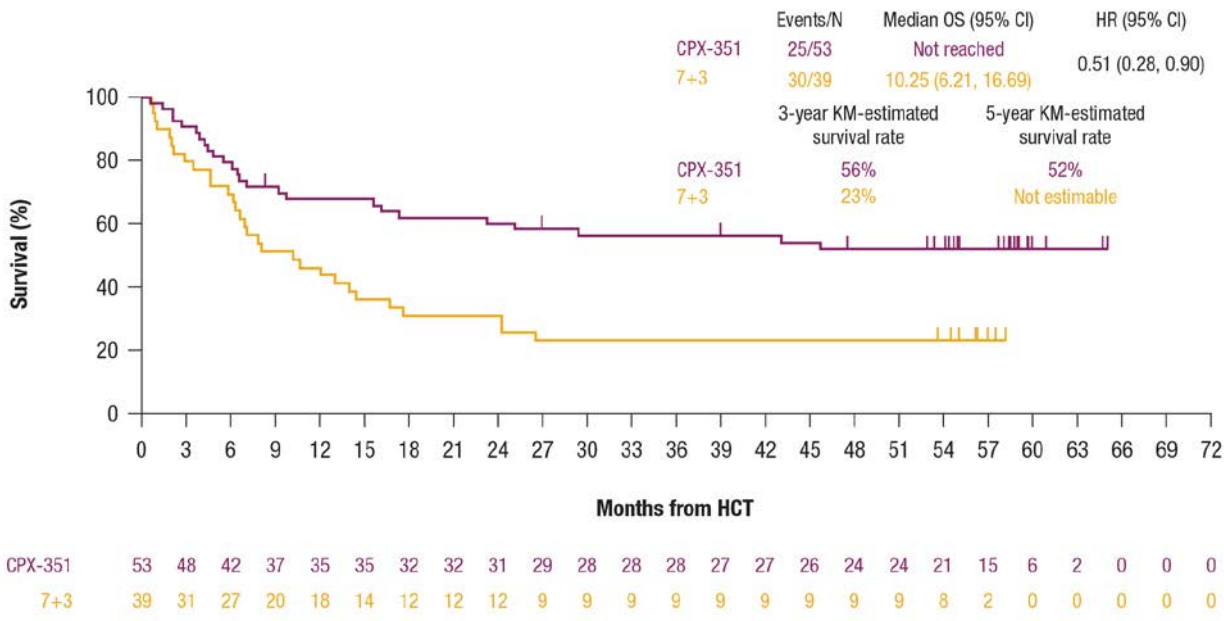


Figure 3. OS Landmarked from the Date of HCT



OS, overall survival; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; HCT, hematopoietic cell transplantation.

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Abstract 3346

Long-Term Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients Enrolled in CPX-351-301, a Randomized Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed, High-Risk and/or Secondary AML

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Background: CPX-351 is a liposomal encapsulation of daunorubicin and cytarabine in a 1:5 molar ratio. In a randomized phase 3 study (CPX-351-301) conducted in older adults (60 to 75 years old) with newly diagnosed, high-risk and/or secondary AML, CPX-351 induction therapy was superior to standard 7+3 with improved rates of complete remission (CR) and overall survival (OS). In both older adults and high-risk AML, allogeneic hematopoietic cell transplantation (HCT) is frequently the preferred post-remission strategy owing to the high rates of relapse and poor overall survival with conventional chemotherapy approaches. After a median follow-up of 20.7 months, the primary pre-planned analysis found that more patients randomized to CPX-351 underwent HCT and an exploratory landmark survival analysis from the time of HCT favored CPX-351 (HR=0.46 [95% CI: 0.24, 0.89]; one-sided *P*=0.009). However, the initial protocol did not collect data related to HCT and the basis for improved HCT outcomes with CPX-351 was previously unknown. Here we present a detailed analysis of HCT outcomes in patients enrolled in the CPX-351-301 study with 5-years of follow-up.

Methods: Patients age 60 to 75 years with high-risk and/or secondary AML were randomized in a 1:1 fashion to receive CPX-351 or 7+3 as induction and consolidation chemotherapy (Lancet J et al, JCO 2018). The protocol was amended to collect additional HCT-specific information, including donor and HCT characteristics and post-HCT outcomes, including rates of relapse and GVHD. Post-HCT outcomes including relapse, GVHD, and death were analyzed as competing events.

Results: Of 309 randomized patients in the CPX-351-301 study, more patients achieved CR/CRi with CPX-351 vs 7+3 (48% vs 33%) allowing more patients to proceed to HCT (35% vs 25%) and more patients to proceed to HCT in remission (CPX-351: 41/73 [56%]; 7+3: 24/52 [46%]). The median age was 66 years with CPX-351 vs 65 years with standard induction among the transplanted cohorts; 16 patients in the CPX-351 transplanted arm were over the age of 70 compared to only 6 in the 7+3 arm. Other pre-HCT patient characteristics were balanced between the CPX-351 and 7+3 groups, including ECOG performance status (8% vs 5% with ECOG PS of 2), HCT-CI (median 4 vs 3), donor type (matched unrelated donor 49% vs 49%), and conditioning regimen intensity (myeloablative [17% vs 13%] vs reduced-intensity conditioning [43% vs 46%]). The Kaplan-Meier–estimated 3-year survival rate among transplanted patients was 56% with CPX-351 vs 23% with 7+3 (**Figure 1A**). The differences in survival consistently favored CPX-351 across patient age, AML subtype, disease status, donor type, and conditioning intensity (**Figure 1B**). Differences in OS were driven by a large reduction in non-relapse mortality (HR=0.42 [95% CI: 0.21, 0.86]; **Figure 1D**). The cumulative incidence of acute GVHD with death as a competing event at 6 months from HCT date was 0.49 (95% CI: 0.35, 0.62) in the CPX-351 arm and 0.38 (95% CI: 0.23, 0.53) in the 7+3 arm.

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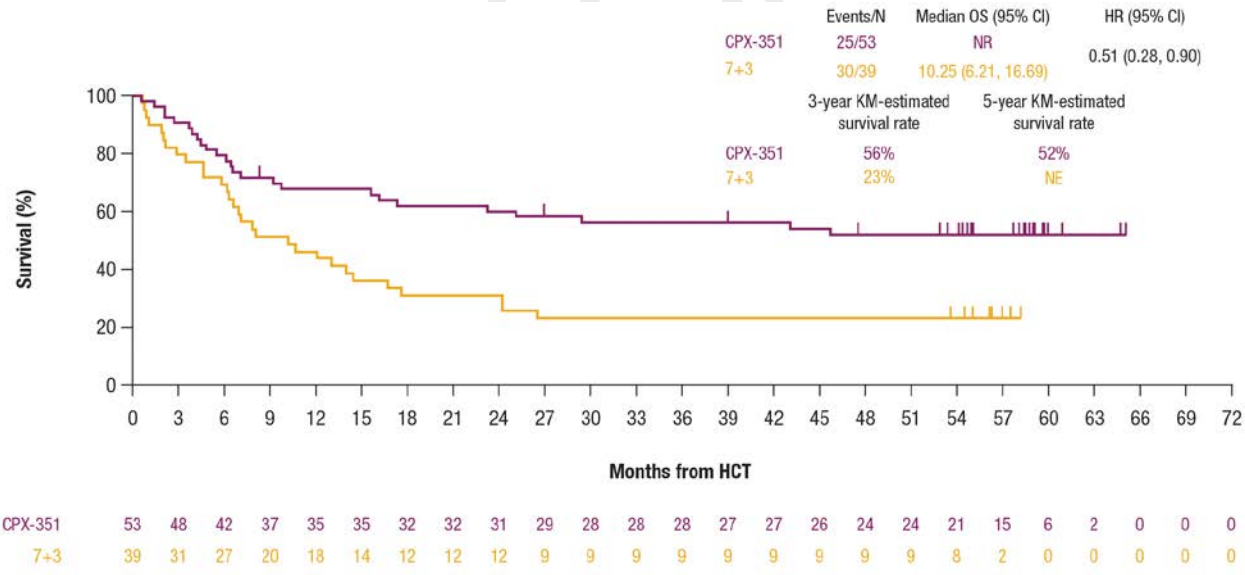
Conclusions: Analysis of HCT outcomes in patients enrolled in the CPX-351-301 study demonstrated that treatment with CPX-351 in older adults with high-risk and/or secondary AML resulted in more patients bridged to HCT and more patients transplanted in CR/CRi compared to 7+3, with improved OS in transplanted patients. The pattern of HCT outcomes suggests improved disease control with CPX-351 induction allowing higher HCT rates, but more importantly improved tolerability with less non-relapse mortality; this data supports the development of CPX-351 in other high-risk AML populations in which allogeneic HCT is the preferred post-remission strategy.

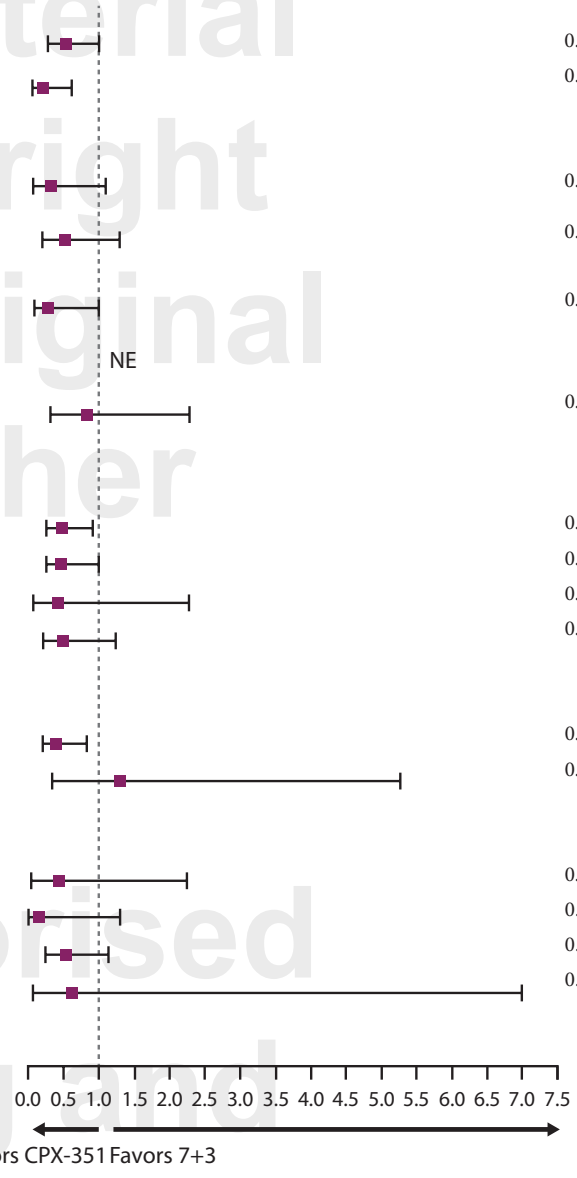
Figure 1

A. OS Landmarked from the Date of HCT

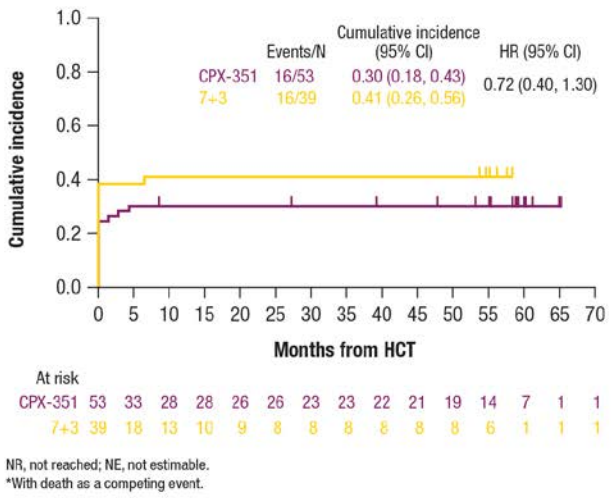


B. Subgroup Analyses of OS Landmarked from the Date of HCT

	CPX-351		7+3			
	n/N (%)	Median OS, months	n/N (%)	Median OS, months	HR (95% CI)	Nominal *P* value
Age category						
60 to 69 years	19/37 (51)	45.70	9/33 (27)	12.19		0.058
70 to 75 years	9/16 (56)	NE	0/6 (0)	6.67		0.005
AML subtype						
Therapy-related AML	7/11 (64)	NE	2/9 (22)	6.60		0.072
AML with antecedent MDS with prior HMA	7/14 (50)	43.14	3/14 (21)	11.88		0.168
AML with antecedent MDS without prior HMA	4/8 (50)	NE	0/5 (0)	2.00		0.053
AML with antecedent CMML	2/3 (67)	NE	0/0 (0)	NE	NE	–
de novo AML with MDS karyotype	8/17 (47)	45.70	4/11 (36)	12.19		0.726
Last response before HCT						
CR+CRi	22/40 (55)	NE	7/24 (29)	11.65		0.030
CR	15/30 (50)	45.70	5/19 (26)	10.25		0.052
CRi	7/10 (70)	NE	2/5 (40)	14.09		0.347
No response	6/13 (46)	23.26	2/15 (13)	7.13		0.137
Conditioning regimen						
Reduced intensity	10/23 (43)	43.14	3/18 (17)	9.03		0.016
Myeloablative	3/9 (33)	4.80	2/5 (40)	7.13		0.709
Transplant donor						
HLA-identical sibling	7/11 (64)	NE	1/3 (33)	12.19		0.306
Haploidentical	3/4 (75)	NE	0/5 (0)	10.25		0.085
Matched unrelated	12/26 (46)	29.44	5/19 (26)	7.03		0.095
Mismatched unrelated	1/2 (50)	NE	0/2 (0)	6.87		0.698

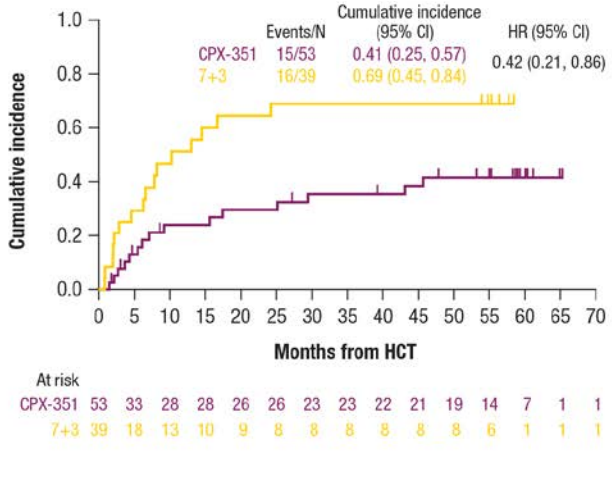


C. Cumulative Incidence of Relapse*



NR, not reached; NE, not estimable.
*With death as a competing event.

D. Cumulative Incidence of Non-relapse Mortality



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Abstract 3781

Post-Marketing Observational Study to Assess the Incidence of Infusion-Related Reactions in Adult Patients with Therapy-Related Acute Myeloid Leukemia (AML) or AML with Myelodysplasia-Related Changes Who Were Treated with CPX-351

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Introduction: CPX-351 (Vyxeos®; daunorubicin and cytarabine liposome for injection), a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio, has been approved by the US FDA and EMA for the treatment of adults with newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes. The primary endpoint analysis of the pivotal phase 3 study (NCT01696084) that formed the basis for the approvals evaluated older patients with newly diagnosed high-risk/secondary AML; after a median follow-up of 20.7 months, CPX-351 significantly improved median overall survival (OS) versus conventional 7+3 (9.56 vs 5.95 months; HR=0.69 [95% CI: 0.52, 0.90]; 1-sided *P*=0.003), with a comparable safety profile and 2 infusion-related reaction events. After 5 years of follow-up, the improved median OS was maintained, with a HR (0.70) consistent with the primary endpoint analysis. Infusion-related reactions are generally common with liposomal drugs; this post-marketing observational study was therefore requested by the FDA to confirm observations from the phase 3 study by assessing the incidence and severity of infusion-related reactions during induction with CPX-351 in adults with AML.

Methods: This was an observational, single-arm study (NCT03526926); prior to enrollment, the decision to prescribe CPX-351 was made based on the approved US indications and dosing. Patients who had been previously treated with CPX-351 or any investigational agent were ineligible. Eligible patients aged ≥18 years were to receive induction with CPX-351 at the label dosage of 100 units/m^2 (cytarabine 100 mg/m^2 and daunorubicin 44 mg/m^2) by 90-minute IV infusion on Days 1, 3, and 5; the observation period included only the first 6 days of the first induction cycle, although patients may have received subsequent treatment cycles at their physician's discretion. The incidence and severity of infusion-related reactions were evaluated during and for 90 minutes after the completion of each infusion. Treatment-emergent adverse events (TEAEs) were collected from the start of the first infusion until 1 day after the last infusion of the first induction cycle (Day 6) and graded according to CTCAE v4.03. TEAEs were followed until resolution, stabilization, or permanent sequelae were identified, or the patient was lost to follow-up.

Results: In total, 52 patients were enrolled in the study. The median age was 64 years (range: 28, 78), with 67% of patients aged ≥60 years; 56% were male; and 23%, 46%, and 23% of patients had an ECOG performance status of 0, 1, and 2, respectively. A majority of patients had no history of allergies (64%), allergic asthma (98%), or autoimmune disorders (87%). Most patients (94%) received all 3 CPX-351 infusions, with a mean of 2.9 infusions per patient (standard deviation: 0.3). Patients received a median cumulative daunorubicin dose of 247.5 mg (range: 88, 339) and cytarabine dose of 562.5 mg (range: 204, 774).

One (2%) patient experienced infusion-related reactions during the study. The patient experienced grade 1 pyrexia on Day 2 (25 hours after the Day 1 infusion) and grade 2 dyspnea on Day 4 (21 hours after the Day 3 infusion). The infusion-related reactions did not lead to dose change, interruption, or discontinuation of treatment.

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In total, 39 (75%) patients experienced any-grade TEAEs, and 13 (25%) patients experienced grade 3 or 4 TEAEs within the 6-day study period. Serious TEAEs were reported by 6 (12%) patients and included respiratory failure (n=2 [4%]), pyrexia, lung infection, sepsis, tumor lysis syndrome, cerebrovascular accident, embolism, and dyspnea (n=1 [2%] each); serious TEAEs resolved after treatment in 2 patients. Three deaths reported during the study were due to serious TEAEs considered unrelated to CPX-351 (sepsis, thromboembolic event, and stroke; n=1 [2%] each).

Conclusions: In this post-marketing observational study in patients with AML, the frequency of infusion-related reactions was low (1 of 52 patients) and the reactions were grade 1–2 in severity. Although this study only collected data on adverse events during and immediately after infusion of the first induction cycle of CPX-351, the TEAEs and serious TEAEs reported were consistent with those seen in AML patients receiving induction chemotherapy. These data support the prior safety profile reported in the pivotal phase 3 study, with no new safety signals identified.

Disclosures: **Jacoby:** *Jazz Pharmaceuticals:* Research Funding; *AbbVie:* Research Funding. **Finn:** *Jazz Pharmaceuticals:* Speakers Bureau; *Celgene:* Speakers Bureau; *Seattle Genetics:* Speakers Bureau. **Emadi:** *Jazz Pharmaceuticals:* Research Funding; *NewLink Genetics:* Research Funding; *Amgen:* Membership on an entity's Board of Directors or advisory committees; *KinaRx:* Other: co-founder and scientific advisor; *Genentech:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Membership on an entity's Board of Directors or advisory committees. **Saba:** *Kyowa Kirin:* Other: Advisory Board; *Janssen:* Other: Advisory Board, Speakers Bureau; *AbbVie:* Consultancy, Other: Advisory Board, Speakers Bureau; *Pharmacyclics:* Other: Advisory Board, Speakers Bureau; *Kite:* Other: Advisory Board. **Powell:** *Pfizer:* Research Funding; *Novartis:* Research Funding; *Jazz Pharmaceuticals:* Consultancy, Other: Advisor, Research Funding; *Rafael Pharmaceuticals:* Consultancy, Other: Advisor, Research Funding; *Genentech:* Research Funding. **Seiter:** *Alexion:* Speakers Bureau; *AbbVie:* Speakers Bureau; *Onconova:* Research Funding; *Forma:* Research Funding; *Jazz Pharmaceuticals:* Honoraria, Research Funding, Speakers Bureau; *Sanofi:* Honoraria, Speakers Bureau; *Incyte:* Honoraria, Speakers Bureau; *Celgene:* Honoraria, Research Funding, Speakers Bureau; *Novartis:* Honoraria, Research Funding, Speakers Bureau; *Sun Pharma:* Research Funding; *Roche:* Research Funding; *Amphivena:* Research Funding. **Garcia:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Faderl:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company.

Abstract 2572

Patient Experiences with Liposomal Daunorubicin and Cytarabine (CPX-351) Versus Conventional Induction Regimens: An Analysis of Patient-Reported Outcomes Data from a Prospective Trial

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Background: CPX-351 (Vyxeos®; daunorubicin and cytarabine liposome for injection) is a treatment for adults with newly diagnosed AML with myelodysplasia-related changes or therapy-related AML. Intensive induction chemotherapy causes marked symptom burden, quality of life (QOL) impairment, and psychological distress, but data on the patient experience with CPX-351 are lacking. We aimed to compare the patient experience of physician-chosen CPX-351 to standard induction regimens using validated patient-reported outcome (PRO) measures collected prospectively in a randomized clinical trial.

Methods: This was an exploratory analysis of a US, multi-site supportive care trial in AML (NCT02975869). PRO assessments were collected at baseline, 2 weeks later (when studies show patients feel their worst during a typical induction hospitalization), and then at 1, 3, and 6 months. PROs assessed the following patient experience domains: symptoms (Edmonton Symptom Assessment Scale [ESAS]), QOL (FACT-Leukemia and FACT-TOI), anxiety (HADS-A), depression (HADS-D), and post-traumatic stress (PTSD Checklist). All analyses were adjusted for baseline PROs, patient age, receipt of additional targeted therapy, and supportive care interventions. Analysis of covariance models were used to find adjusted 2-week PRO scores by treatment, and logistic regression models were used to find adjusted odds ratios (aOR) for dichotomous PROs at 2 weeks. Linear mixed effects models were used to estimate adjusted mean between-group differences in PROs across the 6-month study period (reported as B). Given the exploratory nature of this study, we defined a 2-sided *P* value of <0.20 as hypothesis-generating, consistent with standard approaches to exploratory analysis, and not to imply significance.

Results: Across 4 sites, we enrolled 109 patients with newly diagnosed AML. Thirty-five (32%) received CPX-351 and 74 (68%) received a standard regimen (72 received 7+3, 1 received FLAG, and 1 received MEC). Baseline sociodemographic characteristics and PROs were similar across groups. Mean age was 67 years (SD: 6.8) in the CPX-351 group and 65.2 (SD: 8.9) in the standard group. Most patients were white (>90%) and partnered (>70%). At 2 weeks, those receiving CPX-351 had better PRO scores (adjusted means) for symptoms (ESAS total score: 25.89 vs 31.73; *P*=0.11) and depression (HADS-D: 5.17 vs 7.0; *P*=0.08); CPX-351 was favored on all other PROs, including quality of life (FACT-Leu: 118.02 vs 112.56; *P*=0.44), anxiety (HADS-A: 4.51 vs 5.27; *P*=0.465), and PTSD symptoms (PTSD-checklist: 27.08 vs 28.16; *P*=0.6). At 2 weeks, patients receiving CPX-351 were less likely to have worsening ESAS total symptoms (45.7% vs 54.1%; aOR=0.52; *P*=0.172), physical symptoms (45.7% vs 63.5%; aOR=0.41; *P*=0.064), and clinically significant depression symptoms (27.3% vs 37.7%; aOR=0.48; *P*=0.159), but no difference in clinically significant anxiety symptoms (28.9% vs 30.3%; aOR=0.62; *P*=0.392). In longitudinal analyses, those receiving CPX-351 had better QOL (FACT-TOI: B=6.41; *P*=0.173), lower anxiety (B=−1.47; *P*=0.153), less depression symptoms (B=−1.58; *P*=0.09), and less leukemia symptoms (B=3.67; *P*=0.16), but no differences in total symptom burden (ESAS: B=−0.06; *P*=0.988) or in PTSD symptoms (PTSD Checklist: B=2.23; *P*=0.354). While patients receiving CPX-351 had a longer index hospitalization length of stay compared to standard induction (mean of 44.3 vs 39 days; *P*=0.072), they also had fewer hospitalizations during the 6-month follow-up period (2.82 vs 3.55; *P*=0.158). Furthermore, the total number of days hospitalized after the index admission was lower for those receiving CPX-351 (17.71 vs 22.27 days; *P*=0.199). Patients receiving CPX-351 had an average of 94.08 days alive and out of the hospital, while those receiving standard induction had 91.85 days (*P*=0.849).

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Conclusions: This exploratory analysis supports the observation that patients receiving CPX-351 may have an overall better patient experience during induction treatment, as measured by validated PROs assessing symptoms, QOL, mood, and PTSD. Our ability to draw more definitive conclusions is limited by sample size and the fact that treatment with CPX-351 is only indicated for certain AML subtypes, resulting in a non-random allocation to treatment groups and potential differences in clinical outcomes.

Disclosures: Leblanc: *AstraZeneca:* Research Funding; *Agios, AbbVie, and Bristol Myers Squibb/Celgene:* Speakers Bureau; *UpToDate:* Patents & Royalties: Royalties; *American Cancer Society, BMS, Duke University, NINR/NIH, Jazz Pharmaceuticals, Seattle Genetics:* Research Funding; *AbbVie, Agios, Amgen, AstraZeneca, CareVive, BMS/Celgene, Daiichi-Sankyo, Flatiron, Helsinn, Heron, Otsuka, Medtronic, Pfizer, Seattle Genetics, Welvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Morris:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Hooks:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **El-Jawahri:** *Jazz Pharmaceuticals:* Research Funding.

Abstract 2375

Analysis of Risk Factors for Hepatic Sinusoidal Obstruction Syndrome after Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Patients

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Background: Hepatic sinusoidal obstruction syndrome (SOS), which is also called veno-occlusive disease of the liver, remains a serious complication after hematopoietic stem cell transplantation (HSCT). Over the last years, some risk factors have already been identified to be associated with SOS. However, the cause of SOS is still not fully understood and the mortality remains high, especially for SOS leading to multi-organ failure with a mortality rate up to 84%. The aim of our study was to analyze several risk factors of SOS in pediatric patients undergoing allogeneic HSCT. In addition, we investigated new potential risk factors.

Methods: We retrospectively analyzed 105 children who underwent allogeneic HSCT for the first time and did not receive a defibrotide prophylaxis. All transplantations were performed between January 2007 and December 2018 in a single center. The median age was 8.6 years and stem cell source was either bone marrow (n=74) or peripheral blood (n=31). Underlying diseases were acute lymphoblastic leukemia (n=27), acute myeloid leukemia (n=25), myelodysplastic syndrome (n=14), lymphoma (n=2), solid tumor (n=12) and genetic disease (n=25). All patients received a myeloablative conditioning regimen. We analyzed the transplantation-related factors graft source, donor-recipient human leukocyte antigen match, donor age, donor sex and conditioning regimen based on busulfan or total body irradiation. Furthermore, we investigated the patient-related factors patient age, patient sex, prior treatment with gemtuzumab ozogamicin as well as the following laboratory parameters: aspartate transaminase, alanine transaminase, cholinesterase, glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase, ferritin, albumin, total bilirubin, C-reactive protein and international normalized ratio (INR). All laboratory parameters were measured before HSCT and cutoffs were determined by reference values and receiver operating characteristic (ROC) curves. SOS was defined by modified pediatric Seattle criteria up to day +30 after HSCT because nearly all transplantations were performed before the new pediatric criteria of the European Society for Blood and Marrow Transplantation have been published. In univariate analysis, chi-square test and Fisher's exact test were used. Additionally, the Mann-Whitney U-test was performed to compare the median values of continuous variables. Significant variables ($P<.05$) were entered in multivariate analysis, which was carried out by using backward stepwise logistic regression.

Results: SOS occurred in 15 out of 105 transplantations (14.3%). The median time of SOS onset was 12 days after HSCT (range, 1 day – 26 days). Three patients died of multi-organ failure following SOS (20%). This mortality rate was very low compared to other studies because our patients were treated with defibrotide immediately after being diagnosed with SOS. In univariate analysis, we found a significant association between patient age <1 year and SOS (Odds Ratio (OR)=7.25, $P=.037$). Furthermore, a prior treatment with gemtuzumab ozogamicin (OR=11.00, $P=.020$) showed a significant correlation. Patients who developed SOS had a significantly higher median ferritin level (2816.9 ng/mL vs. 1554.0 ng/mL, $P=.026$). Based on this observation, different ferritin cutoffs were selected by ROC analysis. Ferritin >1500 ng/mL (OR=4.00, $P=.033$), ferritin >2000 ng/mL (OR=4.69, $P=.016$) as well as ferritin >2400 ng/mL (OR=5.29, $P=.005$) revealed significant P values. Besides these results, INR ≥1.3 (OR=5.91, $P=.009$) was significantly associated with SOS. In multivariate analysis, the following variables showed P values less than .05: treatment with gemtuzumab ozogamicin (OR=9.24, $P=.048$), ferritin >2400 ng/mL (OR=5.74, $P=.023$) and INR ≥1.3 (OR=8.02, $P=.007$).

Conclusions: Our data confirm the risk factors of young patient age (<1 year), prior treatment with gemtuzumab ozogamicin and high serum ferritin (>2400 ng/mL) in the pediatric population. Moreover, we report for the first time that there is a significant association between high INR (≥1.3) before HSCT and the occurrence of SOS. Especially this new finding could improve the risk stratification of SOS and should be evaluated in further trails.

Disclosures: No relevant conflicts of interest to declare.

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Abstract 2386

Final Primary Results from the Defifrance Registry Study: Effectiveness and Safety of Defibrotide in the Treatment of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome after Hematopoietic Cell Transplantation

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Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially fatal complication that occurs after hematopoietic cell transplantation (HCT) conditioning. In its most severe form, VOD/SOS is associated with multi-organ failure (MOF) and a mortality rate of >80% if untreated. Defibrotide is approved for the treatment of hepatic VOD/SOS with renal or pulmonary dysfunction post-HCT in adult and pediatric patients in the United States and severe hepatic VOD/SOS post-HCT in patients aged >1 month in the European Union. The DEFIFrance study collected real-world data on the safety and effectiveness of defibrotide in France. This analysis presents final primary data on the subgroup of DEFIFrance patients who received defibrotide for the treatment of severe/very severe VOD/SOS post-HCT.

This post-marketing study collected retrospective and prospective real-world data on patients receiving defibrotide at 53 HCT centers in France from July 15, 2014 to March 31, 2020. VOD/SOS severity was categorized using European Society for Blood and Marrow Transplantation criteria (adults) or study steering committee member adjudication (pediatric patients). The primary endpoints included Kaplan-Meier (KM)–estimated Day 100 (post-HCT) survival and Day 100 complete response (CR; total serum bilirubin <2 mg/dL and MOF resolution per investigators' assessment) in patients with severe/very severe VOD/SOS post-HCT. Secondary endpoints included evaluation of adverse events (AEs) of interest, such as hemorrhage, coagulopathy, injection-site reactions, infections, and thromboembolic events, irrespective of their relationship to treatment.

Of the 775 defibrotide-treated patients included in the study analysis, 250 received defibrotide for the treatment of severe/very severe VOD/SOS post-HCT (severe: 119 [48%]; very severe: 131 [52%]). The median patient age was 45 years (range: 5 months, 74 years) and 52 (21%) patients were less than 18 years of age. A total of 219 (88%) patients had received allogeneic HCT and 95 (38%) patients had an unrelated donor. The Day 100 KM-estimated survival was 58% (95% confidence interval [CI]: 52%, 64%) in patients with severe/very severe VOD/SOS post-HCT. The estimated Day 100 survival rate was higher in patients with severe (74% [95% CI: 65%, 81%]) versus very severe (43% [95% CI: 35%, 52%]) VOD/SOS. Among patients with severe/very severe VOD/SOS post-HCT, the CR rate at Day 100 was 53% (95% CI: 47%, 59%). The Day 100 CR rate was higher in patients with severe (68% [95% CI: 60%, 77%]) versus very severe (39% [95% CI: 30%, 47%]) VOD/SOS. Treatment emergent AEs of interest occurred in 41% of patients with severe/very severe VOD/SOS, with infection (23%) and bleeding (17%) being the most commonly reported.

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The DEFIFrance study represents the largest collection of real-world data on the use of defibrotide. The effectiveness and safety observed in this study build upon prior studies supporting the utility of defibrotide for treating severe/very severe VOD/SOS post-HCT in a real-world setting. Among patients receiving defibrotide for VOD/SOS post-HCT, outcomes were better in patients with severe versus very severe disease, highlighting the importance of early diagnosis and treatment of VOD/SOS before patients reach the most severe stage of VOD/SOS.

Disclosures: Mohty: *Novartis:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *BMS:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Sanofi:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Takeda:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Amgen:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Stemline:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Celgene:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *GSK:* Consultancy, Honoraria, Research Funding, Speakers Bureau. **Yakoub-Agha:** *Celgene:* Honoraria; *Novartis:* Honoraria; *Gilead/Kite:* Honoraria, Other: travel support; *Jazz Pharmaceuticals:* Honoraria; *Janssen:* Honoraria. **Labopin:** *Jazz Pharmaceuticals:* Honoraria. **Blaise:** *Jazz Pharmaceuticals:* Honoraria. **Renard:** *Jazz Pharmaceuticals:* Research Funding. **Jubert:** *Jazz Pharmaceuticals:* Research Funding. **Ryan:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Bouvatier:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Dalle:** *Bellicum:* Consultancy, Honoraria; *Sanofi-Genzyme:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Medac:* Consultancy, Honoraria; *Gilead:* Honoraria; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *AbbVie Pharmacyclics:* Membership on an entity's Board of Directors or advisory committees; *Incyte:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Orchard:* Consultancy, Honoraria; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *bluebird bio:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Peffault De Latour:** *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Alexion Pharmaceuticals Inc.:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Apellis:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Research Funding; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau.

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