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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%).

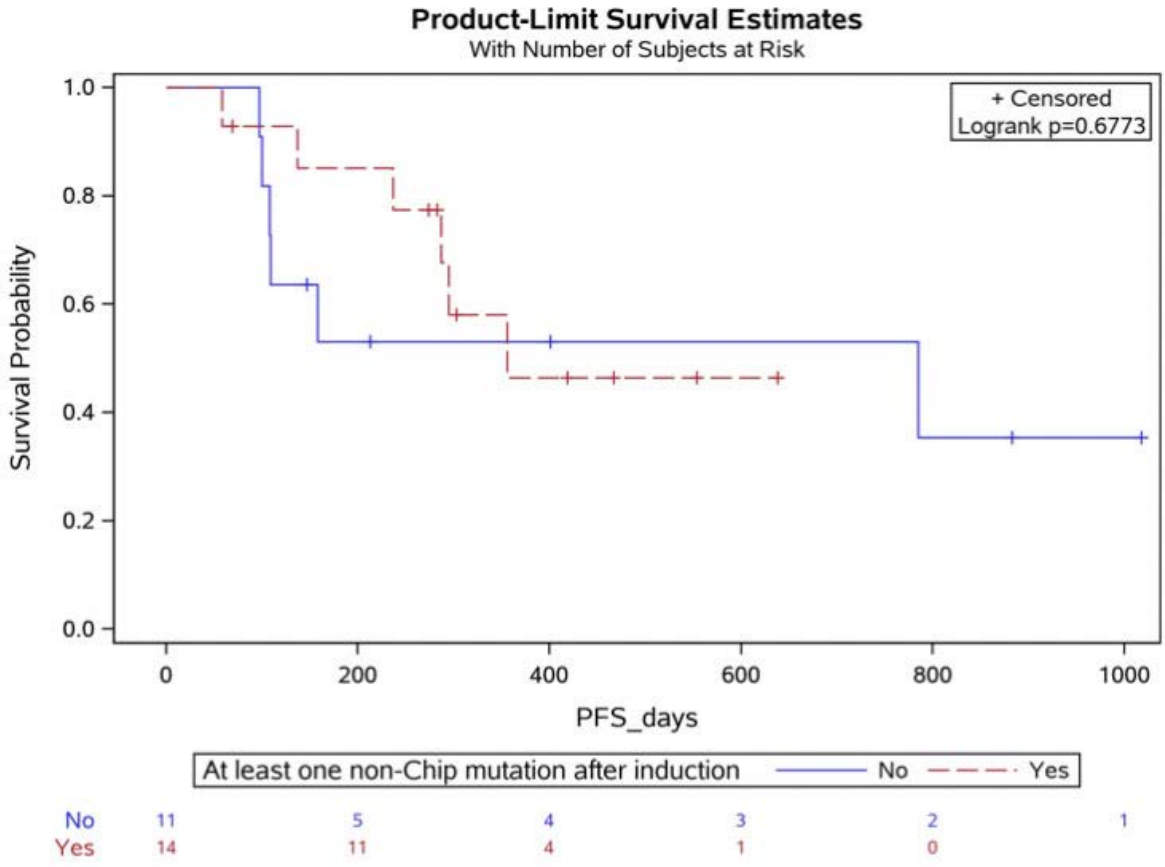
Median OS was 10.4 mos. Median OS was similar for patients older or younger than 60 years (p=0.76). For patients achieving a CR/CRi, median OS had not been reached at the time of analysis but was significantly improved compared to those with refractory disease (6.1 mos, p=0.0007). Median OS or PFS did 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 [2^{nd} 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 [2^{nd} 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 (10^{th} to 90^{th} 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

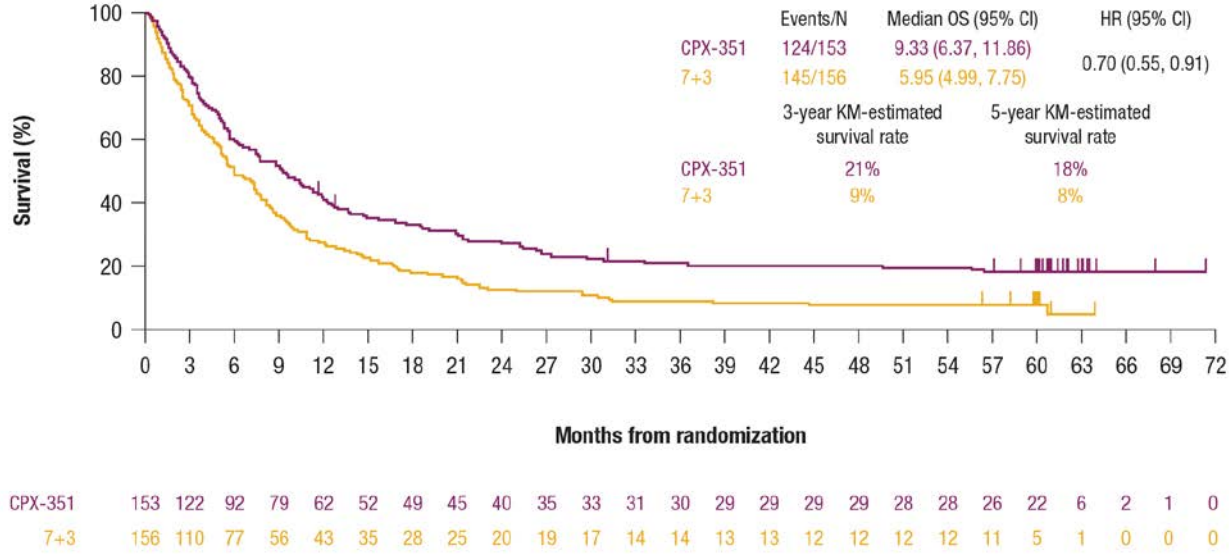


Figure 2. Os by Age Subgroup

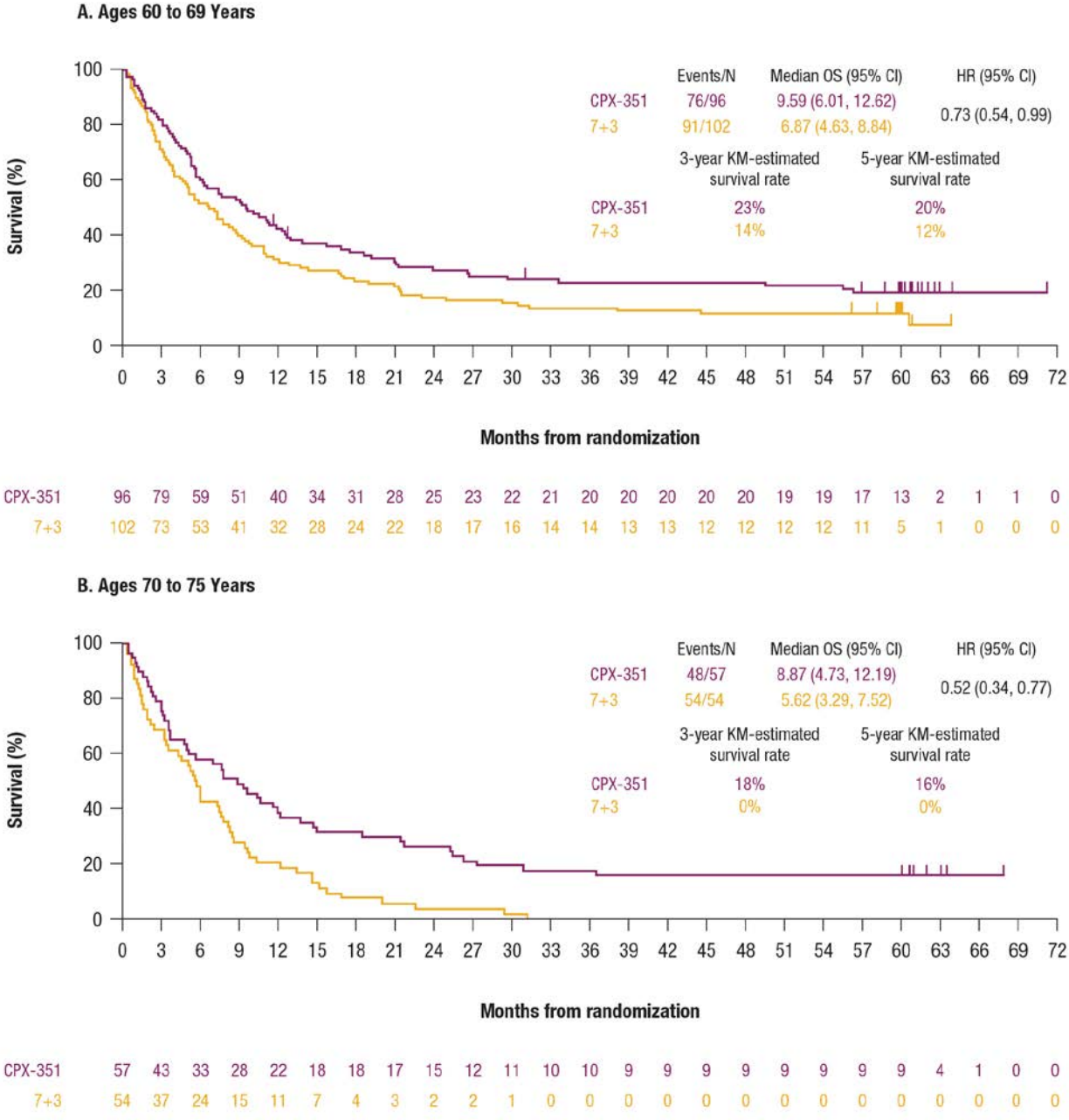
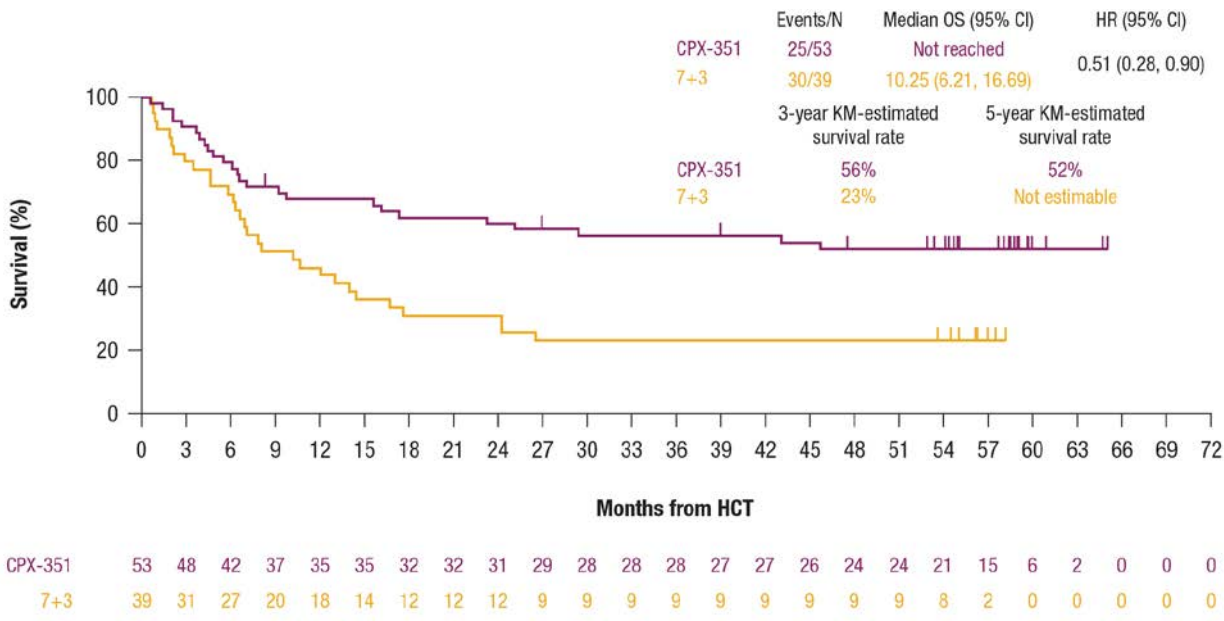


Figure 3. OS Landmarked from the Date of HCT



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

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Abstract 1946

Quality-Adjusted Time without Symptoms of Disease and Toxicity (Q-TWiST) Analysis of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed High-Risk/Secondary Acute Myeloid Leukemia (AML)

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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 the EMA for the treatment of adults with newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes. The primary analysis of the pivotal phase 3 study (NCT01696084) that formed the basis for these approvals evaluated patients aged 60 to 75 years with newly diagnosed high-risk/secondary AML and found that, with a median follow-up of 20.7 months, CPX-351 significantly improved median overall survival (OS) versus conventional 7+3, with a comparable safety profile. Final 5-year follow-up results recently reported demonstrated that the OS benefit was maintained. To evaluate both quality and quantity of life, we conducted a Q-TWiST analysis of the phase 3 study to compare survival between patients receiving CPX-351 versus 7+3.

Methods: Q-TWiST is used to evaluate outcomes in oncology trials by measuring how much of the survival improvement time is spent with toxicities, how much after disease progression or relapse, and how much is valuable time (ie, Time Without Symptoms of Disease and Toxicity [TWiST]). For this analysis, the OS for each patient from the 5-year follow-up analysis was partitioned into 3 health states: TOX (time before response plus any additional time with a grade 3 or 4 toxicity), TWiST (time without relapse or grade 3 or 4 toxicity), and REL (time after relapse). Q-TWiST gain was assessed as the mean time spent in each state weighted by its respective quality of life, represented by health utility (U; scale of 0.0 [indicates death] to 1.0 [indicates "perfect" health]). Q-TWiST gain was calculated as follows: Q-TWiST=(U_{TWiST} × TWiST) + (U_{TOX} × TOX) + (U_{REL} × REL). The base case scenario used the intent-to-treat population, any grade 3 or 4 toxicities, TOX and REL utility weights of 0.5, and a TWiST utility weight of 1.0. Sensitivity analyses were performed for all treated patients (CPX-351: n=153; 7+3: n=151) and the intent-to-treat population, any and treatment-related grade 3 or 4 toxicities, and TOX and REL utility weights of 0, 0.5, and 1.0. A variation of the base case scenario was also performed for the subset of patients who achieved complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CR+CRi; CPX-351: n=73; 7+3: n=52).

When comparing across populations or studies, reporting relative Q-TWiST gains is an effective measure for evaluating clinical benefit (ie, Q-TWiST gains compared to a control; Solem CT, et al. *Expert Rev Pharm Out* 2018). A relative Q-TWiST gain of 15% or greater is considered a clinically important difference (CID) in oncology studies (Revicki DA, et al. *Qual Life Res* 2006). The relative Q-TWiST gain was calculated using the following equation: Q-TWiST difference ÷ mean OS of control arm × 100.

Results: In total, 309 patients were randomized to CPX-351 (n=153) or 7+3 (n=156). In the base case scenario, the means difference (95% CI) for CPX-351 versus 7+3 was 183 days (60, 306) for the TWiST state, 7 days (−63, 78) for the TOX state, and 22 days (5, 38) for the REL states. The resulting means difference (95% CI) for Q-TWiST gain was 197 days (76, 319) for CPX-351 versus 7+3, and the relative Q-TWiST gain was 53.6%. Among patients who achieved CR or CRi, the means difference (95% CI) for Q-TWiST gain was 248 days (−1, 496) for CPX-351 versus 7+3, and the relative Q-TWiST gain was 39.8%. Both relative Q-TWiST gains were considerably above the standard CID of 15% for

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oncology. Across the various sensitivity analyses, the relative Q-TWiST gains for CPX-351 versus 7+3 varied from 48.0% to 57.6%, remaining all well above the standard CID threshold (**Table**).

Conclusions: Results of this *post hoc* analysis suggest the survival benefit with CPX-351 for patients with high-risk/secondary AML are mostly from valuable time (TWiST), thus supporting the clinical benefit for patients. The relative Q-TWiST gains were well above what is considered CID (15%) in the cancer literature and were maintained across various sensitivity analyses, supporting the robustness of the benefit. In the absence of direct measures of quality of life, these results can be used together with the antileukemia effect when considering treatment options for this patient population.

Table. Q-TWiST Results

Population	AEs	TOX utility weight	REL utility weight	Mean Q-TWiST gain (95% CI), days[a]	Relative Q-TWiST gain
Base case analysis					
ITT population[b]	All grade 3–4 AEs	0.5*TOX	0.5*REL	197 (76, 319)	53.6%
CR+CRi analysis					
Achieved CR+CRi	All grade 3–4 AEs	0.5*TOX	0.5*REL	248 (–1, 496)	39.8%
Sensitivity analyses					
ITT population[b]	All grade 3–4 AEs	0*TOX	0*REL	183 (60, 306)	49.7%
			0.5*REL	194 (71, 316)	52.6%
			1*REL	204 (81, 327)	55.6%
		0.5*TOX	0*REL	186 (65, 308)	50.7%
			0.5*REL	197 (76, 319)	53.6%
			1*REL	208 (87, 329)	56.6%
		1*TOX	0*REL	190 (59, 321)	51.7%
			0.5*REL	201 (71, 331)	54.6%
			1*REL	212 (82, 342)	57.6%
Safety population[c]	All grade 3–4 AEs	0*TOX	0*REL	177 (52, 302)	48.0%
			0.5*REL	188 (63, 312)	50.9%
			1*REL	198 (73, 323)	53.8%
		0.5*TOX	0*REL	183 (60, 307)	49.8%
			0.5*REL	194 (71, 317)	52.7%
			1*REL	205 (81, 328)	55.5%
		1*TOX	0*REL	190 (57, 323)	51.5%
			0.5*REL	200 (68, 333)	54.4%
			1*REL	211 (79, 343)	57.3%
ITT population[b]	Treatment-related grade 3–4 AEs	0*TOX	0*REL	186 (62, 310)	50.5%
			0.5*REL	197 (73, 320)	53.4%
			1*REL	207 (83, 331)	56.4%
		0.5*TOX	0*REL	188 (65, 310)	51.1%
			0.5*REL	199 (77, 321)	54.0%
			1*REL	210 (88, 332)	57.0%
		1*TOX	0*REL	190 (59, 321)	51.7%
			0.5*REL	201 (71, 331)	54.6%
			1*REL	212 (82, 342)	57.6%

Safety population[c]	Treatment-related grade 3–4 AEs	0*TOX	0*REL	180 (54, 306)	48.8%
			0.5*REL	191 (65, 316)	51.7%
			1*REL	201 (75, 327)	54.6%
		0.5*TOX	0*REL	185 (60, 309)	50.2%
			0.5*REL	196 (72, 319)	53.1%
			1*REL	206 (82, 330)	55.9%
		1*TOX	0*REL	190 (57, 323)	51.5%
			0.5*REL	200 (68, 333)	54.4%
			1*REL	211 (79, 343)	57.3%

Q-TWiST, Quality-adjusted Time Without Symptoms of Disease and Toxicity; TOX, time with any grade 3 or 4 toxicity before relapse; TWiST, time without relapse or grade 3 or 4 toxicity; REL, time after relapse; SD, standard deviation; CR, complete remission; CRi, CR with incomplete neutrophil or platelet recovery; AE, adverse event; ITT, intent-to-treat.

[a]Q-TWiST gain was assessed as the mean time spent in each state weighted by its respective quality of live, represented by health utility (U; scale of 0.0 [indicates death] to 1.0 [indicates "perfect" health]) and was calculated as follows: $Q\text{-}TWiST=(U_{TWiST}\times TWiST)+(U_{TOX}\times TOX)+(U_{REL}\times REL)$. All analyses used a TWiST utility weight of 1.0.

[b]The ITT population included all patients who were randomized to induction treatment.

[c]The safety population contained all patients who received ≥1 dose of study treatment.

Disclosures: Cortes: *Sun Pharma:* Research Funding; *BioPath Holdings:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Merus:* Research Funding; *Daiichi Sankyo:* Consultancy, Research Funding; *Immunogen:* Research Funding; *Bristol-Myers Squibb:* Research Funding; *BiolineRx:* Consultancy, Research Funding; *Arog:* Research Funding; *Amphivena Therapeutics:* Research Funding; *Astellas:* Research Funding; *Telios:* Research Funding; *Takeda:* Consultancy, Research Funding; *Jazz Pharmaceuticals:* Consultancy, Research Funding; *Pfizer:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding. **Lin:** *Aptevo:* Research Funding; *Abbvie:* Research Funding; *Gilead Sciences:* Research Funding; *Genetech-Roche:* Research Funding; *Incyte:* Research Funding; *Celyad:* Research Funding; *Celgene:* Research Funding; *Jazz:* Research Funding; *Mateon Therapeutics:* Research Funding; *Ono Pharmaceutical:* Research Funding; *Bio-Path Holdings:* Research Funding; *Astellas Pharma:* Research Funding; *Prescient Therapeutics:* Research Funding; *Pfizer:* Research Funding; *Trovagene:* Research Funding; *Tolero Pharmaceuticals:* Research Funding; *Seattle Genetics:* Research Funding. **Uy:** *Daiichi Sankyo:* Consultancy; *Pfizer:* Consultancy; *Agios:* Consultancy; *Genentech:* Consultancy; *Jazz Pharmaceuticals:* Consultancy; *Astellas Pharma:* Honoraria. **Ryan:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Faderl:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Lancet:** *Abbvie:* Consultancy; *Agios Pharmaceuticals:* Consultancy, Honoraria; *Astellas Pharma:* Consultancy; *Celgene:* Consultancy, Research Funding; *Daiichi Sankyo:* Consultancy; *ElevateBio Management:* Consultancy; *Jazz Pharmaceuticals:* Consultancy; *Pfizer:* Consultancy.

Abstract 2844

Exploratory Analysis of the Efficacy and Safety of CPX-351 Versus 7+3 By European Leukemianet (ELN) 2017 Risk Groups in a Phase 3 Study of Older Adults with High-Risk/Secondary Acute Myeloid Leukemia

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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, is approved by the US FDA and EMA for the treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes. A phase 3 study (NCT01696084) in older patients aged 60 to 75 years with newly diagnosed high-risk/secondary AML demonstrated significantly longer overall survival (OS) with CPX-351 vs conventional 7+3, with a comparable safety profile. This exploratory *post hoc* analysis of the phase 3 study evaluated outcomes by AML risk subgroups according to the ELN 2017 criteria.

Methods: Inclusion criteria did not consider risk classification. 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-minute infusion on Days 1, 3, and 5 [2nd induction: Days 1 and 3]) or 7+3 (cytarabine 100 mg/m^2/day continuously for 7 days + daunorubicin 60 mg/m^2 on Days 1, 2, and 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 a hematopoietic cell transplant (HCT) at the physician's discretion. In this subgroup analysis, patients from the phase 3 study were classified retrospectively into risk subgroups per the ELN 2017 criteria: favorable-risk AML, intermediate-risk AML, or adverse-risk AML.

Results: Of 309 patients enrolled in the study, 149/153 in the CPX-351 arm and 148/156 in the 7+3 arm had molecular data available for ELN 2017 risk classification and were included in this analysis. In the CPX-351 and 7+3 arms, respectively, 10 (7%) and 7 (5%) had favorable-risk AML, 40 (27%) and 41 (28%) had intermediate-risk AML, and 99 (66%) and 100 (68%) had adverse-risk AML by ELN. Due to small patient numbers, outcomes for the subgroup of patients with favorable-risk AML were not evaluated.

In patients with intermediate-risk AML, CR+CRi was achieved by 23 (58%) patients with CPX-351 vs 16 (39%) patients with 7+3; in those with adverse-risk AML, CR+CRi was achieved by 41 (41%) vs 26 (26%). Median OS was longer with CPX-351 vs 7+3 in patients with intermediate-risk AML (11.9 vs 7.8 months; HR=0.68 [95% CI: 0.41, 1.16]; **Figure 1A**) and adverse-risk AML (7.7 vs 5.5 months; HR=0.63 [95% CI: 0.46, 0.86]; **Figure 1B**). In patients with *TP53* mutations in the adverse-risk group, median OS was 5.7 months with CPX-351 (n=24/99) vs 5.1 months with 7+3 (n=31/100; HR=1.00 [95% CI: 0.57, 1.75]); in patients without *TP53* mutations in the adverse-risk group, median OS was 9.6 vs 5.6 months (HR=0.55 [95% CI: 0.38, 0.81]).

In patients with intermediate-risk AML, HCT was received by 14 (35%) in the CPX-351 arm vs 14 (34%) in the 7+3 arm; median OS landmarked from the HCT date was not reached with CPX-351 vs 13.0 months with 7+3 (HR=0.46 [95% CI: 0.16, 1.39]). In patients with adverse-risk AML, HCT was received by 32 (32%) patients in the CPX-351 arm vs 24 (24%) patients in the 7+3 arm; median OS landmarked from the HCT date was not reached with CPX-351 vs 7.1 months with 7+3 (HR=0.44 [95% CI: 0.21, 0.93]). In patients with *TP53* mutations in the adverse-risk group who underwent HCT, median OS landmarked from the HCT date was 10.0 months (n=4) vs 6.4 months with 7+3 (n=10); in patients without *TP53* mutations in the adverse-risk group who underwent HCT, median OS landmarked from the HCT date was not reached with CPX-351 (n=28) vs 11.2 months with 7+3 (n=14).

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Early mortality rates by Day 60 were 13% vs 20% with CPX-351 vs 7+3, respectively, in patients with intermediate-risk AML and 15% vs 25% in patients with adverse-risk AML. Adverse events in ≥50% of patients with intermediate-risk AML were febrile neutropenia (CPX-351: 85%; 7+3: 70%), nausea (48%; 63%), diarrhea (45%; 68%), peripheral edema (45%; 53%), and constipation (33%; 50%), and in patients with adverse-risk AML were febrile neutropenia (63%; 70%), nausea (47%; 51%), and diarrhea (44%; 66%).

Conclusions: In this *post hoc* analysis, CPX-351 improved median OS, remission rates, and post-HCT outcomes vs 7+3 in patients with intermediate- or adverse-risk AML per the ELN 2017 criteria, with a safety profile consistent with the overall study population and the known safety profile of 7+3. Abstract previously published by EHA in *HemaSphere*, 2020;4:S1.

Figure 1A. Kaplan-Meier OS in Patients with Intermediate-risk AML by ELN 2017 Risk Criteria

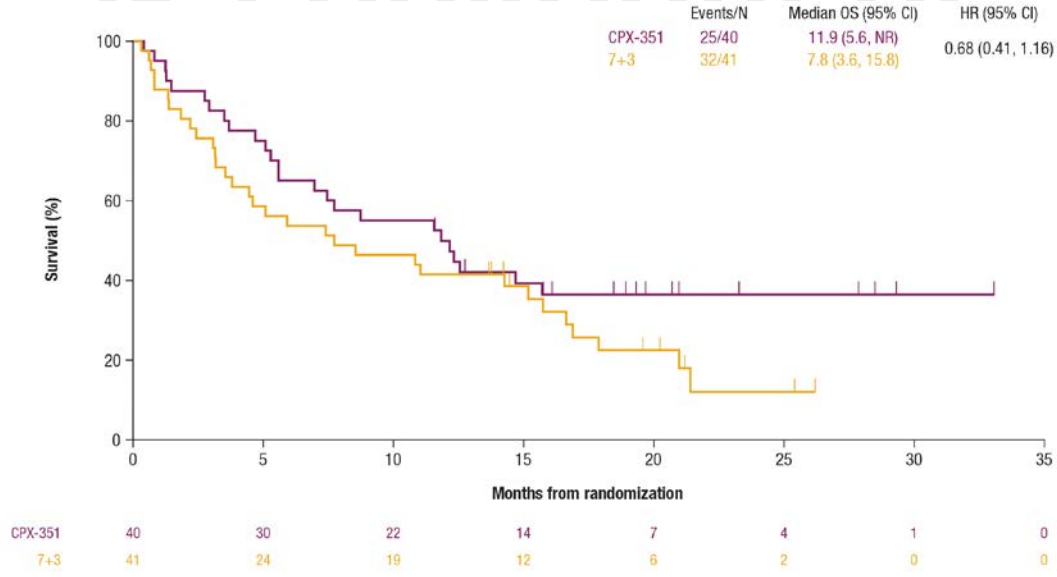
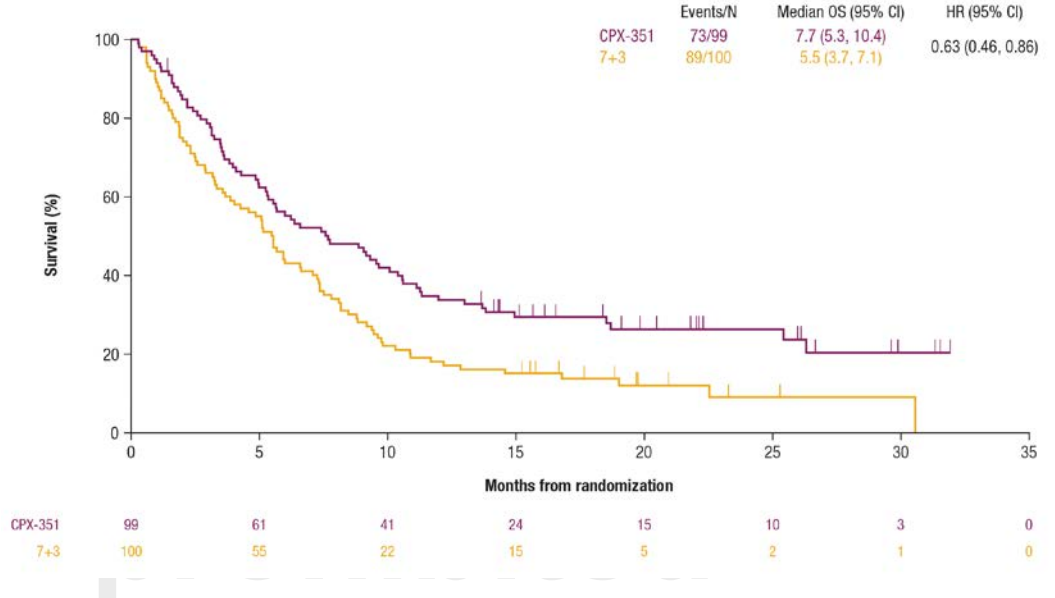


Figure 1B. Kaplan-Meier OS in Patients with Adverse-risk AML by ELN 2017 Risk Criteria



Disclosures: Prebet: *Jazz Pharmaceuticals:* Consultancy, Research Funding. **Ryan:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Faderl:** *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company.

Abstract 1929

Analysis of Treatments and Outcomes for Patients with *De Novo* AML, Therapy-Related AML, and Secondary AML (Prior MDS and CMML) Diagnosed in England between 2011 and 2016 Using Hospital Episode Statistics®

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Introduction: Historically, patients with therapy-related acute myeloid leukemia (t-AML) or secondary AML (s-AML; prior myelodysplastic syndrome [$_{MDS}$AML] or chronic myelomonocytic leukemia [$_{CMML}$AML]) have poor outcomes when treated with conventional intensive chemotherapy (IC). Alternative, less-intensive therapies include azacitidine and low-dose cytarabine (LDAC). The objective of this retrospective study was to utilize the Hospital Episode Statistics® (HES) database to describe the historical treatment patterns in England from 2011 to 2016 and to analyze long-term outcomes for patients with *de novo* AML, t-AML, or s-AML.

Methods: The HES database contains details of all admissions, accident and emergency attendances, and outpatient appointments at National Health Service (NHS) hospitals in England. Adult patients (≥18 years) diagnosed with AML between NHS years (April–March) 2011/2012 to 2016/2017 were identified through *International Classification of Diseases, Tenth Revision* (ICD-10) codes (C92*, excluding C921, C922, and C927). There are no ICD-10 codes specific to t-AML or s-AML, so these patients were identified through a history of relevant cancer and specific OPCS-4 procedure codes for prior chemotherapy (X7*) or radiotherapy (X65*), or a history of MDS (ICD-10: D46*, excluding D463) or CMML (ICD-10: C931). Patients with AML who did not fall into these criteria were classified as *de novo* AML. Based on OPCS-4 codes, patients were allocated to the following AML treatment pathways: IC ± hematopoietic cell transplantation (HCT), azacitidine, or LDAC. Patients who did not receive active systemic therapy (ie, best supportive care alone) were excluded. Median patient follow-up was 5.3 years (100% range: 2.5, 8.8).

Results: In total, 9,758 patients with AML were identified, comprising 7,499 (77%) with *de novo* AML, 803 (8%) with t-AML, 1,305 (13%) with $_{MDS}$AML, and 151 (2%) with $_{CMML}$AML. Patients with *de novo* AML were younger (median [interquartile range] age: 63 years [50, 72]) compared to those with t-AML (67 years [56, 73]), $_{MDS}$AML (70 years [63, 76]), and $_{CMML}$AML (68 years [62, 74]). Patients with *de novo* AML were more likely to receive IC ± HCT overall and across all age groups. In patients 60 to 69 and 70 to 79 years, 76% and 36% of those with *de novo* AML received IC ± HCT, respectively, compared to 54% to 56% and 15% to 22% of patients with t-AML/s-AML. The lower use of IC ± HCT in older patients with t-AML/s-AML versus *de novo* AML was due to the preferential use of azacitidine. In patients 60 to 69 and 70 to 79 years, 35% to 38% and 54% to 57% of patients with t-AML/s-AML received azacitidine, respectively, compared to 17% and 32% with *de novo* AML.

Patients with *de novo* AML had longer Kaplan-Meier-estimated overall survival (OS) versus those with t-AML/s-AML combined (median: 1.79 vs 0.94 years; unadjusted hazard ratio=1.66 [95% confidence interval: 1.58, 1.75]; nominal $P<0.0001$). For patients treated with IC ± HCT (all ages), the 5-year Kaplan-Meier OS estimates were higher for patients with *de novo* AML versus those with t-AML or s-AML (46% vs 36% and 24%, respectively). Compared to azacitidine or LDAC, 5-year OS estimates were consistently higher with IC ± HCT across all AML subgroups (see **Table**).

Conclusions: This large, retrospective analysis has confirmed the poor historical outcomes for patients diagnosed with t-AML or s-AML in England. Compared to patients with *de novo* AML, those with t-AML or s-AML were less likely to receive IC ± HCT across all age groups. In addition, when treated with IC ± HCT, their outcomes were inferior to those of patients with *de novo* AML. However, despite this poor prognosis, 5-year OS estimates for patients with t-AML or s-AML were improved with IC ± HCT versus both azacitidine and LDAC therapy.

Abstract previously published by EHA in *HemaSphere*, 2020;4:S1.

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Table. 60-day and 5-year OS by Treatment and AML Subtype

Treatment	AML subtype	Total patients	Kaplan-Meier OS estimate	
			60-day	5-year
IC±HCT	*de novo* AML	5,062	93%	46%
	t-AML	397	92%	36%
	s-AML (prior MDS/CMML)	581	92%	24%
Azacitidine	*de novo* AML	1,192	92%	18%
	t-AML	280	88%	17%
	s-AML (prior MDS/CMML)	623	87%	6%
LDAC	*de novo* AML	1,245	73%	15%
	t-AML	126	77%	10%
	s-AML (prior MDS/CMML)	252	69%	4%

Disclosures: Legg: *Jazz Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Ellison:** *Harvey Walsh, which was contracted by Jazz Pharmaceuticals for the conduct of this analysis:* Current Employment. **O'Connell:** *Harvey Walsh, which was contracted by Jazz Pharmaceuticals for the conduct of this analysis:* Current Employment. **Evans:** *Harvey Walsh, which was contracted by Jazz Pharmaceuticals for the conduct of this analysis:* Current Employment.

Abstract 34

The Application of Machine Learning to Improve the Subclassification and Prognostication of Acute Myeloid Leukemia

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Genetic mutations (somatic or germline), cytogenetic abnormalities and their combinations contribute to the heterogeneity of acute myeloid leukemia (AML) phenotypes. To date, prototypic founder lesions [e.g., t(8;21), inv(16), t(15;17)] define only a fraction of AML subgroups with specific prognoses. Indeed, in a larger proportion of AML patients, somatic mutations or cytogenetic abnormalities potentially serve as driver lesions in combination with numerous acquired secondary hits. However, their combinatorial complexity can preclude the resolution of distinct genomic classifications and overlap across classical pathomorphologic AML subtypes, including *de novo*/primary (pAML) and secondary AML (sAML) evolving from an antecedent myeloid neoplasm (MN). These prognostically discrete AML subtypes are themselves nonspecific due to variable understanding of their pathogenetic links, especially in cases without overt dysplasia. Without dysplasia, reliance is mainly on anamnestic clinical information that might be unavailable or cannot be correctly assigned due to a short prodromal history of antecedent MN. We explored the potential of genomic markers to sub-classify AML objectively and provide unbiased personalized prognostication, irrespective of the clinicopathological information, and thus become a standard in AML assessment.

We collected and analyzed genomic data from a multicenter cohort of 6788 AML patients using standard and machine learning (ML) methods. A total of 13,879 somatic mutations were identified and used to predict traditional pathomorphologic AML classifications. Logistic regression modeling (LRM) detected mutations in *CEBPA* (both monoallelic "*CEBPA*^{Mo}" and biallelic "*CEBPA*^{Bi}"), *DNMT3A*, *FLT3*^{ITD}, *FLT3*^{TKD}, *GATA2*, *IDH1*, *IDH2*^{R140}, *NRAS*, *NPM1* and *WT1* being enriched in pAML while mutations in *ASXL1*, *RUNX1*, *SF3B1*, *SRSF2*, *U2AF1*, -5/del(5q), -7/del(7q), -17/del(17P), del(20q), +8 and complex karyotype being prevalent in sAML. Despite these significant findings, the genomic profiles of pAML *vs.* sAML identified by LRM resulted in only 74% cross-validation accuracy of the predictive performance when used to re-assign them. Therefore, we applied Bayesian Latent Class Analysis that identified 4 unique genomic clusters of distinct prognoses [low risk (LR), intermediate-low risk (Int-Lo), intermediate-high risk (Int-Hi) and high risk (HR) of poor survival) that were validated by survival analysis. To link each prognostic group to pathogenetic features, we generated a random forest (RF) model that extracted invariant genomic features driving each group and resulted in 97% cross-validation accuracy when used for prognostication. The model's globally most

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important genomic features, quantified by mean decrease in accuracy, included *NPM1*^{MT}, *RUNX1*^{MT}, *ASXL1*^{MT}, *SRSF2*^{MT}, *TP53*^{MT}, -5/del(5q), *DNMT3A*^{MT}, -17/del(17p), *BCOR/L1*^{MT} and others. The LR group was characterized by the highest prevalence of normal cytogenetics (88%) and *NPM1*^{MT} (100%; 86% with VAF>20%) with co-occurring *DNMT3A*^{MT} (52%), *FLT3*$^{ITD\text{-}MT}$ (27%; 91% with VAF<50%), *IDH2*$^{R140\text{-}MT}$ (16%, while absent *IDH2*$^{R172\text{-}MT}$), and depletion or absence of *ASXL1*^{MT}, *EZH2*^{MT}, *RUNX1*^{MT}, *TP53*^{MT} and complex cytogenetics. Int-Lo had a higher percentage of abnormal cytogenetics cases than LR, the highest frequency of *CEBPA*$^{Bi\text{-}MT}$ (9%), *IDH2*$^{R172K\text{-}MT}$ (4%), *FLT3*$^{ITD\text{-}MT}$ (14%) and *FLT3*$^{TKD\text{-}MT}$ (6%) occurring without *NPM1*^{MT}, while absence of *NPM1*^{MT}, *ASXL1*^{MT}, *RUNX1*^{MT} and *TP53*^{MT}. Int-Hi had the highest frequency of *ASXL1*^{MT} (39%), *BCOR*/L1^{MT} (16%), *DNMT3A*^{MT} without *NPM1*^{MT} (19%), *EZH2*^{MT} (9%), *RUNX1*^{MT} (52%), *SF3B1*^{MT} (7%), *SRSF2*^{MT} (38%) and *U2AF1*^{MT} (12%). Finally, HR had the highest prevalence of abnormal cytogenetics (96%), -5/del(5q) (68%), -7del(7q) (35%), -17del(17p) (31%) and the highest odds of complex karyotype (76%) as well as *TP53*^{MT} (70%). The model was then internally and externally validated using a cohort of 203 AML cases from the MD Anderson Cancer Center. The RF prognostication model and group-specific survival estimates will be available via a web-based open-access resource.

In conclusion, the heterogeneity inherent in the genomic changes across nearly 7000 AML patients is too vast for traditional prediction methods. Using newer ML methods, however, we were able to decipher a set of prognostic subgroups predictive of survival, allowing us to move AML into the era of personalized medicine.

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Abstract 986

Validation of the European Leukemianet 2017 Prognostic Classification for Patients with De Novo Acute Myeloid Leukemia Treated with a Risk-Adapted Protocol (CETLAM 2012)

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Introduction: The European LeukemiaNet (ELN) 2017 classification for acute myeloid leukemia (AML) stratifies patients in 3 risk categories, according to genetic features of the disease. ELN classification is commonly used to guide post-remission treatment; favorable risk patients do not seem to benefit from allogeneic hematopoietic transplantation (alloHCT) in first complete remission (CR1) while this procedure is highly recommended in adverse risk patients. Post-remission treatment in intermediate risk patient is still debated. This classification has not been prospectively validated. Herein we analyze the prognostic impact of ELN 2017 classification in patients treated with the same protocol (CETLAM-12), including a well-defined preplanned alloSCT policy according to genetic risk.

Methods: We analyzed characteristics and outcome of patients diagnosed with de novo AML, included in CETLAM-12 protocol for patients up to 70 years, with an available genetic characterization at diagnosis allowing an accurate ELN 2017 stratification. Genetic risk allocation was based on cytogenetic analysis and pre-specified RT-PCR of determined markers (including CBF-rearrangement, NPM1, FLT3, CEBPA, and MLL-PTD) performed in all patients, and targeted Next Generation Sequencing testing (available in 143 patients). CETLAM-12 protocol defines a genetic risk stratification in three groups, closely similar to that proposed by the ELN 2017 classification, and recommends a post-remission strategy based on this risk assessment. Patients from the favorable group received three courses of consolidation with high-dose cytarabine (HiDAC), whereas alloSCT in CR1 is strongly recommended for intermediate and adverse risk patients following one HiDAC-based consolidation course.

Results: We included in the study 813 patients (400F/413M; median age 56, 17–76); with a 37 months median estimated follow-up (range 0.1–92). The outcomes of the entire cohort are shown in **table 1**. Out of all patients, 641 could be classified according to the ELN 2017 classification, due to the presence of risk defining genetic features identified by any of described methods.

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In the group of patients allocated in the favorable risk category (n=316; 49%), twenty-seven patients died during induction. Fifty-eight relapses were observed, mostly in patients with *NPM1* mutation (n=41). AlloSCT was finally performed in CR1 in 84 patients (27%) due to MRD persistence or reappearance (n=40), overt hematological relapse (n=27), persistent aplasia following chemotherapy (n=3) and protocol deviation (n=14).

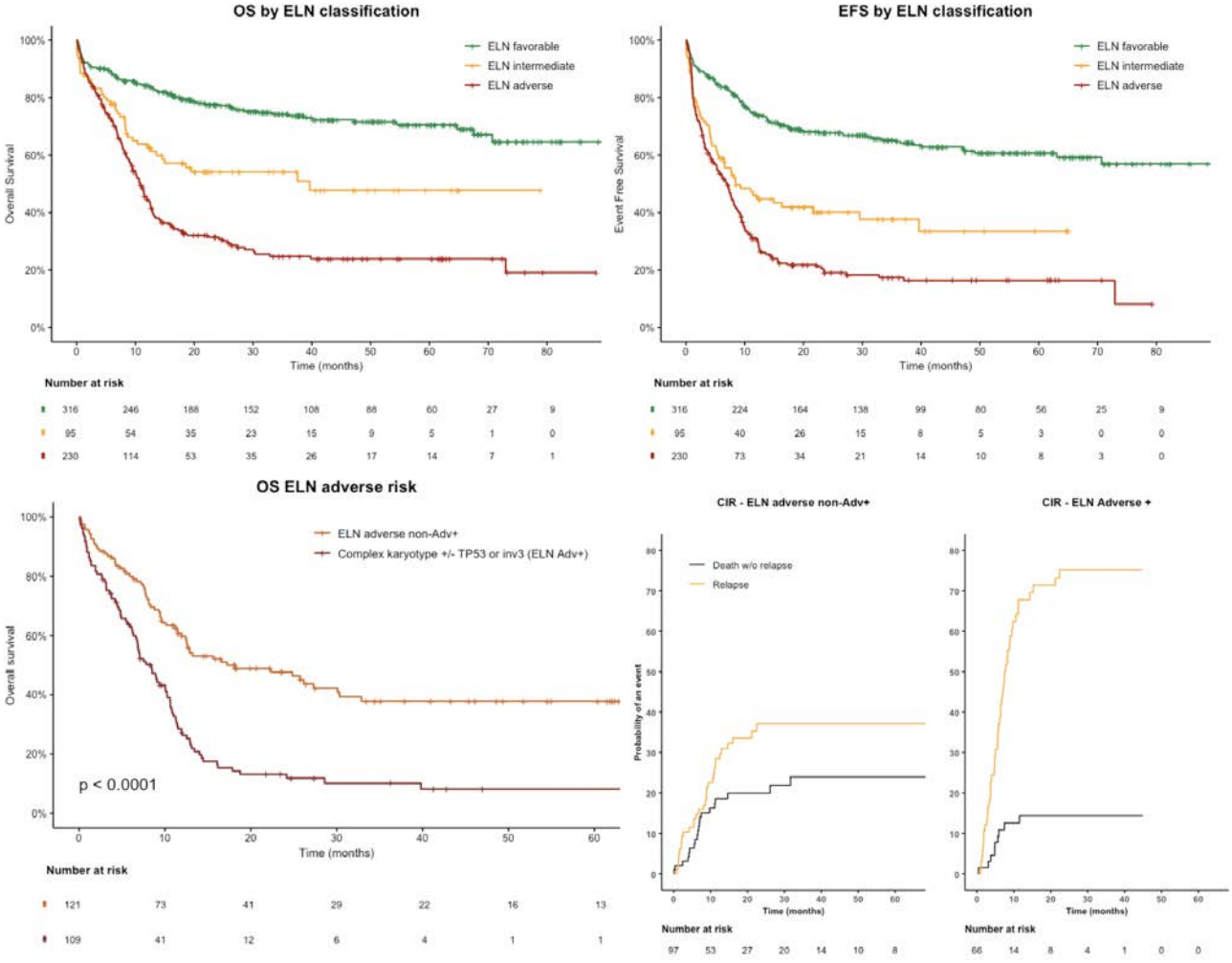
In the group of patients allocated in the intermediate risk category (n=95; 15%), twelve patients died during induction. AlloSCT in CR1 was performed in 62 patients (67%), with 5 patients receiving an alloSCT in CR2.

In the group of patients allocated in the adverse risk category (n=230; 36%), twenty-five patients died during induction. AlloSCT could be finally performed in CR1 in 138 patients (60%) and 88 relapses occurred (42 before alloSCT, 46 after alloSCT). Amongst ELN adverse risk patients, a subgroup with a significant worse outcome has been identified, defined by AML with complex karyotype +/- TP53 mutation or chromosome 3q26/MECOM-GATA2 rearrangement. This group (ELNadv+) presented a lower CR rate, with a higher relapse rate and fewer proportion of patients who receive a pre-planned alloSCT in CR1. OS and EFS of ELNadv+ is significantly lower than ELN adverse patients. In the multivariate analysis for OS including age, sex, WBC count at diagnosis and number of cycles to achieve CR, only age and ELNadv+ status showed independent prognostic value.

Outcome data is summarized in **table** and **figures** attached.

Conclusions : The initial risk-adapted post-remission assignment planned in CETLAM-12 could be performed in the majority of patients. Despite this different proposed post-remission treatment, ELN risk classification was able to identify three groups of patients with a markedly different outcome. Interestingly, within the unfavorable ELN category, a very high-risk ELNadv+ subgroup can be distinguished, with a dismal outcome with current approach, warranting the implementation of innovative pre and post-transplant strategies aimed to prevent treatment failure.

	CR1 n (%)	**OS 2 and 5 years** % (standard error)	**EFS 2 and 5 years** % (standard error)	**CI relapse 2 and 5 years** % (standard error)	**CI non-relapse mortality 2 and 5 years** % (standard error)	**AlloSCT n (%)**
All patients (n=813)	657 (81)	54.9 (1.8) 45.6 (2)	43.4 (1.8) 37.3 (2)	33.8 (2) 38.1 (2.2)	10.5 (1.2) 13.8 (1.5)	390 (48)
ELN favorable (n=316)	286 (90.5)	77.7 (2.5) 70.6 (3)	67.7 (2.7) 60.7 (3.1)	21.4 (2.6) 26.5 (3)	3.7 (1.1) 6.9 (1.8)	84 (26.6)
ELN intermediate (n=95)	75 (78.9)	54.1 (5.5) 47.8 (6.4)	40.1 (5.4) 33.5 (6.3)	32.4 (5.9) 35.3 (6.3)	10.4 (3.8) 14.6 (5.5)	67 (70.5)
ELN adverse (n=230)	163 (70.9)	31.4 (3.1) 23.9 (3.3)	19.1 (2.8) 16.4 (2.8)	52.8 (4.3)	17.2 (3.1) 20 (3.4)	138 (60.3)
p value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
ELN adverse (n=121)	97 (80.2)	47.7 (4.8) 37.9 (5.1)	33.9 (4.6) 28.8 (4.8)	37.1 (5.4)	20 (4.3) 24 (4.9)	87 (71.9)
ELN adverse + (n=109)	66 (60.5)	13.2 (3.5) 8.1 (3.2)	3.1 (1.8) –	75.2 (5.8) –	14.4 (4.5) –	51 (46.8)
p value	<0.01	<0.01	<0.01	<0.01	0.267	<0.01



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Abstract 2883

Prognosis of Acute Myeloid Leukemia with Myelodysplasia-Related Changes According to the Different Subgroups of the WHO 2016 Classification in Patients Candidates to Intensive Chemotherapy

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Introduction: In the WHO 2016 classification, within the category of Acute Myeloid Leukemia with Myelodysplasia-Related Changes (AML-MRC), 3 subgroups are distinguished: 1) AML with Defining Cytogenetic Abnormality (AML-DCA) 2) AML with Previous History of MDS or MDS/MPN (AML-PHM) and 3) AML with Multilineage Dysplasia (AML-MD). The prognostic impact of significant Multilineage Dysplasia in patients without accompanying adverse cytogenetics or a history of prior hematologic malignancy is currently unclear.

Objectives: To analyze the impact of MD as a classification criterion of AML-MRC compared to the rest of AML-MRC subgroups in terms of survival. To analyze if there are characteristics in global cohort that could us to predict worse survival outcomes.

Material and methods: We performed a retrospective analysis of 48 patients candidates to intensive chemotherapy treated in a single center between 2013 and 2019. We divided our cohort into 2 groups 1) AML-MD and 2) AML-DCA + AML -PHM. The baseline characteristics of each group were compared using the Chi^2 test. The survival analysis was performed through Kaplan-Meier method and the risk was calculated with Cox regression. The Overall Survival (OS) was defined as the time from diagnosis to death and the Event-Free Survival (EFS) as the time from diagnosis to either relapse or death. $P<0.05$ was defined as statistically significant difference.

Results: The baseline characteristics of the global cohort are reflected in **Table 1**. The median follow-up of the entire population was 15 months (0–77). The median OS and EFS were 18 months and 11 months, respectively. The median OS was 14 months in group 1 vs 19 months in group 2 with a Hazard Ratio (HR) of 0.9 (95% CI 0.3–2.2, p=0.8). The median EFS in Group 1 was 10 months vs 14 months in group 2 (HR 0.9 95% CI (0.4–2.1), p=0.9) (**Image 1**). In global cohort, 11 patients had a complex karyotype at diagnosis. The median OS in these patients was 23 vs 16 months in those with other cytogenetic alterations or normal karyotype (HR 0.8 (95% CI (0.3–2.1), p=0.8) and EFS 14 vs 10 months [HR 1.1 (95% CI (0.5–2.5), p=0.6]. 34 patients received transplantation (HSCT) as consolidation therapy (33 allogeneic, 1 autologous). In transplanted patients the median OS was 26 months vs 4 months in those that did not consolidate with transplant [HR 4.5 (95% CI 2–10, p<0.0001] and the EFS 14 months vs 3 months [HR=4.2, 95% CI (2–8.5), p=<0.001] (**Image 2**). We performed a multivariate analysis including AML-DM vs AML-DCA + AML -PHM, complex karyotype, European LeukemiaNet classification at diagnosis, response to induction and consolidation with transplantation vs not received transplantation. The variables with a significant HR for EFS were not received transplantation as consolidation therapy [HR 2.8, 95% CI (1.2–6.1), p=0.01] and the response to induction [HR 1.6, 95% CI (1.05–2.4), p=0.3]. The only variable with a significant HR for OS was consolidation with transplantation (HR 3.3 (CI 95 % 1.4–8), p<0.01).

Conclusions: Patients with AML-MRC are a high-risk group in terms of OS and EFS. Although allogeneic transplantation in these patients improves survival, the prognosis remains poor. In our cohort, morphological dysplasia without cytogenetic criteria or previous hematological neoplasia identified a high-risk subgroup with similar results

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to the other two subgroups. The results in the AML-MD subgroup are currently controversial, so we probably need to better characterize this subgroup in future studies.

Table 1. Baseline characteristics of entire cohort

Variables	AML-MD	AML-DCA + AML -PHM
Sex (Male/Female)	5/4	13/26
Age, median (range)	54 (36–64)	59 (32–71)
% of blasts at diagnosis, median (range)	29% (20–40%)	32% (15–100%)
Complex karyotype, n (%)	NA	11 (28.2%)
Previous hematologic malignancy	NA	25 (64.1%)
Previous exposure to hypomethylating agents, n (%)	NA	11 (28.2%)
European LeukemiaNet Classification, n (%)		
– Favorable	0 (0%)	1 (2.1%)
– Intermediate	9 (100%)	20 (51.3%)
– Adverse	0 (0%)	18 (46.2%)
Best response to induction (1 or 2 cycles), n (%)		
– CR/CRi with MRD-	3 (33.3%)	17 (44.7%)
– CR/CRi with MRD+	4 (44.4%)	5 (13.2%)
– Refractory	2 (22.2%)	14 (36.8%)
– Death in induction	0 (0%)	2 (5.3%)
Transplantation consolidation, n (%)	8 (88.9%)	26 (70.8%)
State disease prior to transplantation, n (%)		
– CR/CRi MRD-	4 (50%)	15 (60%)
– CR/CRi MRD+	3 (37.5%)	6 (24%)
– Active Disease	1 (12.5%)	4 (16%)
N° cycles prior to transplant, median	3.3	3.4

CR: Complete Remission; CRi: Complete Remission without hemoperipheral recovery; MRD: Minimal Residual Disease

Image 1. Overall Survival (A) and Event-free Survival (B) comparing Group 1 vs Group 2

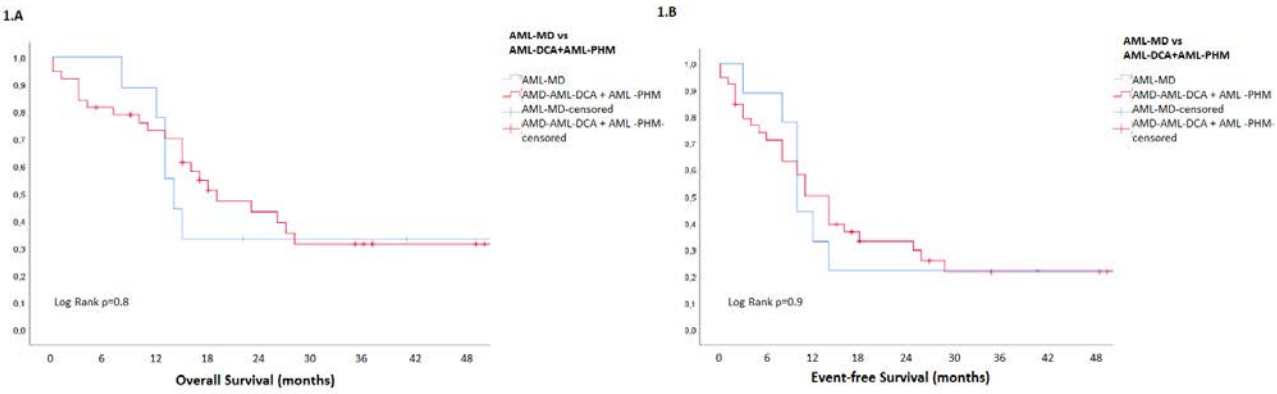
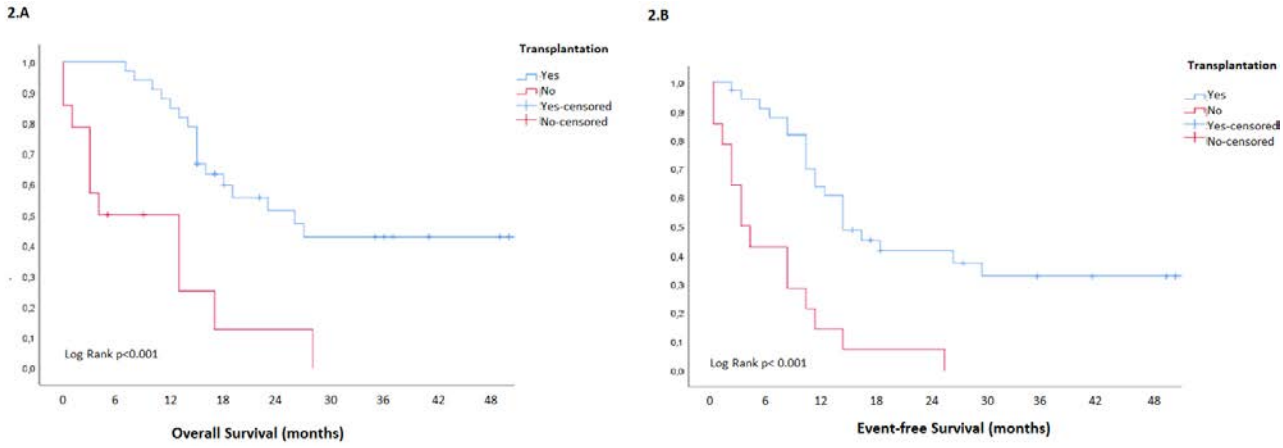


Image 2. Overall Survival (A) and Event-free Survival (B) according to consolidation with allogeneic transplant



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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.

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