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615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

A Phase 1 Dose-Escalation Study of the Cladribine Added to CPX-351 in Patients with Relapsed/Refractory Acute Myeloid Leukemia (AML) - the Polish Adult Leukemia Group AML-1/2018 Study

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Introduction: There is no standard salvage therapy in relapsed/refractory AML (R/R AML). CPX-351, a dual-drug liposomal encapsulation of daunorubicin (DNR) and cytarabine (AraC) in a synergistic 1:5 molar ratio, shows effective antileukemia activity (*Lancet JE, JCO 2018*). Favorable results of cladribine-based salvage regimens (CLAG-M, CLAG) (*Wierzbowska A; Eur J Hematol 2008, Scheckel CJ, Leuk Res. 2020*) as well as first-line therapies (*Hołowiecki J, JCO 2012; Kadia TM Lancet Haematol 2021, Kadia TM JCO 2022*) confirmed a value of cladribine in the treatment of AML.

Aim: This phase I study was designed to explore safety (MTD), toxicity and efficacy of increasing doses of cladribine in combination with standard dose of CPX-351 in R/R AML patients (pts). (EudraCT number: 2020-002535-29).

Results: Twelve pts were enrolled with a median age 65 (range 61-69) years. Importantly, 8 pts (67%) were refractory to the former first- or second- line treatment. Nine pts (75%) were in the adverse risk group according to ELN 2022 including 4 pts with *TP53* ^{mut}. Four pts (33%) were refractory to venetoclax (VEN)-based therapy and 3 pts (25%) had previous alloHCT (Table 1). Three patients (2 in DL1 and 1 in DL2) required two inductions. One patient in DL3 experienced a CNS and GI hemorrhage due to thrombocytopenia refractory to platelet transfusion, which was considered a DLT requiring enrollment of additional 3 pts. No patients discontinued therapy due to intolerance.

Toxicities of grade ≥3 during the induction cycle were mainly infections. All patients developed infections during 1-st cycle of treatment. Blood stream infections (n=5; 42%), febrile neutropenia (n=4; 33%), and pneumonia (n=3; 25%) were the most common infectious events. One episode of grade 5 hemorrhage occurred in a patient with thrombocytopenia refractory to platelet transfusions. Cytopenias in responding pts treated with CPX-351 and cladribine were similar to that observed with CPX-351 alone.

The composite CR (cCR=CR+CRi+CRp) rate was 50% (6/12 pts), 5 pts (42%) not responded and 1 patient died due to CNS hemorrhage before response evaluation but with significant BM blasts clearance at D14. cCR was achieved in 2 out of 3 pts (66%) with intermediate-risk and 4/9 pts (44%) with adverse-risk according ELN 2022. Within the high-risk population, pts with *TP53* ^{mut} had lower probability to achieve remission (1/4; 25%) than pts with myelodysplasia related mutations (3/5; 60%). No remissions were observed in pts refractory or relapsed after VEN-based therapy.

Measurable residual disease (MRD)-negative cCR assessed via multiparameter flow cytometry was achieved in 60% ($n = 3/5$) of MRD-evaluable pts, including all pts (n = 3/3; 100%) in DL3.

All pts achieving cCR had post remission therapy with one (n=1; 8%) or two (n=5; 92%) courses of CPX-351+ cladribine consolidation and 3 pts proceeded to alloHCT. After a median (Me) follow-up of 12.8 months (mos), Me overall survival (OS) was 6.6 mos (95% CI, 2.3-not reached [NR]) for all pts and 9.8 mos (95% CI, 8.07-NR) for those who achieved cCR. Median event-free survival (EFS) was 3.28 mos (95% CI, 0.8-NR) for the study population.

Conclusions: Combination of cladribine with standard dose of CPX-351 is well tolerated. Cladribine dose 5 mg/m ^{2} was selected as RP2D. Safety profile does not indicate any significant additional myelosuppression. Cladribine with CPX-351 shows satisfying clinical activity with cCR rate of 50%, cCR-MRD ^{neg} of 60% and durable remission in some R/R AML patients. Further evaluation of the efficacy and safety of this regimen is needed.

Disclosures Wierzbowska: *Gilead:* Honoraria; *Pfizer:* Honoraria; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Celgene/BMS:* Honoraria; *Novartis:* Honoraria; *Astellas:* Consultancy, Honoraria; *Servier:* Honoraria; *JazzPharmaceuticals/swixx:* Honoraria. **Pluta:** *Jazz Pharmaceuticals (Swixx):* Honoraria, Research Funding; *Celgene/BMS:* Honoraria; *Astellas:* Honoraria; *Pfizer:* Honoraria; *Abbvie:* Honoraria. **Stelmach:** *Novartis:* Honoraria. **Czemerska:** *Celgene/BMS:* Honoraria; *Abbvie:* Honoraria; *Pfizer:* Honoraria; *Sandoz:* Honoraria. **Sobas:** *Abbvie:* Honoraria; *Celgene/BMS:* Honoraria; *Novartis:* Honoraria. **Rybka:** *Pfizer:* Honoraria; *Sanofi:* Honoraria; *Roche:* Honoraria; *Takeda:* Honoraria; *Janssen:* Honoraria; *Amgen:* Honoraria; *Celgen/BMS:* Honoraria; *Abbvie:* Honoraria; *Novartis:* Honoraria. **Wróbel:** *Abbvie:* Honoraria; *Gilead:* Honoraria; *Celgen/BMS:* Honoraria; *Roche:* Honoraria, Research Funding; *Novartis:* Honoraria; *Janssen:* Honoraria; *Amgen:* Honoraria, Research Funding; *Takeda:* Honoraria; *Beigene:* Honoraria; *GSK:* Honoraria. **Prejzner:** *Novartis:* Honoraria; *BMS:* Honoraria; *Pfizer:* Honoraria. **Zaucha:** *Takeda:* Honoraria; *BMS:* Research Funding; *Roche:* Honoraria; *Janssen:* Honoraria; *MSD:* Research Funding; *Novartis:* Honoraria; *Gilead:* Honoraria; *Abbvie:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Gil:** *Abbvie:* Honoraria; *Astellas:* Honoraria; *Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Honoraria; *Celgene/BMS:* Honoraria; *Novartis:* Honoraria; *Janssen:* Honoraria. **Giebel:** *Zentiva:* Consultancy, Honoraria; *BMS:* Honoraria, Speakers Bureau; *Angelini:* Honoraria, Speakers Bureau; *Swixx:* Honoraria, Speakers Bureau; *Servier:* Honoraria, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Speakers Bureau; *Pfizer:* Consultancy, Honoraria, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Speakers Bureau; *Gilead:* Consultancy, Honoraria, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Speakers Bureau; *Amgen:* Consultancy, Honoraria, Speakers Bureau; *Roche:* Consultancy, Honoraria, Speakers Bureau.

OffLabel Disclosure: Cladribine in combination with CPX-351 in AML

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Table 1. Characteristic of patients

Characteristic	Overall (N = 12)	DL1 (N = 3)	DL2 (N = 3)	DL3 (N = 6)
Age, median (range)	65 (61-69)	66 (66-69)	65 (63-65)	64 (61-66)
Gender, n/N (%)				
Female	7/12 (58%)	3/3 (100%)	1/3 (33%)	3/6 (50%)
Male	5/12 (42%)	0/3 (0%)	2/3 (67%)	3/6 (50%)
Bone marrow blasts %, median (range)	60 (20-83.5)	68.5 (38.8-76.4)	52 (30-83.5)	53 (20-72)
ECOG , n/N (%)				
0	2/12 (17%)	0/3 (0%)	0/3(0%)	2/6 (33%)
1	10/12 (83%)	3/3 (100%)	3/3 (100%)	4/6 (67%)
Disease, n/N (%)				
Relapse	4/12 (33%)	0/3 (0%)	1/3 (33%)	3/6 (50%)
Refractory	8/12 (67%)	2/3 (67%)	2/3 (67%)	4/6 (67%)
Prior treatment, n/N (%)	12/12 (100%)	3/3 (100%)	3/3 (100%)	6/6 (100%)
Lines of therapy, n/N (%)				
1	6/12 (50%)	0/3 (0%)	2/3 (67%)	4/6 (67%)
2	6/12 (50%)	3/3 (100%)	1/3 (33%)	2/6 (33%)
Prior Ven based therapy, n/N (%)	5/12 (42%)	2/3 (67%)	1/3 (33%)	2/6 (33%)
Prior allo-SCT therapy, n/N (%)	3/12 (25%)	1/3 (33%)	0/0 (0%)	2/6 (33%)
2022 ELN risk group, n/N (%)				
Intermediate	3/12 (25%)	0/0 (0%)	1/3 (33%)	2/6 (33%)
Adverse	9/13 (75%)	3/3 (100%)	2/3 (67%)	4/6 (67%)

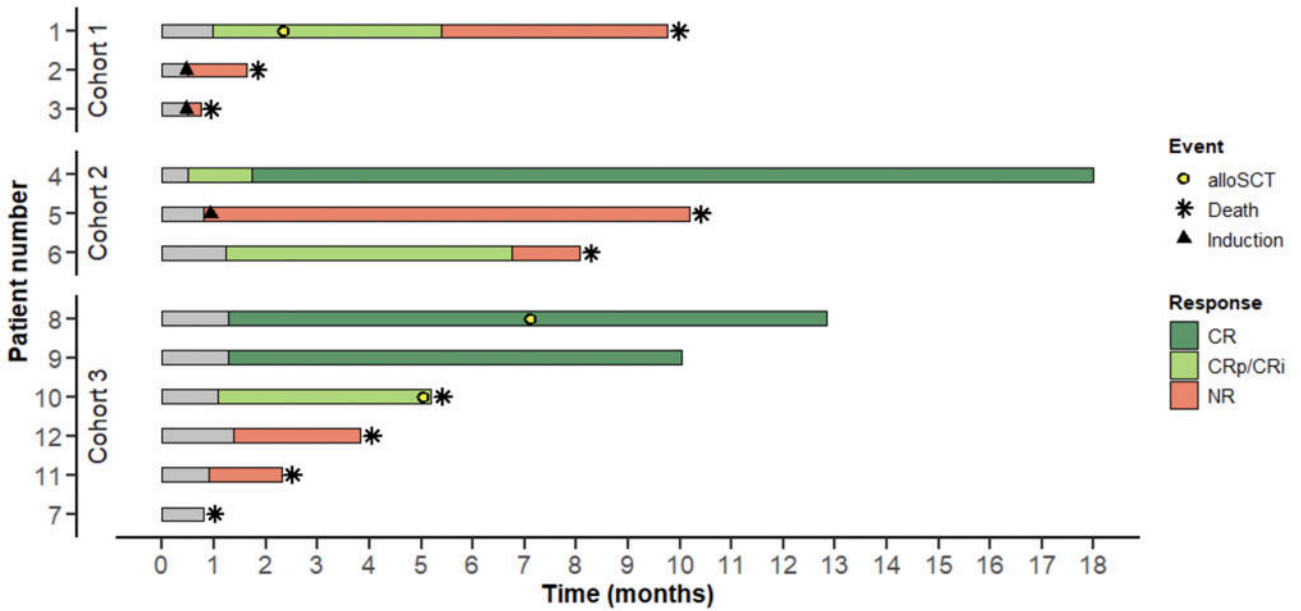

Figure 1. Response to treatment and overall survival

Figure 1