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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Results of a Phase 1/2 Study of Lower Dose CPX-351 for Patients with Int-2 or High Risk IPSS Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia after Failure to Hypomethylating Agents

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INTRODUCTION: Hypomethylating agents (HMAs) are the standard of care for patients (pts) with higher-risk myelodysplastic syndromes (HR-MDS) and chronic myelomonocytic leukemia (CMML). HMA failure (HMA-F) is associated with poor outcomes and median survival of 4 to 6 months. CPX-351 is a drug liposomal encapsulation of cytarabine (araC) and daunorubicin (dauno) at a synergistic 5:1 molar ratio approved for the treatment of pts with therapy-related acute myeloid leukemia (AML) or AML with MDS-related changes. Here we present the results of a phase I-II study of lower dose CPX-351 for HR-MDS and CMML after HMA-F.

METHODS: We conducted a phase I/II clinical trial of CPX-351 for pts with MDS or CMML after HMA-F with Int-2 or High risk by IPSS, or Int-1 with >10% bone marrow (BM) blasts. The study included an initial phase I dose-escalation portion, following a 3+3 design, followed by a phase II dose expansion portion. Dose escalation included 4 dose levels of CPX-351: 10 units/m ^{2} (dauno 4.4mg/m ^{2} and araC 10mg/m ^{2}), 25 units/m ^{2} (dauno 11mg/m ^{2} and araC 25mg/m ^{2}), 50 units/m ^{2} (dauno 22mg/m ^{2} and araC 50mg/m ^{2}) and 75 units/m ^{2} (dauni 33mg/m ^{2} and araC 75mg/m ^{2}). Therapy was administered intravenously on days 1, 3 and 5 of 28-day cycles during induction and on days 1 and 3 of re-induction or consolidation. Re-induction was allowed in pts not achieving response after induction. The primary end point was to evaluate safety and determine the maximum tolerated dose of CPX-351. Responses were evaluated following 2006 IWG criteria. The Kaplan-Meir product-limit method was used to estimate median survival.

RESULTS: Between June 2019 and September 2022, 23 pts have been treated: 15 in the phase I portion, and 8 in the phase II. A total of 17 pts had MDS, and 6 had CMML. Four (17%) pts had intermediate-1 risk IPSS and >10% blasts, 15 (65%) had intermediate-2 and 4 (17%) had high-risk IPSS. Median number of prior therapies was 1 (range 1-4) including 4 (17%) pts with failure to prior venetoclax therapy and 2 (9%) with prior HSCT.

In the phase I portion, 3 pts received CPX-351 at dose level 1, 3 at dose level 2, 3 at dose level 3 and six at dose level 4. One pt treated at dose level 4 developed grade 2 congestive heart failure with grade 2 reduction in left-ventricular ejection fraction (LVEF). No additional DLTs were detected during the 28-day DLT evaluation window. The initial two pts treated at the P2RD of 75units/m ^{2} during phase II experienced cardiac complications: grade 3 congestive heart failure without reduction in LVEF and grade 3 right-sided heart failure, respectively. Study was amended to continue further treatment in phase II at dose level 3 (50units/m ^{2}).

Most common adverse events (AEs) were lower extremity edema (n=12, 52%), febrile neutropenia (n=11, 48%), dyspnea (n=10, 44%), mucositis (n=10, 44%), constipation (n=9, 39%), diarrhea (n=9, 39%), and generalized muscle weakness (n=9, 39%). Most common grade 3-4 AEs were febrile neutropenia (n=11, 48%), neutropenia (n=5, 22%), lung infection (n=4, 17%), diarrhea (n=4, 17%) and thrombocytopenia (n=3, 13%). The 4-week and 8-week cumulative incidences of mortality were 0% and 4%, respectively. Median number of days to cycle 2 was 47 days (range 30-83). Dose reductions of CPX-351 occurred in 4 (17%) pts. Median number of cycles was 3 (range 1-9). Median cycles to best response was 1 (range 1-3). Among pts with HR-MDS, the ORR was 71% (n=12): CR in 1 (6%), mCR with HI in 1 (6%) and mCR in 11 (59%) pts (Fig 1A). Among pts

with BM blast reduction to <5% by the end of cycle 1, 11 (65%) and 9 (53%) had ANC recovery to >0.5x10 ^{9}/L and >1x10 ^{9}/L, respectively, and 8 (47%) and 6 (35%) had platelet recovery to >50x10 ^{9}/L and >100x10 ^{9}/L, respectively. Based on 2023 IWG response criteria, the ORR was 59% (n=10) including CR in 1 (6%), CR bilineage (CRbi) in 4 (24%) and CR unilineage in 5 (29%). Of 11 (65%) pts with baseline cytogenetic abnormalities, 2 (18%) and 2 (18%) achieved complete and partial cytogenetic responses, respectively. Three (13%) pts underwent HSCT at time of best response. Among pts with CMML (n=6), only one (17%) achieved response. Median response duration was 4.5 months (95% CI 0.7-8.2 months) and the median OS was 12.6 months (95% CI 3.6-21.7 months) (Fig 1B).

CONCLUSIONS: Lower doses of CPX-351 in HR-MDS after HMA-F can induce clinically meaningful responses and be used as a bridge to allogeneic stem-cell transplant. Therapy is associated with median OS of 12.6 months in this population with expected survival of 4-6 months.

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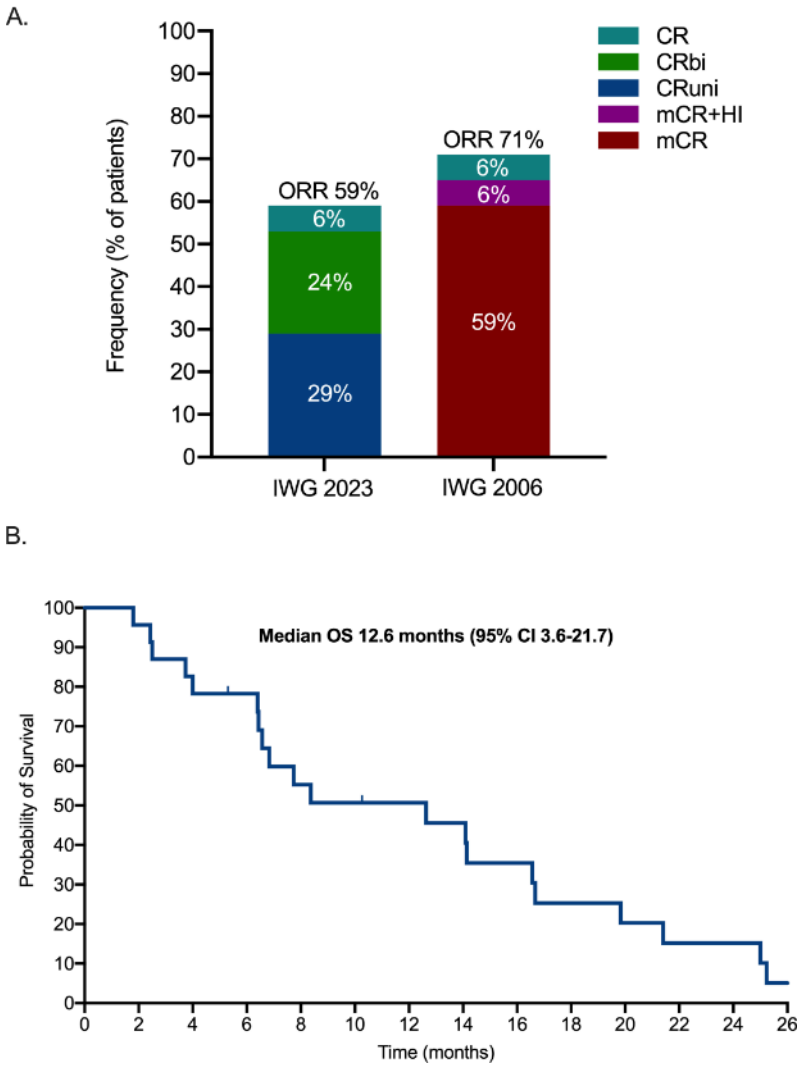

Figure 1

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