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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Results of Phase I/II Study of Azacitidine in Combination with Quizartinib for Patients with Myelodysplastic Syndromes and Myelodysplastic/Myeloproliferative Neoplasms with *FLT3* or *CBL* Mutations

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Introduction: FMS-like tyrosine kinase 3 (*FLT3*) mutations occur in approximately 1% of patients (pts) with newly diagnosed myelodysplastic syndrome (MDS) and up to 19% of pts at time of failure to hypomethylating agents (HMA). In addition, mutations in the Casitas B-lineage Lymphoma gene (*CBL*) are observed in 10% of pts with MDS/MPN and up to 15% of pts with CMML. Preclinical studies suggest that *CBL*-mutant cells are dependent on FLT3 signaling. Here we present results of a phase I-II study of the FLT3 inhibitor quizartinib in combination with azacitidine for pts with *FLT3* and *CBL* mutant MDS and MDS/MPN.

Methods: We conducted a phase I/II clinical trial of azacitidine in combination with quizartinib for pts with MDS and MDS/MPN with detectable *FLT3* and/or *CBL* mutations and with/without prior failure to HMA (HMA-F). 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 3 dose levels of quizartinib: 30, 40 and 60 mg administered p.o daily on days 1-28 of each 28 day cycle. Therapy consisted on quizartinib (at corresponding dose level) in combination with azacitidine 75 mg/m ^{2}/day i.v os s.c on days 1-5. The primary endpoint was to evaluate safety, tolerability and maximum tolerated dose of quizartinib. Responses were evaluated following 2006 IWG criteria. The Kaplan-Meier product-limit method was used to estimate median survival.

Results: Between July 2020 and June 2023 a total of 16 pts have been treated: 12 in the phase I portion and 4 in the phase II. A total of 4 pts had MDS with excess blasts, 2 had MDS/MPN with neutrophilia and 10 had CMML. Eight (50%) pts had *FLT3-ITD* mutations and 8 (50%) had *CBL* mutations. Four (25%) pts had HMA-F one of which had received 4 lines of therapy including hematopoietic stem-cell transplant (HSCT) prior to enrollment. Based on the Molecular IPSS, 8 (50%), 3 (19%) and 5 (31%) pts had very high, high and moderate high risk disease. Among CMML pts, 3 (30%) pts had high and 7 (70%) had intermediate-2 risk by CPSS-Molecular score.

In the phase I portion, 3 pts received quizartinib at dose level 1, 3 at dose level 2 and 6 at dose level 3. No dose limiting toxicities were detected during the 28-day DLT evaluation window. Dose level 2 was selected as the P2RD.

Most common adverse events (AEs) were constipation (56%), fatigue (50%), insomnia (44%), anorexia (38%), cough (38%), diarrhea (38%) and arthralgia (31%). Most common grade 3-4 AEs were anemia (31%), thrombocytopenia (31%), lung infection (13%), skin infection (13%), hyponatremia (13%) and sepsis (13%). Arrythmias were observed 5 pts: atrial fibrillation (grade 2, n=2; grade 3, n=1), Mobitz type II atrioventricular block (grade 3, n=1), atrial flutter (grade 2, n=1), QTC prolongation (grade 2, n=1). The 4-week and 8-week cumulative incidences of mortality were 0%. Median number of days to cycle 2 was 30 (range 27-51). Median number of days to cycle 2 of therapy by dose level were: 30, 30 and 37 days for dose levels 1, 2 and 3, respectively (p=0.301). Dose reductions due to myelosuppression were required in 5 (31%) pts including dose reductions of azacitidine in 3 pts and of quizartinib in 3 pts. Median number of cycles was 4 (range 1-17). Median cycles to to best response was 1 (range 1-6). The overall response rate was 69% (n=11): CR in 1 (6%), mCR with HI in 2 (13%), mCR in 8 (50%) pts. *FLT3* mutant pts were more likely to respond to therapy (100% vs 50%, p=0.038). Clearance (n=6, 75%) or allelic burden reductions (n=2, 25%) of *FLT3-ITD* mutations were observed in all *FLT3* mutant pts. No clearance of *CBL* mutations were observed.

Dynamics of absolute neutrophil count, platelets and hemoglobin during cycle 1 are shown in Figure 1A. Median response duration was 3.5 months (range 0-22 moths). With a median follow up of 19.1 months (95% CI 2.6-35.6), the median event-free survival has not been reached and the median overall survival is 17.5 months (NR vs 10.1 months in *FLT3* vs *CBL* mutant pts, p=0.084, Figure 1B)

Five (31%) pts discontinued study to proceed with HSCT at time of best response, 3 (19%) due to transformation to AML, 2 (12%) due to pt choice, 1 (6%) due to treating physician choice and 1 (6%) due to relapse. Four (25%) pts remain on study.

Conclusion: Therapy with azacitidine in combination with quizartinib for pts with higher-risk MDS and MDS/MPN with *FLT3* or *CBL* mutations has acceptable toxicity profile and is associated with promising responses mainly among *FLT3*-mutant pts.

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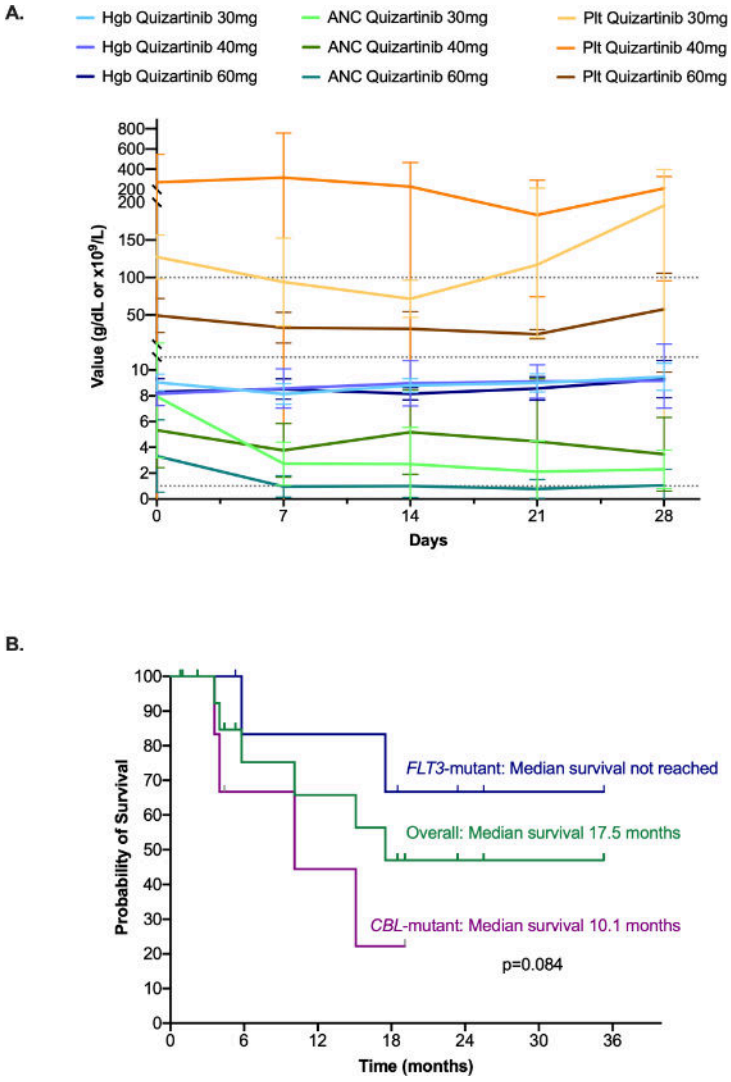

Figure 1

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