Abstract: P540

Title: SAFETY AND ACTIVITY OF REVUMENIB IN COMBINATION WITH FLUDARABINE/CYTARABINE (FLA) IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE LEUKEMIAS

Abstract Type: Poster Presentation

Topic: Acute myeloid leukemia - Clinical

Background:

The menin-KMT2A interaction is a critical dependency in many acute leukemias, including *KMT2A*-rearranged (*KMT2Ar*) acute leukemia, *NPM1*-mutant (*NPM1m*) acute myeloid leukemia (AML), and *NUP98*-rearranged (*NUP98r*) AML. Patients with these aberrations, particularly relapsed infant and pediatric patients, have dismal response rates and poor overall survival. Single-agent revumenib, an oral selective inhibitor of the menin-KMT2A complex, has demonstrated encouraging activity with acceptable safety in patients (pts) with multiply relapsed acute leukemias (*Nature*. 2023;615[7954]:920-924).

Aims:

To describe safety and preliminary activity of revumenib in combination with multi-agent chemotherapy and determine the recommended phase 2 dose (RP2D) (NCT05326516).

Methods:

Eligible pts were aged ≥30 d with *KMT2Ar*, *NPM1m*, or *NUP98r* and adequate organ function. Pts with extramedullary and/or medullary relapse were allowed. Revumenib, administered every 12 h x 28 d, was combined with fludarabine (30 mg/m2 intravenously [IV] x 5 d) and cytarabine (2000 mg/m2 IV x 5 d) (FLA). Revumenib dose escalation used a Bayesian optimal interval design with 2 dose levels (DLs): DL1 (113 mg/dose [65 mg/m2 if <40 kg]) and DL2 (163 mg/dose [95 mg/m2 if <40 kg]). Disease response was assessed before initiation of each cycle.

Results:

As of 15 January 2024, 27 pts (median age, 6 y [range, 0.8–78]) received revumenib plus FLA at DL1 (n=9) or DL2 (n=18). Twenty (74%) were aged <18 y, and 5 (19%) were <2 y. *KMT2Ar, NPM1m*, and *NUP98r* acute leukemias were reported in 24 (89%), 2 (7%), and 1 (4%) pts, respectively. Nineteen pts (70%) had ≥3 prior lines of treatment, including 11 pts (41%) with prior hematopoietic stem cell transplants (HSCTs). Most common adverse events (>50%) were decreased platelet count and anemia (**Table**). QTc prolongation (grade ≥2) was reported in 4 pts (15%). No differentiation syndrome (DS) was reported. Dose-limiting toxicities occurred at DL1 (increased alanine aminotransferase [grade 3]) and DL2 (decreased neutrophil count [grade 4] in pt with multiple prior transplants); both pts recovered. There was 1 adverse event leading to death (sepsis in DL1). Among 9 pts treated at DL1, 4 (44% [95% CI, 13.7–78.8]) achieved a composite complete response (CRc=CR+CRi+CRp), 1 (11%) had stable disease, 2 (22%) progressed, and 2 (22%) died before first assessment. Among 18 pts treated at DL2, 9 (50% [95% CI, 26.0–74.0]) achieved CRc, 6 (33%) had stable disease, and 3 (17%) had progressive disease. Nearly all pts with CRc and available data achieved MRD negativity (12/13, 92%); 5 pts (38%) underwent HSCT, 2 pts underwent HSCT after additional chemotherapy, 2 pts relapsed, and 4 pts were still on treatment at data cutoff. For DL2, median time to response was 1.0 mo; median duration of response was not reached (95% CI, 9.2 mo– NR)

Summary/Conclusion:

Revumenib combined with FLA was tolerable in heavily pretreated pts with *KMT2Ar*, *NUP98r*, or *NPM1m* acute leukemias without increased frequency or severity of adverse events compared with historic FLA data or revumenib monotherapy. Fewer cytopenias were reported in DL2 than DL1, consistent with faster remission at

DL2. There were no cases of DS or grade 3 QTc prolongation. Preliminary efficacy in this mostly pediatric population was similar to that observed with revumenib monotherapy. Results support selection of DL2, corresponding with the monotherapy RP2D of revumenib, as a safe and effective dose for the FLA combination. Additional trials of revumenib combination therapy are ongoing.

Table. Safety Profile[a]

All terms	Dose level 1 (n=9)	Dose level 2 (n=18)	Overall (N=27)
Adverse events, n (%)			
Any adverse event	9 (100)	17 (94)	26 (96)
>20% adverse event (overall)			
Decreased platelet count	7 (78)	10 (56)	17 (63)
Anemia	5 (56)	9 (50)	14 (52)
Diarrhea	6 (67)	7 (39)	13 (48)
Febrile neutropenia	5 (56)	8 (44)	13 (48)
Vomiting	3 (33)	10 (56)	13 (48)
Decreased white blood cell count	4 (44)	6 (33)	10 (37)
Decreased neutrophil count	5 (56)	4 (22)	9 (33)
Increased alanine aminotransferase	3 (33)	5 (28)	8 (30)
Increased aspartate aminotransferase	2 (22)	6 (33)	8 (30)
Nausea	3 (33)	5 (28)	8 (30)
Pyrexia	2 (22)	6 (33)	8 (30)
Headache	3 (33)	3 (17)	6 (22)
Decreased lymphocyte count	3 (33)	3 (17)	6 (22)
Sepsis	3 (33)	3 (17)	6 (22)
Grade ≥3 adverse events	9 (100)	16 (89)	25 (93)
>20% adverse event (overall)			
Decreased platelet count	7 (78)	10 (56)	17 (63)
Anemia	5 (56)	9 (50)	14 (52)
Febrile neutropenia	5 (56)	8 (44)	13 (48)
Decreased white blood cell count	4 (44)	6 (33)	10 (37)
Decreased neutrophil count	5 (56)	4 (22)	9 (33)
Increased alanine aminotransferase	3 (33)	3 (17)	6 (22)
Decreased lymphocyte count	3 (33)	3 (17)	6 (22)
Sepsis	3 (33)	3 (17)	6 (22)
Adverse event leading to revumenib discontinuations	2 (22)	1 (6)	3 (11)
Sepsis	1 (11)	1 (6)	2 (7)
Increased alanine aminotransferase	1 (11)	0	1 (4)
Bacteremia	1 (11)	0	1 (4)
Increased blood bilirubin	1 (11)	0	1 (4)
Adverse event leading to revumenib reductions	1 (11)	0	1 (4)
Increased alanine aminotransferase	1 (11)	0	1 (4)

[a]Data cutoff: 15 January 2024.

Keywords: Relapsed acute myeloid leukemia, Relapsed acute lymphoblastic leukemia, KMT2A, NUP98