5206: Revumenib in combination with intensive induction and consolidation for newly diagnosed patients with *NPM1*-mutated or *KMT2A*-rearranged Acute Myeloid Leukemia: Preliminary results from the Phase 1b ETCTN 10596 study

Alice S. Mims[1], Lai Wei[1], Eric McLaughlin[1], Jayanshu Jain[1], Joshua F. Zeidner[2], Olatoyosi Odenike[3], Sangeetha Venugopal[4], James S. Blachly[1], Vu Duong[5], Anand Patel[3], Eric Eisenmann[6], Shelley Orwick[6], Daelynn Buelow[6], Gregory Behbehani[1], Richard Little[7], Steven Gore[7], Sharyn D. Baker[6]

[1]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [2]University of North Carolina, Chapel Hill, NC; [3]University of Chicago, Chicago, IL; [4]University of Miami, Miami, FL; [5]University of Maryland, Baltimore, MD; [6]The Ohio State University College of Pharmacy, Columbus, OH; [7]National Cancer Institute, Bethesda, MD

Background

- Revumenib is a first-in-class FDA-approved, oral menin inhibitor that has shown efficacy in patients with relapsed and refractory (R/R) Acute Myeloid Leukemia with *NPM1* mutations (*NPM1m*) or *KMT2A*-rearrangements (*KMT2Ar*) Acute Leukemias (AL)
- Revumenib has also shown activity in other subtypes of AL, including NUP98 alterations
- *NPM1m* occur in approximately 30% of adult patients with newly diagnosed AML while *KMT2Ar* occur in approximately 10% of this population
- Given the clinical activity in R/R AML, we investigated whether revumenib can be safely added to intensive induction and consolidation therapy in the upfront treatment setting for adult patients with AML

Methods

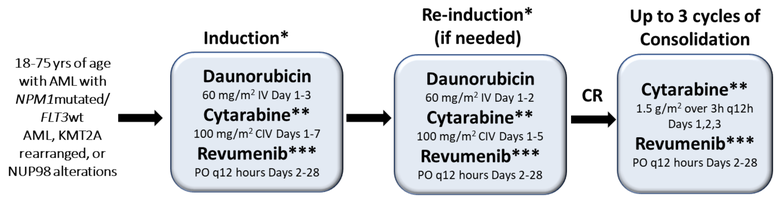
- Phase 1, multi-center, dose-escalation and expansion study through the Experimental Therapeutics Clinical Trials Network (ETCTN)
- Primary Endpoints: To determine the safety and recommended phase 2 dose of Revumenib with 1) Induction and 2) Consolidation
- Secondary Endpoints: 1) Pharmacokinetic analysis of revumenib 2) Complete Remission (CR) and CR with incomplete recovery rate (CRi)
- Abbreviated Inclusion: adults aged 18-75 years with newly diagnosed AML with high-risk *NPM1*m/*FLT3* wildtype (age ≥ 60 years, secondary AML, or ELN 2022 adverse-risk genetics) or *KMT2Ar* or *NUP98* alterations; adequate organ function; WBC <25,000x10^9/L; EF>50%
- Abbreviated Exclusion: baseline QTcF > 450ms; meeting lifetime anthracycline exposure; strong or moderate inhibitors or strong inducers of CYP3A4 within 7 days of enrollment with exception of azole antifungals
- Bayesian optimal interval design (BOIN) with a target dose-limiting toxicity (DLT) rate of 20% guided dose-escalation. This was assessed separately for induction and consolidation. This design used a 75% dose-elimination cut-off, cohort size of 3, and the maximum sample size of 18 dose-limiting toxicity evaluable patients.
- DLT window for induction, reinduction (if needed) and cycle 1 consolidation is Days 1-42 or until full count recovery with recovery to grade 1 toxicity from treatment, whichever comes first.

Table 1. Dose Levels of Revumenib

Revumenib Induction Dose Levels	Revumenib Dose (mg) (BID dosing)	Dose (mg) adjustment with strong CYP3A4 inhibitor antifungal use (BID dosing)	Dosing Schedule
-1a	160	75	Q12H on Days 2-28
1a	220	110	
2a	270	160	

Study Schema

Figure 1. Study Schema for Dose Escalation



*Reinduction allowed if midcycle marrow with significant morphological residual disease without a hypocellular marrow (specific criteria in protocol)

**Cytarabine is given as a continuous intravenous infusion (CIV) during induction and reinduction. During consolidation, cytarabine dosing will be given as 1 or 1.5g/m² based on age and creatinine clearance

***Revumenib will be given per dose assignment

Results

Table 2. Baseline characteristics.

Characteristic	Patient n=15
Age, median (range), y	55 (26-72)
Female, n (%)	7 (46.6%)
High risk *NPM1*/*FLT3*wt, n (%)	8 (53.3%)
KMT2Ar, n (%)	7 (46.6%)

AEs of special interest: There were no reports at any grade of Differentiation syndrome, QTcF prolongation, or neuropathy

Table 3. Most frequent grade ≥ 3 adverse events.

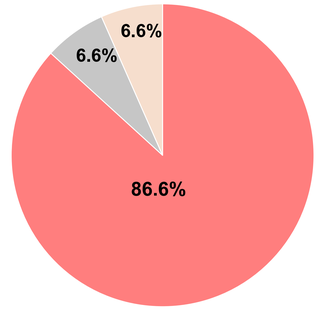
Grade ≥ 3 AEs	n (%)
Hematologic	
WBC decrease	12 (80%)
Neutrophil decrease	12 (80%)
Platelet decrease	11 (73%)
Anemia	11 (73%)
Lymphocyte decrease	10 (67%)
Febrile neutropenia	7 (47%)
Metabolic	
Hypokalemia	3 (20%)
Hypocalcemia	2 (13%)
Hyperglycemia	2 (13%)
Infection	
Lung	2 (13%)
Skin	2 (13%)
Sepsis	2 (13%)
Typhlitis	2 (13%)

Table 4. Dose limiting toxicities (DLTs)

Dose Level	Treatment Course	Patients Treated, n	DLT, n	Event(s)
1	Induction	6	0	None
2	Induction	9	2	1) Gr 5 typhlitis 2) failure to recover platelet count to ≥ 50,000/µby Day 42
1	Consolidation	3	0	None
2	Consolidation	10	0	None

Results (continued)

Figure 2. Response Rates after Induction



- 15 patients have been enrolled
- 6 patients (40%) remain on treatment
- 5 patients (33.3%) proceeded to allogeneic stem cell transplant (allo-SCT)
- 2 patients have died (13%)
  - 1 during induction
  - 1 from complications of allo-SCT
- 6 patients had mid-induction bone marrow biopsies with elevated blast counts (7-18%)
  - All achieved CR without requiring reinduction

Conclusions/Next Steps

- Revumenib can be combined safely at a dose of 270mg PO BID with both 7+3 induction and high-dose cytarabine consolidation.
- The complete remission rate with induction was high at 86.6% with a CR/CRi rate of 93.2%
- There have been no reported cases of differentiation syndrome or QTcF prolongation that have occurred to date.
- Mid-induction bone marrow biopsies in patients receiving differentiating agents may not be warranted.
- Pharmacokinetic/pharmacodynamic analysis are ongoing.
- Two dose expansion cohorts will be opening: a) to further assess the safety, tolerability, efficacy, and PK/PD to confirm the RP2D of revumenib with induction and consolidation and b) to assess the impact of revumenib on cell cycle with a monotherapy lead-in prior to induction.

References

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