Revumenib in Patients With Acute Leukemias: Compassionate-Use (Single-Patient Protocol) Program Experience

P561

Jeffrey Rubnitz,[1] Ghayas C. Issa,[2] Eytan M. Stein,[3] Neerav Shukla,[3] Wendy Stock,[4] Andrius Žučenka,[5,6] Sajad Khazal,[2] Nandita Khera,[7] Elliot Stieglitz,[8] Jeremy Rubinstein,[9] Galit Rosen,[10] Rachel Ghiraldi,[10] Huy Van Nguyen,[10] Nicole McNeer,[10] C. Michel Zwaan[11]

[1]St. Jude Children's Research Hospital, Memphis, TN, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]University of Chicago, Chicago, IL, USA; [5]Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; [6]Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [7]The Mayo Clinic, Phoenix, AZ, USA; [8]The University of California, San Francisco, San Francisco, CA, USA; [9]Cincinnati Children's Hospital, Cincinnati, OH, USA; [10]Syndax Pharmaceuticals, Inc, Waltham, MA, USA; [11]Princess Máxima Center, Utrecht, and Erasmus MC, Rotterdam, The Netherlands

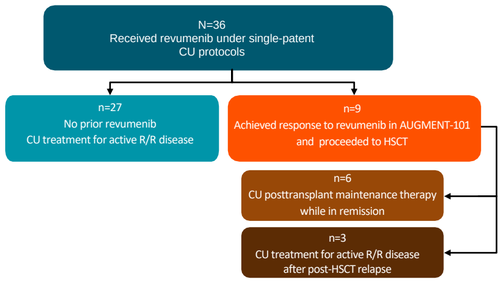
INTRODUCTION

- Revumenib (SNDX-5613) is a menin inhibitor under investigation in patients with relapsed/refractory (R/R) acute leukemias harboring either histone-lysine N-methyltransferase 2A rearrangements (*KMT2Ar*, previously *MLLr*) or nucleophosmin 1 mutations (*NPM1*^{mut})[1]
- The menin-KMT2A interaction is important in acute leukemias with *KMT2Ar* or *NPM1*^{mut}
  - *KMT2Ar* occurs in ~5% to 10% of patients with acute leukemia, and the menin-KMT2A fusion protein interaction drives aberrant expression of *HOX* cluster genes and *MEIS1*, activating a leukemogenic transcription program[2,3]
  - *NPM1*^{mut} are found in >30% of patients with acute myeloid leukemia (AML) and are associated with overexpression of *HOXA*, *HOXB*, and *MEIS1* genes via the menin-KMT2A wild-type interaction[4,5]
- A phase 1/2 study of revumenib in pediatric and adult patients with R/R acute leukemias, AUGMENT-101 (NCT04065399), is ongoing and initial results in 68 phase 1 patients were recently published[1]
  - In phase 1, 18 of 60 evaluable patients (30% [95% CI, 18.8-43.2]) had complete response (CR) or complete response with partial hematologic recovery (CRh); 14 of these 18 patients (78%) had no measurable residual disease (MRD) as assessed by multiparameter flow cytometry
  - Revumenib was associated with a low frequency of grade ≥3 treatment-related adverse events (TRAEs); asymptomatic prolongation of the QT interval on electrocardiography was the only dose-limiting toxicity identified
  - Phase 2 of AUGMENT-101 was initiated with a recommended dose of 163 mg every 12 hours to be taken with a strong cytochrome P450 3A4 inhibitor (CYP3A4; eg, an azole antifungal)
- A compassionate-use program was made available for patients with R/R acute leukemias ineligible for AUGMENT-101
  - Data on clinical activity of revumenib treatment among pediatric patients with R/R acute leukemias on AUGMENT-101 and compassionate-use protocols have been presented at the American Society of Pediatric Hematology/Oncology 2023[6]
- Here we report the clinical activity and safety of single-agent revumenib as posttransplant maintenance after AUGMENT-101 together with its use as salvage therapy in patients with characteristics or comorbidities that exclude them from AUGMENT clinical trials

METHODS

- Patients from the United States, the United Kingdom, France, Israel, Lithuania, Canada, and the Netherlands with R/R acute leukemias with genetic alteration associated with *HOXA* overexpression who had exhausted all other approved treatment options were treated with compassionate-use revumenib with or without concomitant strong azole CYP3A4 inhibitors under single-patient protocols (Figure 1)
  - In patients receiving treatment for active disease, revumenib dose holds were permitted to allow for intensive treatment in attempts to control disease
- Demographic data were collected from individual patient medical histories noted within the single-patient protocols
- Clinical activity and adverse event (AE) reporting were requested in each protocol
  - Events were extracted from physician reports and communications; therefore, data may be more limited than typically reported in clinical trials
- Data are summarized separately for patients who received treatment for active disease versus maintenance therapy

Figure 1. Distribution of patients enrolled in single-patient protocols in a compassionate-use program.



CU, compassionate use; HSCT, hematopoietic stem cell transplant; R/R, relapsed/refractory.

RESULTS

BASELINE DEMOGRAPHICS

- From October 2019 to December 2022, 36 patients with R/R acute leukemia received revumenib monotherapy under single-patient compassionate-use protocols (Figure 1)
  - Reasons for trial ineligibility included age <18 years (before AUGMENT-101 amendment reduced the minimum age to 30 days), concurrent malignancy, presence of central nervous system disease, isolated myeloid sarcoma, ongoing graft-versus-host disease, uncontrolled infection, poor performance status, and prior menin inhibitor exposure
  - Before an AUGMENT-101 protocol amendment that allowed patients to return to trial after hematopoietic stem cell transplant (HSCT), a subset of patients (n=9) received compassionate-use therapy after achieving a response to revumenib in AUGMENT-101 and proceeding to HSCT (Figure 1)
    - Of these 9 patients, 6 received revumenib as posttransplant maintenance therapy while in continuous remission and 3 patients received revumenib after posttransplant relapse
  - 27 patients were revumenib treatment naive with active R/R disease

CLINICAL ACTIVITY AND SAFETY

Posttransplant Maintenance Therapy

- Posttransplant maintenance with revumenib monotherapy was associated with prolonged remissions, with 4 of 6 patients remaining in remission for >5 months (Table 1)
  - 3 patients had >1 prior transplants before receiving compassionate-use maintenance therapy
  - 3 patients remained on maintenance therapy at data cutoff
- In the compassionate-use setting, maintenance therapy with revumenib demonstrated a manageable safety profile similar to that reported in the clinical trial setting
  - AEs reported during posttransplant maintenance therapy (n=6 patients) included thrombocytopenia, cytopenias, anemia, neutropenia, and peripheral neuropathy (improved after dose reduction)

Table 1. Patients Who Achieved Remissions on Revumenib Monotherapy for R/R Disease in AUGMENT-101 Trial and Subsequently Received Revumenib Compassionate-Use Therapy for Posttransplant Maintenance

	BASELINE CHARACTERISTICS					INVESTIGATOR ASSESSMENT OF EXPERIENCE ON COMPASSIONATE-USE THERAPY				
Patient number	Age, y/ Sex	Disease type	No. prior regimens	Prior HSCT, yes/no (n)	Best response on revumenib clinical trial	Initial Dose	DOT, days	Best response	Reason for discontinuation	TRAEs
1	12/M	*KMT2Ar* AML	3	Y	MLFS	163 mg q12h	158+	CR, MRD−	Ongoing	Anemia, neutropenia, thrombocytopenia
2	22/F	*KMT2Ar* AML (*NRAS* G12A, *GATA2*)	4	Y (3)	CRp, MRD−	138 mg q12h	338+	CR, MRD−	Ongoing	Peripheral neuropathy
3	25/F	*KMT2Ar* AML	3	Y	MLFS	163 mg q12h	30	-	AE; clinically well day 285	Cytopenias
4	41/F	*KMT2Ar* AML	2	Y (2)	CRp, MRD−	163 mg q12h	223+	CRp, MRD−	Ongoing	Thrombocytopenia
5	42/F	*KMT2Ar* AML	4	Y	N/A	163 mg q12h	34	-	PD	NR
6	71/F	*KMT2Ar* AML	1	Y (2[a])	CRh, MRD−	339 mg q12h	160	CR, MRD−	PD	Thrombocytopenia

[a]CD34+ selected donor cells from previous donor after clinical trial. AE, adverse event; AML, acute myeloid leukemia; CR, complete response; CRh, complete response with partial hematologic recovery; CRp, complete response with incomplete platelet recovery; *GATA2*, GATA binding factor 2; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; N/A, not available; NR, not reported; *NRAS*, neuroblastoma RAS viral oncogene homolog; PD, progressive disease; q12h, every 12 hours; TRAE, treatment-related adverse event.

CLINICAL ACTIVITY AND SAFETY

Treatment of Active Disease

- Antileukemic activity was demonstrated in 5 of the 27 patients who were revumenib treatment naive and ineligible for treatment within the AUGMENT-101 clinical trial, including in difficult-to-treat patients such as those with a history of central nervous system disease
  - 4 pediatric patients achieved a response, with 2 CR MRD−, 1 CR, and 1 CR with incomplete hematologic recovery; 3 of these patients proceeded to HSCT
  - 1 adult with *KMT2Ar* AML who had MRD+ morphologic remission after exhausting all therapies, including 5 prior regimens and 2 prior HSCTs, converted to MRD− remission with revumenib treatment
- Among the 3 patients from AUGMENT-101 who were re-treated with revumenib for relapse post HSCT, 2 were treated for 80 and 113 days, respectively, before discontinuing owing to PD and 1 was ongoing at data cutoff (day 63 of treatment)
- 5 patients received ≤15 days of therapy due to rapid PD, death, or withdrawal of consent to move into hospice care
- In the compassionate-use salvage setting, AEs reported during treatment with revumenib included the following:
  - AEs reported during treatment of active disease (n=30 patients) included nausea, QTc prolongation, differentiation syndrome, thrombocytopenia, vomiting, bruising, febrile neutropenia, fever, generalized muscle weakness, hepatobiliary disorder, increased alanine transaminase/aspartate transferase, intracranial hemorrhage, neck swelling, and rash
  - Among patients on revumenib treatment for active disease (n=30), 11 patients discontinued owing to PD/no response; 12 patients died; 3 patients proceeded to HSCT; 2 patients discontinued owing to AE (hepatotoxicity, n=1; thrombocytopenia, n=1); 1 patient withdrew; 1 patient remained on treatment at the time of data cutoff

SUMMARY

- Compassionate use of revumenib on single-patient protocols demonstrated clinical activity in a population of heavily pretreated patients with R/R *KMT2Ar* AML, including those with complex medical conditions making them ineligible for trial (eg, central nervous system disease, concurrent malignancy, graft-versus-host disease)
- Maintenance treatment post HSCT was feasible and led to prolonged remissions even in this patient population transplanted beyond first-line therapy; no new safety risks were reported
  - Revumenib maintenance therapy is being further evaluated in the AUGMENT-101 trial
- Overall, reported AEs were consistent with common AEs in trials of patients with R/R acute leukemia, including thrombocytopenia, and with those of ongoing revumenib trials, including differentiation syndrome and QTc prolongation
- Response and AE data extracted from individual patient narratives are limited because of the nature of the compassionate-use program

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Presenting Author: C. Michel Zwaan; c.m.zwaan@prinsesmaximacentrum.nl

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