

Revumenib Monotherapy in Patients with Relapsed/Refractory *KMT2Ar* Acute Leukemia: Efficacy and Safety Results from the AUGMENT-101 Phase 1/2 Study

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INTRODUCTION

- Revumenib (SNDX-5613), a small-molecule inhibitor of the menin–histone-lysine N-methyltransferase 2A (KMT2A) interaction, is being investigated in pediatric and adult patients with relapsed/refractory (R/R) *KMT2A*-rearranged (*KMT2Ar*) and nucleophosmin 1–mutated (*NPM1m*) acute leukemias in the phase 1/2 AUGMENT-101 study (NCT04065399)<sup>1</sup>
- In the phase 1 study, patients were assigned to 1 of 6 dose-escalation cohorts designed to identify a recommended phase 2 dose (RP2D) for concomitant administration of a cytochrome P450 3A4 inhibitor (CYP3A4i; moderate or strong) or no CYP3A4i
- RP2D was determined based on review of pharmacokinetics, clinical activity, safety, and tolerability data
- An initial analysis of the phase 1 study has been reported<sup>1</sup>
  - Revumenib resulted in deep, durable responses in heavily pretreated R/R acute leukemias; 37.5% of responders proceeded to hematopoietic stem cell transplant (HSCT)
  - Grade ≥3 treatment-related adverse events (TRAEs) were reported in 16.2% of patients; asymptomatic prolongation of the QT interval was the only dose-limiting toxicity identified
- Here we provide an update of >1-year additional experience of patients with R/R *KMT2Ar* acute leukemia in the phase 1 portion of the AUGMENT-101 study, which has completed enrollment; we also report pharmacokinetic studies, including considerations for pediatric dosing, to support the RP2D with and without strong CYP3A4i
- Additionally, we highlight topline efficacy and safety results from the phase 2 AUGMENT-101 study
  - Detailed analysis of the phase 2 results will be presented as a late-breaking abstract titled, “Revumenib Monotherapy in Patients with Relapsed/Refractory *KMT2Ar* Acute Leukemia: Topline Efficacy and Safety Results from the Pivotal AUGMENT-101 Phase 2 Study (LBA-5)”

METHODS

- The phase 1/2 study used a highly innovative trial design enabling an early phase pivotal study for both pediatric and adult patients, with *KMT2Ar* acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and mixed phenotype acute leukemia (MPAL). The study also includes a separate *NPM1m* AML cohort
- In phase 1, patients aged ≥30 days with R/R acute leukemias received revumenib, at a flat dose (if body weight ≥40 kg) or a body surface area (BSA)–based dose (if body weight <40 kg), every 12 hours (q12h) or 3 times per day
  - Safety and efficacy are reported for all patients who received ≥1 dose of revumenib
  - Pharmacokinetic parameters of revumenib were evaluated
- The pivotal phase 2 portion of the study was initiated after identification of an RP2D of 163 mg (or 95 mg/m<sup>2</sup> if body weight <40 kg) q12h with a strong CYP3A4i in 28-day cycles until unacceptable toxicity or lack of at least morphological leukemia-free state (MLFS) by end of cycle 4
  - Phase 2 study enrolled patients in 2 subgroups: those with R/R *KMT2Ar* acute leukemia (including AML, ALL, MPAL) and patients with R/R *NPM1m* AML
  - Phase 2 primary objectives were the assessment of the complete remission (CR)+CR with partial hematologic recovery (CRh) rate and evaluation of safety and tolerability of revumenib
  - A planned interim analysis (IA) of adult and pediatric patients with *KMT2Ar* acute leukemia was conducted with data cutoff in July 2023, and topline data are reported here
  - Enrollment of R/R *NPM1m* AML in cohort 2C is ongoing, and data for this cohort are not included in this analysis

RESULTS

PHASE 1

BASELINE CHARACTERISTICS

- As of July 24, 2023, 132 patients aged 0.8 years to 82.0 years with R/R acute leukemia were enrolled in the phase 1 study and were included in the overall population (Table 1)
- 77 patients with R/R *KMT2Ar* acute leukemia were treated with revumenib in the 6 dose-escalation arms
  - Most patients were female (59.7%)
  - Patients received a median of 3 prior lines of therapy, and 46.8% had prior HSCT

Table 1. Phase 1 Patient Demographics and Baseline Characteristics<sup>a</sup>

Parameter	Phase 1 <i>KMT2Ar</i> population				
	Adult AML (n=51)	ALL/Other subtype <sup>b</sup> (n=15)	Pediatric <sup>c</sup> (n=15)	Overall <i>KMT2Ar</i> (n=77)	Overall population (n=132)
Median age, y (range)	40.0 (19.0-79.0)	34.0 (1.0-74.0)	9.0 (1.0-16.0)	33.0 (1.0-79.0)	41.0 (0.8-82.0)
Sex, n (%)					
Female	30 (58.8)	10 (66.7)	10 (66.7)	46 (59.7)	70 (53.0)
Male	21 (41.2)	5 (33.3)	5 (33.3)	31 (40.3)	62 (47.0)
Ethnicity, n (%)					
Hispanic/Latino	12 (23.5)	1 (6.7)	9 (60.0)	21 (27.3)	31 (23.5)
Not Hispanic/Latino	34 (66.7)	13 (86.7)	6 (40.0)	50 (64.9)	95 (72.0)
Unknown	5 (9.8)	1 (6.7)	0	6 (7.8)	6 (4.5)
Race					
White	28 (54.9)	11 (73.3)	8 (53.3)	46 (59.7)	93 (70.5)
Non-White	14 (27.5)	2 (13.3)	5 (33.3)	19 (24.7)	26 (19.7)
Unknown	9 (17.6)	2 (13.3)	2 (13.3)	12 (15.6)	13 (9.8)
Leukemia type, n (%)					
AML	51 (100.0)	0	11 (73.3)	62 (80.5)	114 (86.4)
ALL	0	13 (86.7)	4 (26.7)	13 (16.9)	14 (10.6)
MPAL/Other	0	2 (13.3)	0	2 (2.6)	4 (3.0)
Number of prior lines of therapy, median (range)	3 (1-8)	3 (1-9)	3 (1-9)	3 (1-9)	3 (1-12)
≥4 prior lines of therapy, n (%)	16 (31.4)	5 (33.3)	7 (46.7)	26 (33.8)	44 (33.3)
Prior venetoclax, n (%)	33 (64.7)	5 (33.3)	9 (60.0)	46 (59.7)	85 (64.4)
Prior HSCT, n (%)	26 (51.0)	5 (33.3)	6 (40.0)	36 (46.8)	58 (43.9)
>1 prior HSCT	12 (23.5)	2 (13.3)	2 (13.3)	15 (19.5)	20 (15.2)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MPAL, mixed phenotype acute leukemia; *NPM1m*, mutated nucleophosmin 1. <sup>a</sup>Data cutoff: July 24, 2023. Some patients may have had <4 months of follow-up. Two pediatric patients switched from *KMT2Ar* to *NPM1m*. Another patient's *KMT2Ar* status changed to "no" at screening. <sup>b</sup>Includes all ages. <sup>c</sup>Includes all leukemia subtypes.

EFFICACY AND SAFETY

- Phase 1 *KMT2Ar* patients demonstrated CR+CRh of 31.2%, and overall response rate (ORR) of 64.9%, with 38% proceeding to HSCT
- In adults with AML (n=51), CR+CRh rate was 37.3% and ORR was 68.6%, with 40% of responders proceeding to HSCT
  - Smaller subgroups of ALL/other, and pediatric patients demonstrated consistent response rates
  - A similar percentage of pediatric patients and adult AML patients proceeded to HSCT (Table 2)

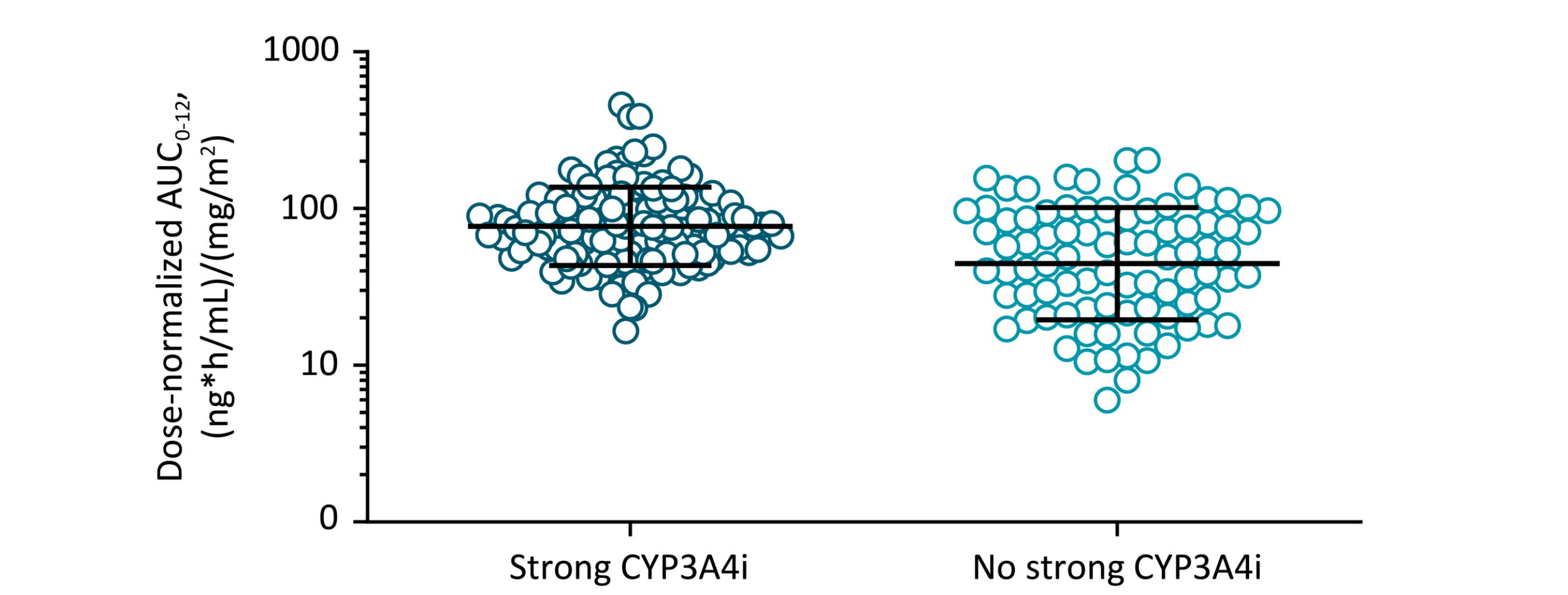
Table 2. Phase 1 Response and Safety<sup>a</sup>

Parameter	Adult AML (n=51)	ALL/Other subtype <sup>b</sup> (n=15)	Pediatric <sup>c</sup> (n=15)	Overall <i>KMT2Ar</i> (n=77)
ORR, n (%)	35 (68.6)	8 (46.7)	10 (66.7)	50 (64.9)
Best response, n (%)				
CR	15 (29.4)	3 (20.0)	1 (6.7)	18 (23.4)
CRh	4 (7.8)	1 (6.7)	2 (13.3)	6 (7.8)
CRi	2 (3.9)	0	0	2 (2.6)
CRp	5 (9.8)	1 (6.7)	2 (13.3)	8 (10.4)
MLFS	9 (17.6)	2 (13.3)	5 (33.3)	15 (19.5)
PR	0	1 (6.7)	0	1 (1.3)
Other <sup>d</sup>	16 (31.4)	7 (46.7)	5 (33.3)	27 (35.1)
CR+CRh rate, n (%)	19 (37.3)	4 (26.7)	3 (20.0)	24 (31.2)
CRc, n (%)	26 (51.0)	5 (33.3)	5 (33.3)	34 (44.2)
Negative MRD status in CRc, n (%)	18/24 (75.0)	4/4 (100.0)	4/4 (100.0)	25/31 (80.6)
Negative MRD status in CR+CRh, n (%)	12/17 (70.6)	3/3 (100.0)	2/2 (100.0)	16/21 (76.2)
No. of responders who proceeded to HSCT, n (%)	14/35 (40.0)	1/8 (12.5)	4/10 (40.0)	19/50 (38.0)
<b>Safety (all patients)</b>				
<b>All terms</b>				<b>Overall population (n=132)</b>
Any grade TEAE, n (%)	128 (97.0)			
Any grade TEAEs that occurred in ≥25% patients, n (%)				
Nausea	63 (47.7)			
QTc prolongation	48 (36.4)			
Vomiting	46 (34.8)			
Febrile neutropenia	40 (30.3)			
Fatigue	38 (28.8)			
Diarrhea	33 (25.0)			
≥Grade 3 TEAE, n (%)	107 (81.1)			
≥Grade 3 TEAE that occurred in ≥10% patients, n (%)				
Febrile neutropenia	39 (29.5)			
Decreased platelet count	20 (15.2)			
Anemia	18 (13.6)			
Sepsis	17 (12.9)			
Decreased neutrophil count	15 (11.4)			
Decreased white blood cell count	15 (11.4)			
Serious AE, n (%)	89 (67.4)			
TEAE leading to dose reduction	13 (9.8)			
TEAE leading to discontinuation	14 (10.6)			
TEAE leading to death	21 (15.9)			

AE, adverse event; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MLFS, morphological leukemia-free state; MRD, measurable residual disease; *NPM1m*, mutated nucleophosmin 1; ORR, overall response rate; CR+CRh+CRp+CRi, partial remission; TEAE, treatment-emergent adverse event. <sup>a</sup>Data cutoff: July 24, 2023. Some patients may have had <4 months of follow-up. Two pediatric patients switched from *KMT2Ar* to *NPM1m*. Another patient's *KMT2Ar* status changed to "no" at screening. <sup>b</sup>Includes all ages. <sup>c</sup>Includes all leukemia subtypes. <sup>d</sup>Includes no response, disease progression, and patients without postbaseline disease assessment.

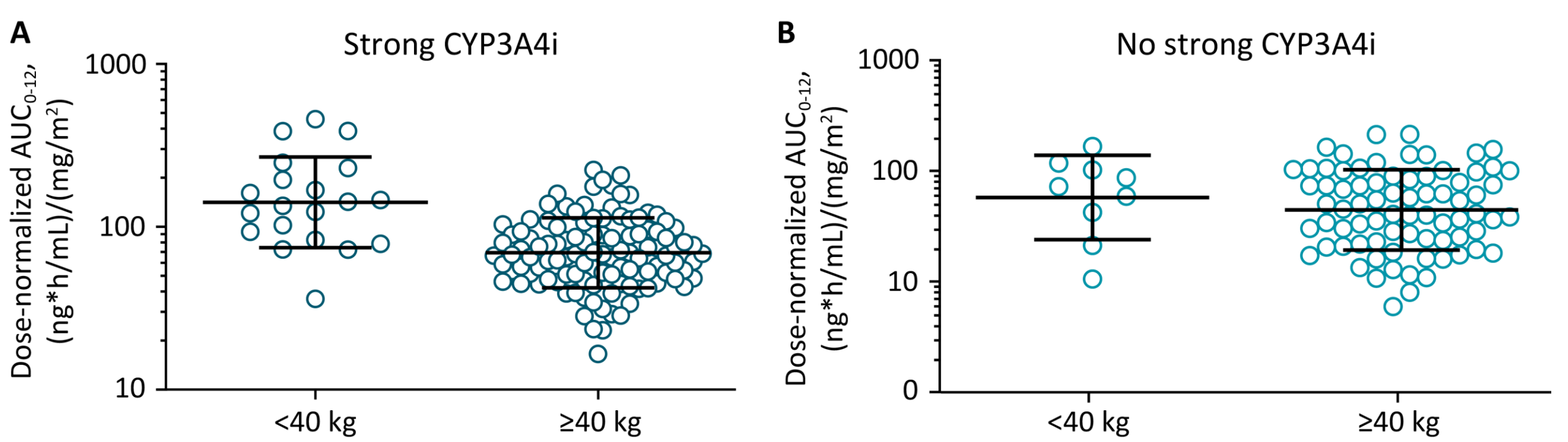
- In the overall population (n=132), 25.0% of patients had a ≥Grade 3 TRAE, with Grade 3 QTc prolongation in 8.3% of patients and Grade 3 differentiation syndrome in 2.3%
- 10.6% of patients discontinued revumenib due to TRAEs
- Based on AUGMENT-101 phase 1 pharmacokinetics, clinical activity, and safety data, an RP2D of 276 mg q12h (or 160 mg/m<sup>2</sup> if body weight <40 kg) without a strong CYP3A4i was established
  - For concomitant use with a strong CYP3A4i, an RP2D of 163 mg (95 mg/m<sup>2</sup> if <40kg) was established
- SIMILARITY IN EXPOSURES OF REVUMENIB AMONG PATIENT SUBGROUPS**
- BSA-based dosing strategy for patients <40 kg yielded exposures that overlapped with their counterparts ≥40 kg with or without strong CYP3A4i (Figures 1 and 2)
  - The appropriateness of the BSA-based dosing is supported by the ontogeny of revumenib clearance pathways and the relationship between body weight and oral clearance
- Impaired mild-to-moderate renal or hepatic function (Figure 3) and sex, race, or ethnicity did not impact exposure (Figure 4)

Figure 1. Dose-normalized exposures indicated dosing with strong CYP3A4i resulted in higher exposures compared with those without strong CYP3A4i.<sup>a</sup>



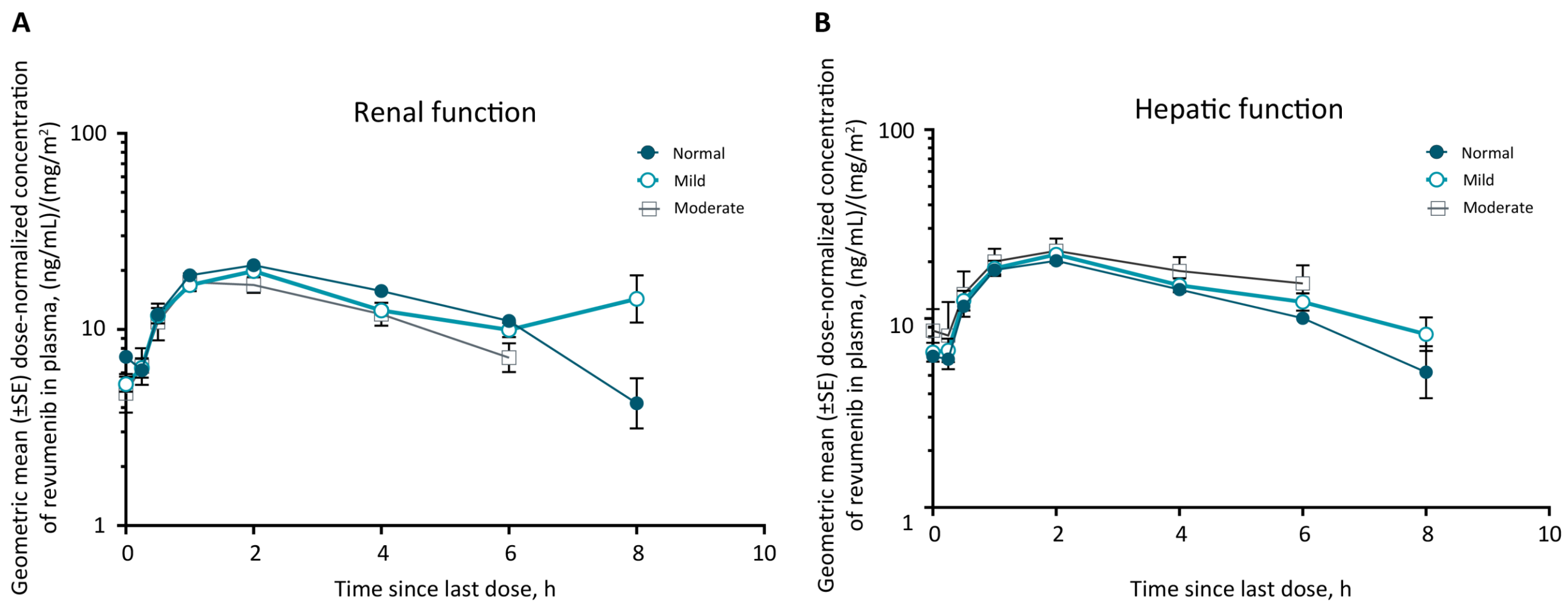
Dose-normalized (BSA-adjusted) AUC<sub>0-12</sub> of revumenib when given without and with a strong CYP3A4i in patients with acute leukemia with pharmacokinetic data. Circles represent individual patients; error bars represent geometric mean and geometric coefficient of variation. AUC, area under the curve; BSA, body surface area; CYP3A4i, cytochrome P450 3A4 inhibitor. <sup>a</sup>Data cutoff July 24, 2023. Includes all phase 1 and phase 2 data regardless of mutation status.

Figure 2. Body surface area–based dosing strategy of revumenib in patients <40 kg yielded exposures that overlapped with those of fixed-dose patients ≥40 kg when given with or without strong CYP3A4i.<sup>a</sup>



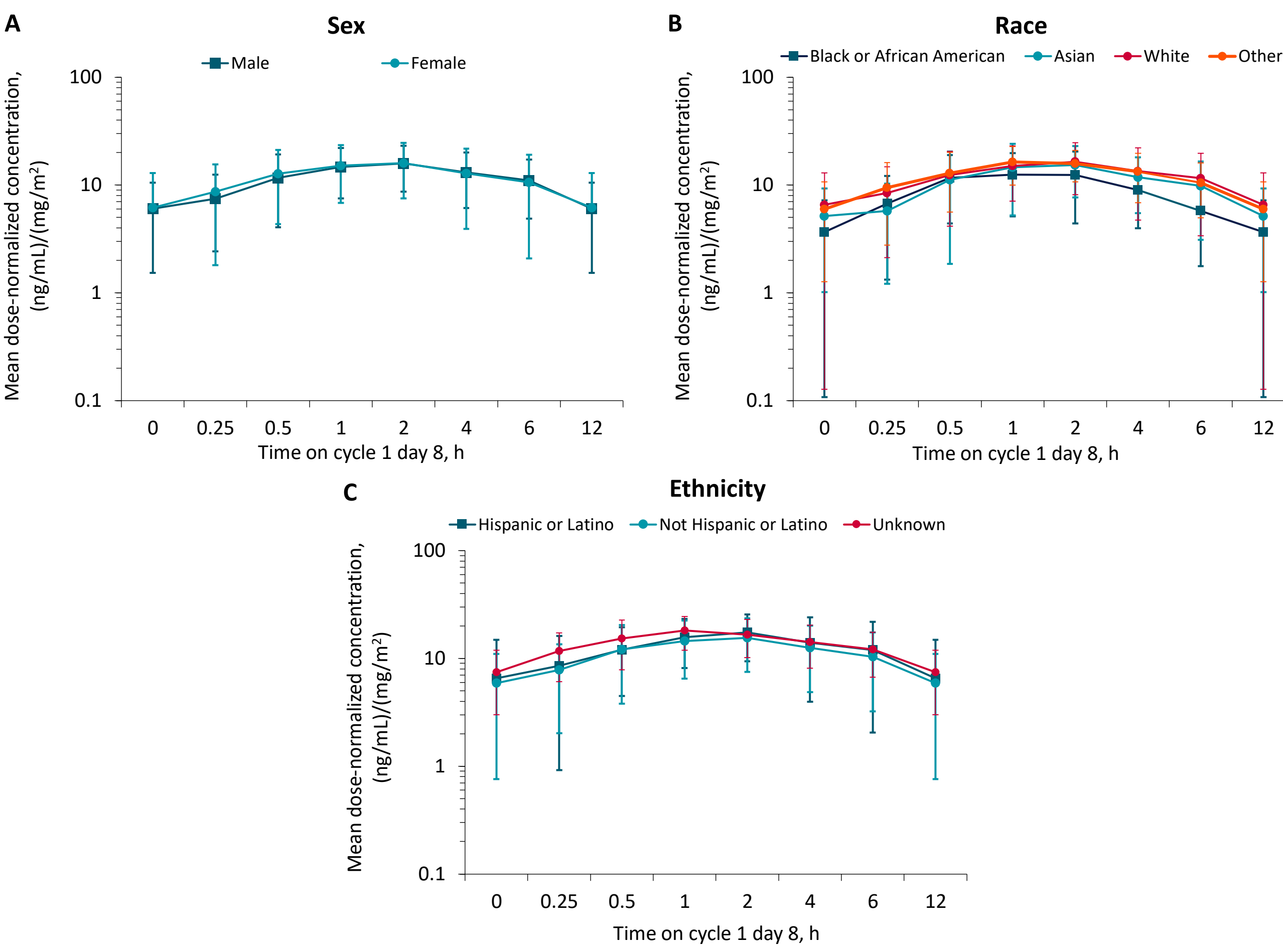
Dose-normalized (BSA-adjusted) AUC<sub>0-12</sub> of revumenib when given with and without a strong CYP3A4i. Circles represent individual patients; error bars represent geometric mean and geometric coefficient of variation. AUC, area under the curve; BSA, body surface area; CYP3A4i, cytochrome P450 3A4 inhibitor. <sup>a</sup>Data cutoff July 24, 2023. Includes all phase 1 and phase 2 data regardless of mutation status.

Figure 3. Exposure to revumenib was not impacted by impaired renal or hepatic function.<sup>a</sup>



Data represent mean ± SD. SD, standard deviation. <sup>a</sup>Data cutoff July 24, 2023. Includes all phase 1 and phase 2 data regardless of mutation status.

Figure 4. Revumenib exposure was not impacted by sex, race, or ethnicity.<sup>a</sup>



Data represent mean ± SD. SD, standard deviation. <sup>a</sup>Data cutoff July 24, 2023. Includes all phase 1 and phase 2 data regardless of mutation status.

PHASE 2

EFFICACY AND SAFETY

- As of July 24, 2023, 94 patients aged 1.3 years to 75 years with R/R *KMT2Ar* acute leukemia had received ≥1 dose of study drug and were included in the safety analysis
  - TRAEs leading to treatment discontinuation were infrequent at 6%
  - Most common TRAEs (≥20%) were nausea (27.7%), differentiation syndrome (26.6%), and QTc prolongation (23.4%)
- The efficacy population for the IA (n=57) included all phase 2 patients who had centrally confirmed *KMT2Ar* acute leukemia, had ≥5% blasts in bone marrow at baseline, had received ≥1 dose of study drug, and had started treatment at the same time as or before the 38th adult AML efficacy evaluable patient
  - The analysis was conducted when 57 patients (adult and pediatric) had completed 6 months of follow-up or discontinued therapy.
- The primary endpoint of the pivotal phase 2 study was met with a CR+CRh rate of 22.8% (13/57; 95% confidence interval [CI], 12.7-35.8); 1-sided *P* value=0.0036, with 70% achieving negative measurable residual disease status in patients with measurable residual disease status available
  - ORR was 63.2% (95% CI, 49.3-75.6); CRc was 43.9% (95% CI, 30.7-57.6)

CONCLUSIONS

- Updated follow-up on phase 1 data continues to demonstrate clinically meaningful response, high percentage of responders proceeding to transplant, consistency of response across subgroups, and a manageable safety profile in heavily pretreated patients with R/R *KMT2Ar* acute leukemia**
- Pharmacokinetic and clinical data identified 276 mg as the RP2D for patients not taking strong CYP3A4i; BSA-adjusted dosing for patients <40 kg produced exposure ranges that overlapped with those of the fixed-dose RP2D for patients ≥40 kg**
- Revumenib exposure was not affected by mild-to-moderate renal or hepatic impairment; sex, race, and ethnicity also had no detectable effect on exposure**
- At the phase 2 IA, this pivotal study of revumenib in *KMT2Ar* acute leukemia met its primary endpoint with a CR+CRh rate of 22.8% (13/57; 95% CI, 12.7-35.8) and a 1-sided *P* value of 0.0036; the *KMT2Ar* cohorts were stopped early for efficacy**
  - Overall, data are consistent with those reported in phase 1; a detailed analysis of the phase 2 results will be presented at the late-breaking abstract session on Tuesday, December 12, 2023, at 10:00 AM (LBA-5)

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**REFERENCE:** 1. Issa GC, Aldoss I, DiPersio J, et al. *Nature*. 2023;615(7954):920-924.