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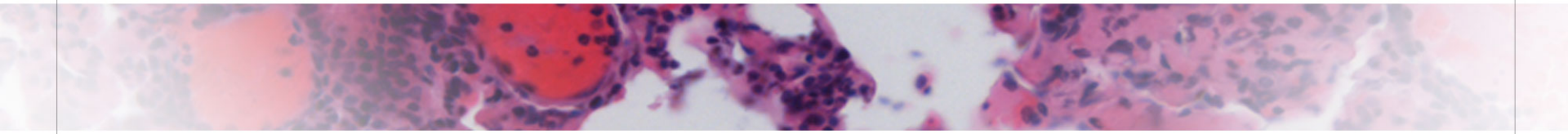


The Menin Inhibitor Revumenib (SNDX-5613) Leads to Durable Responses in Patients with *KMT2A*-Rearranged or *NPM1* Mutant AML: Updated Results of a Phase 1 Study

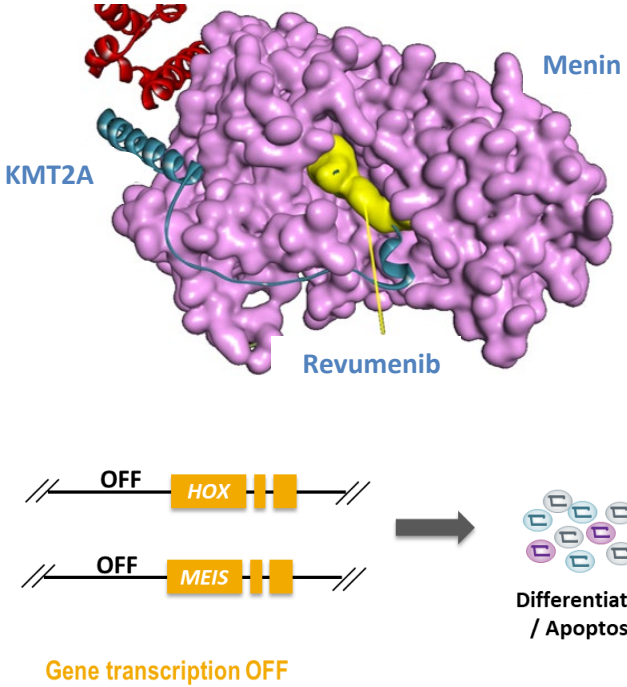
Ghayas C. Issa, MD,[1] Ibrahim Aldoss, MD,[2] John F. DiPersio, MD, PhD,[3] Branko Cuglievan, MD,[1] Richard M. Stone, MD,[4] Martha L. Arellano, MD,[5] Michael Thirman, MD,[6] Manish R. Patel, MD,[7] David Dickens, MD,[8] Shalini Shenoy, MD,[3] Neerav Shukla, MD,[9] Galit Rosen, MD,[10] Rebecca G. Bagley, MA,[10] Michael L. Meyers, MD, PhD,[10] Kate Madigan, MD,[10] Peter Ordentlich, PhD,[10] Yu Gu, PhD,[10] Steven Smith, BS,[10] Gerard M. McGeehan, PhD,[10] and Eytan M. Stein, MD[9]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]City of Hope, Duarte, CA; [3]Washington University School of Medicine, St. Louis, MO; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Emory University School of Medicine, Atlanta, GA; [6]University of Chicago, Chicago, IL; [7]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [8]University of Iowa, Iowa City, IA; [9]Memorial Sloan Kettering Cancer Center, New York, NY; [10]Syndax Pharmaceuticals, Inc., Waltham, MA

Revumenib (SNDX-5613) is a potent, selective menin-KMT2A interaction inhibitor

- The menin-KMT2A interaction is a critical dependency in *KMT2Ar* (*MLL1r*) and *mNPM1* leukemias responsible for the leukemogenic gene expression
  - *KMT2Ar*: ~ 10% AML or ALL (~ 80% infant ALL)[1]
  - *mNPM1*: ~ 30% AML[2]
- Revumenib competitively binds a discrete, well-defined pocket within menin, where both wild-type KMT2A (MLL1) and KMT2A fusion proteins bind

  → disassembling abnormal transcription complexes in *KMT2Ar*, *mNPM1*, and other leukemia subtypes[3]

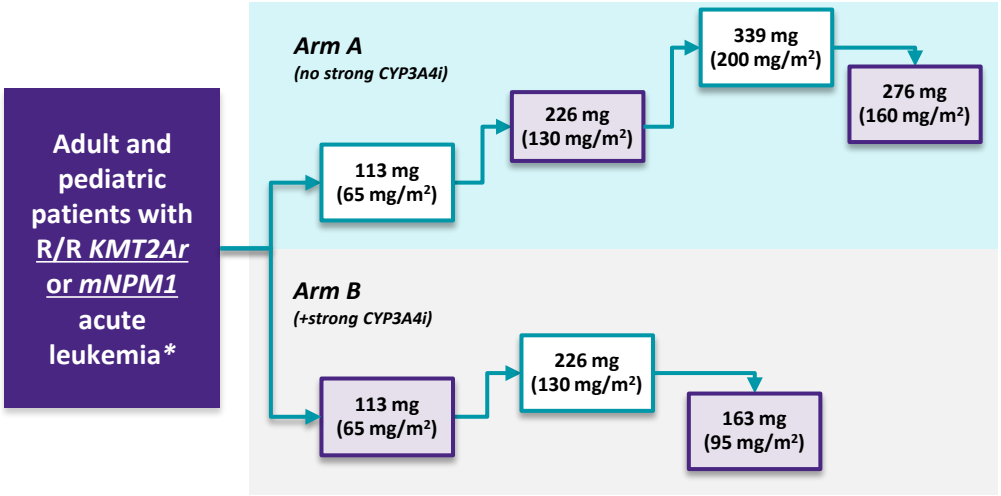


1. Issa GC, et al. *Leukemia.* 2021;35:2482–2495; 2. Papaemmanuil, E. *et al. N Engl J Med.* 2016;374: 2209-2221; 3. Krivtsov A, et al. Cancer Cell. 2019;36(6):660-673.
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; *KMT2Ar*, lysine methyltransferase 2A rearrangements; *MLLr*, mixed lineage leukemia rearranged; *mNPM1*, mutated nucleophosmin 1.

AUGMENT-101 Phase 1 study design and objectives

Treatment

- Revumenib oral, q12h continuous dosing, 28-day cycle
- Accelerated titration into a rolling 6 design



Primary objectives

- Characterize safety, tolerability, PK, and RP2D

Prespecified RP2D selection criteria

- No more than 1 of 6 of evaluable patients experience a DLT
- At least 2/3 of patients receive ≥ 80% of their dose in the first two cycles
- 24-hour AUC (AUC0-24) exceeds 15,000 ng×hr/mL in at least 2/3 of patients

Exploratory objectives

- Anti-leukemic activity within *KMT2Ar* or *mNPM1* population

Populations

- Safety (pts ≥ 1 dose revumenib): N=68
- Efficacy (*KMT2Ar* or *mNPM1)*: n=60

*Protocol originally allowed any R/R leukemia regardless of genotype but was amended to *KMT2Ar* or *mNPM1* patients only. A majority of patients (n=60; 88%) were *KMT2Ar* or *mNPM1* and evaluable as the efficacy population.
AUC, area under the curve; DLT, dose-limiting toxicity; PK, pharmacokinetics; q12h, every 12 hours; RP2D, recommended Phase 2 dose; R/R, relapsed or refractory.

AUGMENT-101 patients are heavily pretreated with a poor prognosis

Baseline Characteristics	Safety Population N=68
Median age, years (range)	42.5 (0.8, 79)
Adult (n=60)	50.5
Pediatric (n=8)	2.5
Female, n (%)	42 (62)
Leukemia type, n (%)	
AML	56 (82)
ALL	11 (16)
MPAL	1 (2)
Median prior therapies (range)	4 (1,12)
Stem cell transplant, n (%)	31 (46)
Venetoclax, n (%)	41 (60)

Baseline Characteristics	Safety Population N=68
***KMT2Ar*, n (%)**	46 (68)
t(9;11)	10 (15)
t(11;19)	9 (13)
t(4;11)	6 (9)
t(6;11)	3 (4)
t(11;17)	2 (3)
Other	16 (24)
***mNPM1*, n (%)**	14 (21)
***KMT2A* and *NPM1* wild type, n (%)**	8 (12)
Co-occurring mutations*, n (%)	
FLT3	14 (25)
RAS	12 (29)
TP53	4 (10)

*In patients for whom co-occurring mutation data were available.
MPAL, mixed-phenotype acute leukemia

Data cutoff: 31 March 2022

2 patients with treatment ongoing and 12 patients proceeded to HSCT while in remission

Patient Disposition	Safety Population N=68
Treatment Ongoing, n (%)	**2 (3)**
Discontinued Treatment, n (%)	**66 (97)**
Progressive disease/No response	39 (57)
Transplant	12 (18)
Adverse event (all unrelated)	7 (10)
Withdrew consent	3 (4)
Other*	3 (4)
Physician decision	2 (3)

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Abstract #376, Issa GC. et al.
Session 723; December 10, 4:00-5:30p

*Other: death (not related to treatment), n=2; donor lymphocyte infusion, n=1
HSCT, hematopoietic stem cell transplant.

Data cutoff: 31 March 2022

Adverse Events across all doses of revumenib

Any-grade treatment-related AE (≥5%)	Safety Population N=68
Patients with ≥1 treatment-related AE, n (%)	53 (78)
ECG QTc prolonged	36 (53)
Nausea	18 (27)
Vomiting	11 (16)
Differentiation syndrome	11 (16)
Diarrhea	7 (10)
Dysgeusia	5 (7)
Decreased appetite	5 (7)

No treatment discontinuations for QTc prolongations, or associated arrhythmias

≥Grade 3 treatment-related AE	Safety Population N=68
Patients with ≥Gr 3 treatment-related AE, n (%)	11 (16)
ECG QTc prolonged	9 (13)
Diarrhea	2 (3)
Anemia	2 (3)
Asthenia	1 (2)
Fatigue	1 (2)
Hypercalcemia	1 (2)
Hypokalemia	1 (2)
Neutropenia	1 (2)
Thrombocytopenia	1 (2)
Tumor lysis syndrome	1 (2)

10% of patients (5/52) had Gr 3 QTc prolongation at doses meeting criteria for RP2D

ECG, electrocardiogram; QTc, corrected QT interval.

Data cutoff: 31 March 2022

Revumenib demonstrates promising antileukemic activity in relapsed/refractory *KMT2Ar* and *mNPM1* leukemias

Best Response, n (%)	Efficacy Population n=60	
ORR*	**32/60 (53%)**	
Best Response		
CR	12 (20%)	
CRh	6 (10%)	
CRp	5 (8%)	
MLFS	9 (15%)	
MRD^{neg} rate†	**18/32 (56%)**	
CR/CRh MRD^{neg}	14/18 (78%)	
CR/CRh/CRp MRD^{neg}	18/23 (78%)	
Genetic alteration	***KMT2Ar* n=46**	***mNPM1* n=14**
ORR	**27/46 (59%)**	**5/14 (36%)**
CR/CRh	15 (33%)	3 (21%)
CR/CRh MRD^{neg} rate	11/15 (73%)	3/3 (100%)

CR/CRh
18 (30%)

Data cutoff: 31 March 2022

*Overall Response Rate = CR + CRh + CRp + MLFS; †MRD status assessed locally by PCR or MCF

CR, complete remission; CRh, complete remission with partial hematologic recovery; CRp, complete remission with incomplete platelet recovery; MLFS, morphologic leukemia free state; MRD, measurable residual disease.

Revumenib demonstrates promising antileukemic activity in relapsed/refractory *KMT2Ar* and *mNPM1* leukemias

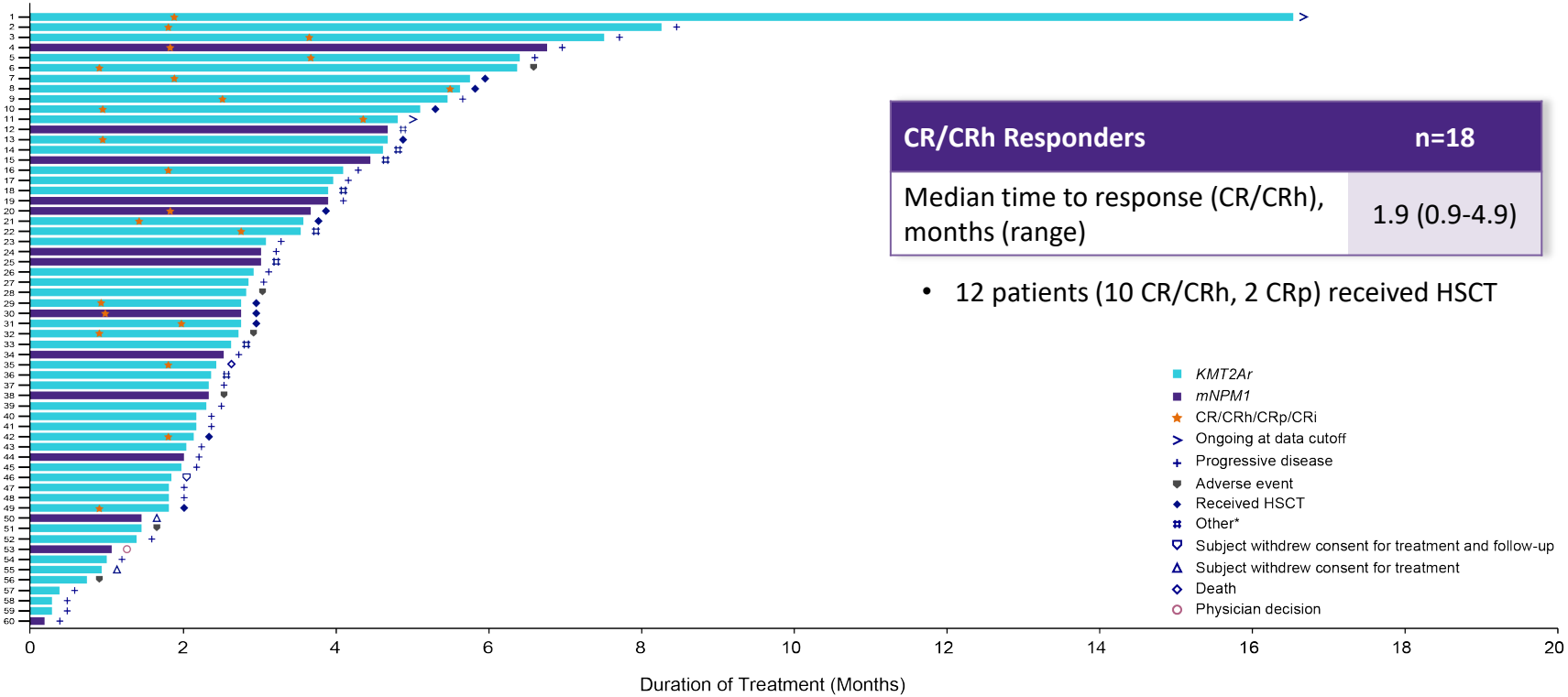
Best Response, n (%)	Efficacy Population n=60		Efficacy Population Doses Meeting Criteria for RP2D n=48	
ORR*	**32/60 (53%)**		**25/48 (52%)**	
Best Response				
CR	12 (20%)		8 (17%)	
CRh	6 (10%)		5 (10%)	
CRp	5 (8%)		5 (10%)	
MLFS	9 (15%)		7 (15%)	
MRD^{neg} rate†	**18/32 (56%)**		**14/25 (56%)**	
CR/CRh MRD^{neg}	14/18 (78%)		10/13 (77%)	
CR/CRh/CRp MRD^{neg}	18/23 (78%)		14/18 (78%)	
Genetic alteration	***KMT2Ar* n=46**	***mNPM1* n=14**	***KMT2Ar* n=37**	***mNPM1* n=11**
ORR	**27/46 (59%)**	**5/14 (36%)**	**20/37 (54%)**	**5/11 (46%)**
CR/CRh	15 (33%)	3 (21%)	10 (27%)	3 (27%)
CR/CRh MRD^{neg} rate	11/15 (73%)	3/3 (100%)	7/10 (70%)	3/3 (100%)

Data cutoff: 31 March 2022

*Overall Response Rate = CR + CRh + CRp + MLFS; †MRD status assessed locally by PCR or MCF

CR, complete remission; CRh, complete remission with partial hematologic recovery; CRp, complete remission with incomplete platelet recovery; MLFS, morphologic leukemia free state; MRD, measurable residual disease.

Duration of revumenib therapy in patients with *KMT2Ar* or *mNPM1*



CR/CRh Responders	n=18
Median time to response (CR/CRh), months (range)	1.9 (0.9-4.9)

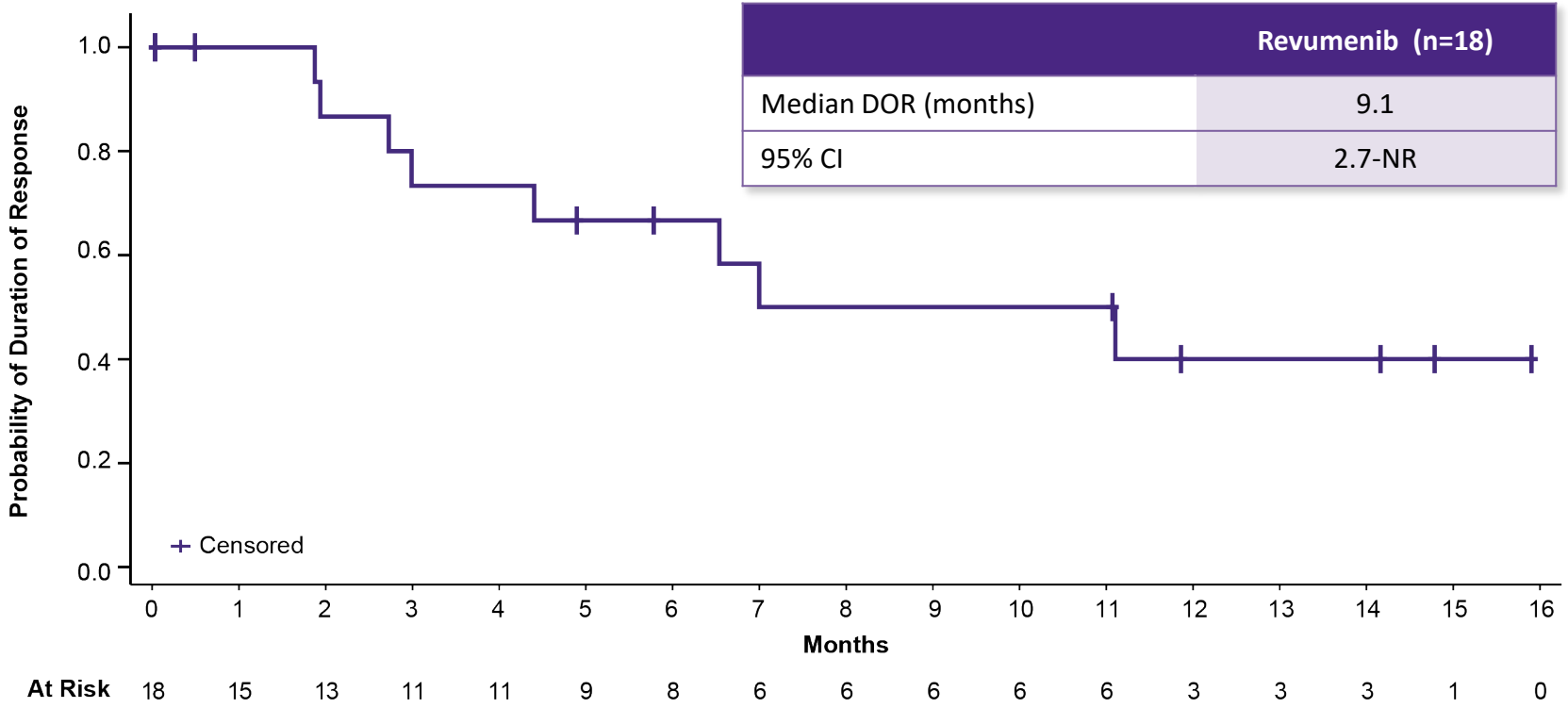
- 12 patients (10 CR/CRh, 2 CRp) received HSCT

*Other reasons for treatment discontinuation included no response, relapse, death, and donor lymphocyte infusion.

Data cutoff: 31 March 2022

Duration of CR/CRh response with revumenib treatment

	Revumenib (n=18)
Median DOR (months)	9.1
95% CI	2.7-NR

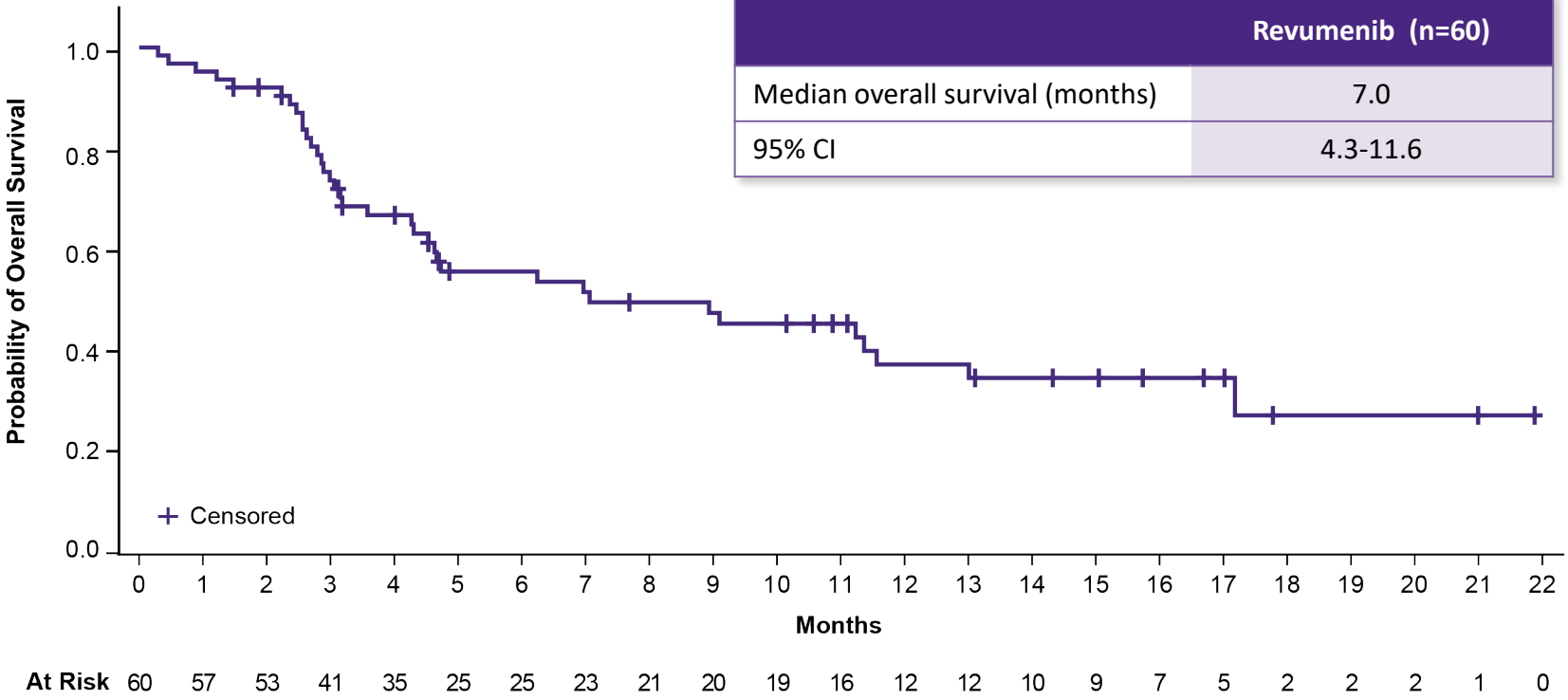


DOR, duration of response; NR, not reached.

Data cutoff: 31 March 2022

Overall survival in revumenib treated patients with *KMT2Ar* or *mNPM1*

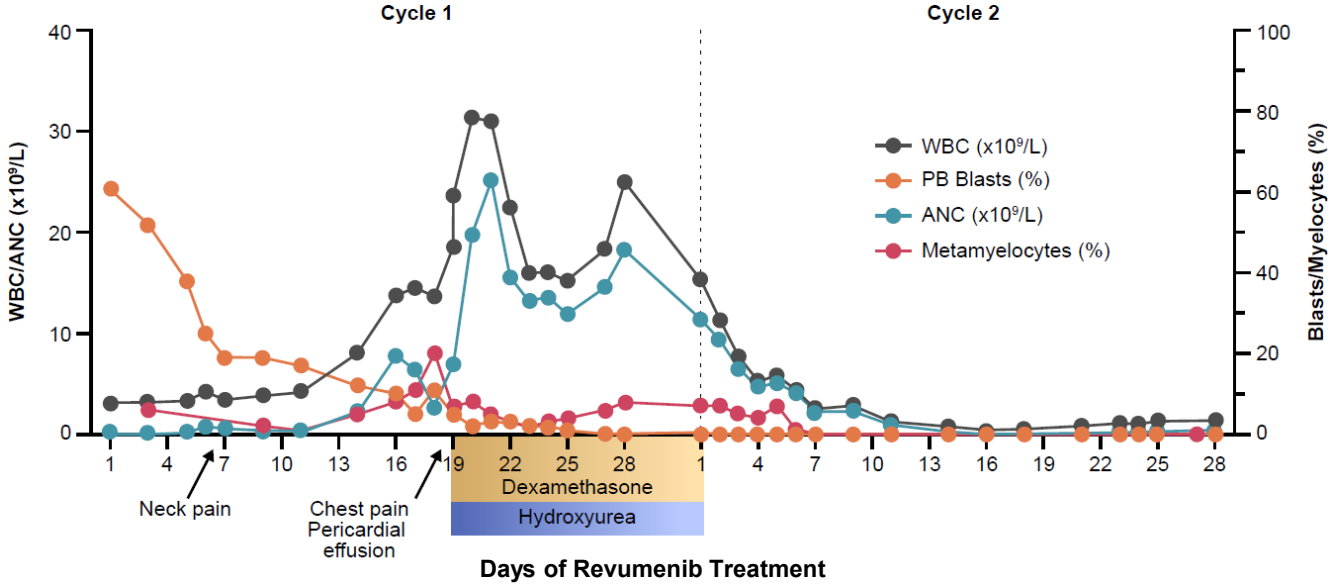
	Revumenib (n=60)
Median overall survival (months)	7.0
95% CI	4.3-11.6



Data cutoff: 31 March 2022

Differentiation syndrome managed with hydroxyurea and steroids

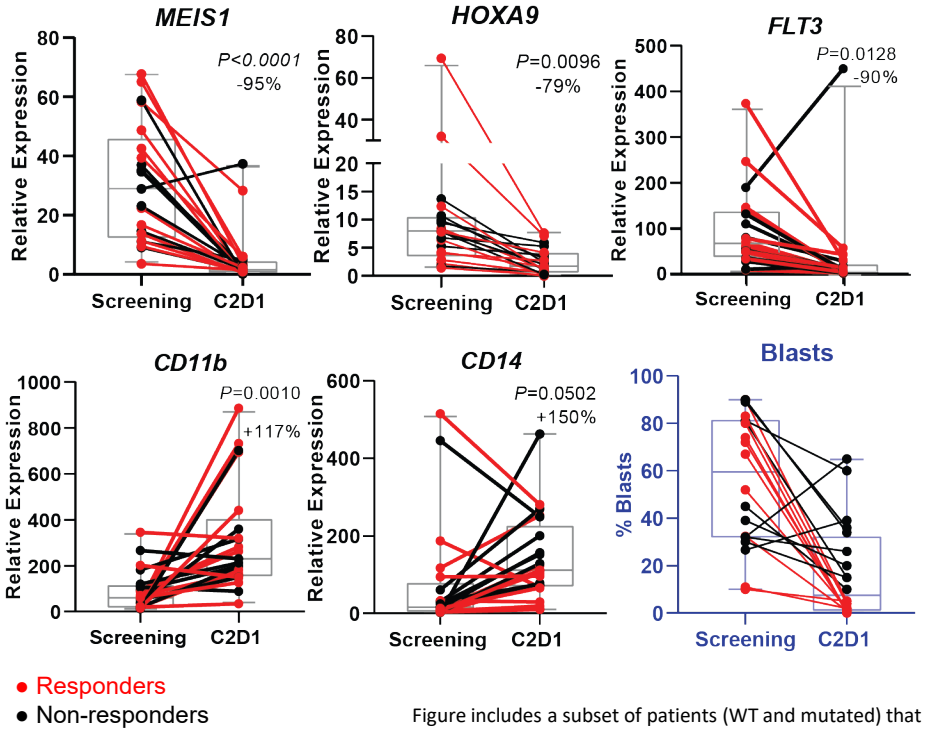
- 71-year-old with *KMT2Ar* AML relapsed after an allogeneic stem cell transplant
- Received revumenib at 339 mg PO q12h (Arm A), and achieved CRh, MRD negative remission



ANC, absolute neutrophil count; PB, peripheral blood; PO, by mouth; WBC, white blood cell.

Revumenib downregulates transcription of *FLT3* and induces responses in patients with *FLT3* co-mutations

- Among *KMT2Ar/mNPM1:* 14 had *mFLT3*
  - 13/14 (93%) previously treated with a FLT3 inhibitor
- Overall response rate:
  - *KMT2Ar/mFLT3:* 2/3 (66%)
  - *mNPM1/mFLT3:* 3/11 (27%)
  - All responders previously treated with FLT3 inhibitor
- Revumenib leads to transcriptional downregulation of *FLT3*, a putative target of *MEIS1*[1,2]

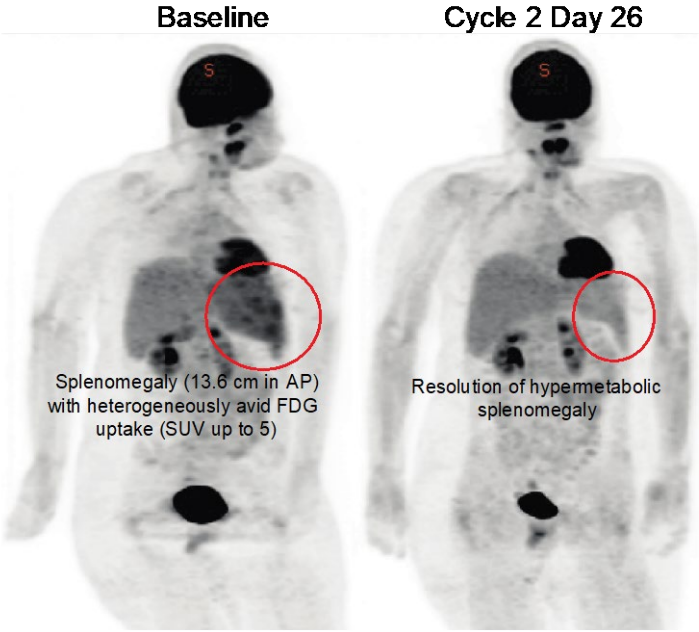


1. Kühn MW, et al. Cancer Discov. 2016 Oct;6(10):1166-1181;
2. Dzama MM, et al. Blood. 2020 Nov 19;136(21):2442-2456

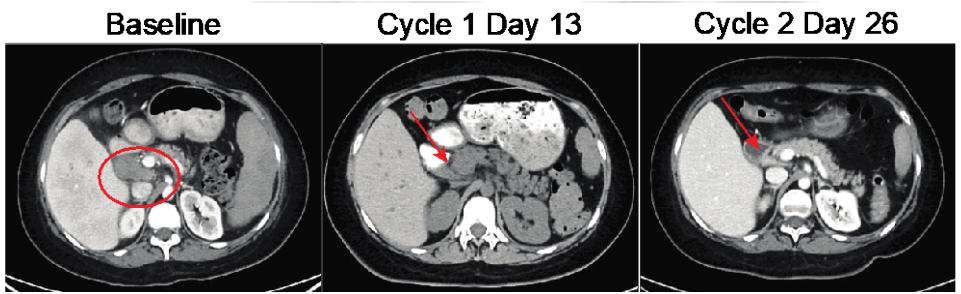
C, cycle; D, day; WT, wild type.

Figure includes a subset of patients (WT and mutated) that were evaluable by gene expression at screening and C2D1.

Revumenib response observed in extra-medullary disease



PET scan



CT scans of target lesions and spleen from a 19-year-old with relapsed *KMT2Ar* AML

- 3 prior lines of therapy, including 2 allogeneic stem cell transplants and local radiation to the spleen and abdominal nodes
- Received revumenib at 276 mg PO q12h
- Achieved CRh, MRD-negative remission with resolution of extramedullary disease in abdominal nodes and spleen

AP, anterior-posterior; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUV, standardized uptake value.

Conclusions

- Revumenib resulted in deep, durable responses in heavily pre-treated R/R *KMT2Ar* and *mNPM1* patients, and demonstrated a clinically manageable safety profile
- 30% of patients attained CR/CRh with a median duration of 9.1 months
  - 78% of patients with CR/CRh attained MRD negativity
- 38% of responders proceeded to transplant
- Median OS was 7 months in this R/R population
- The only DLT, and the only common (≥5%) ≥Grade 3 related TEAE, was asymptomatic Grade 3 QTc prolongation
  - 10% in patients treated at doses meeting criteria for RP2D; 13% in patients treated at all doses tested
- Differentiation syndrome occurred in 16% of patients
  - All cases were Grade 2 and responded to management with steroids with or without hydroxyurea

AUGMENT-101 Phase 2 pivotal trials underway in 3 distinct patient populations

AUGMENT-101

R/R
KMT2Ar (MLLr)
or *mNPM1*
acute leukemia

Dose:
Revumenib 163 mg q12h
with a strong CYP3A4 inhibitor

Independent, pivotal trials

64 adults + up to 20 peds	**AUGMENT-101-2A: *KMT2Ar* ALL**
64 adults + up to 20 peds	**AUGMENT-101-2B: *KMT2Ar* AML**
64 adults + up to 20 peds	**AUGMENT-101-2C: *mNPM1* AML**

Primary objective: CR/CRh*
Secondary objectives: Durability of CR/CRh, OS, transfusion independence

*Patients taken to HSCT can restart treatment with revumenib post-transplant.

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AUGMENT-101: Post-transplant outcomes
Abstract #376
Session 723. Allogeneic Transplantation: Long-term Follow-up and Disease Recurrence II
December 10, 4:00-5:30p