RYVU THERAPEUTICS

Developing therapeutics
at the forefront of oncology

RVU120 Phase II Program:
Progress and Data Update

December 12, 2024

(Data updated with a cutoff of December 11)

Note on the presentation and forward-looking statements

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AGENDA

RVU120 PHASE II

studies progress and data update

- RVU120 program overview
- RIVER-52
- RIVER-81
- POTAMI-61
- REMARK
- RVU120 outlook

PAWEŁ PRZEWIĘŹLIKOWSKI
Chief Executive Officer

KAMIL SITARZ
Chief Operating Officer

HENDRIK NOGAI
Chief Medical Officer

Ryvu is developing novel therapies to address high-value emerging targets and pathways in oncology

FIRST-IN-CLASS CLINICAL PIPELINE

RVU120
Fully-owned

- First-in-class, oral **CDK8/19** inhibitor
- Four Ph II studies ongoing: mono and combo in AML/HR-MDS, LR-MDS, and MF

MEN1703
Partnered

- First-in-class dual **PIM/FLT3** kinase inhibitor in Phase II; DLBCL study to initiate with potential across hematology
- Partnered with Menarini Group

DISCOVERY PLATFORM

SYNTHETIC LETHALITY
Fully-owned

- **RVU305**: best-in-class oral MTA-cooperative **PRMT5** inhibitor in IND/CTA-enabling studies
- **WRN** program
- **Novel SL** targets

IMMUNO-ONCOLOGY
Partnered

- **BioNTech**: STING standalone license and multi-target research collaboration
- **Exelixis**: STING ADC collaboration

FULLY INTEGRATED RESEARCH & DEVELOPMENT ORGANIZATION

- **LISTING:** WSE:RVU (mWIG40 index); cash runway to Q1 2026
- **TEAM:** >300 employees, including ~185 scientists (with ~100 PhDs)
- **SITE:** Fully-owned, state-of-the-art 108,000 sq ft facility

Broad pipeline addressing emerging targets in oncology

PROGRAM	INDICATION	DISCOVERY	PRECLINICAL	PHASE I	PHASE II	PARTNER	EXPECTED MILESTONES
RVU120 (CDK8/19)	R/R AML/HR-MDS (RIVER-52) (monotheraphy)					LEUKEMIA & LYMPHOMA SOCIETY	Updated Ph II data in 2Q25
	R/R AML (RIVER-81) (combo with venetoclax)						Updated Ph II data in 2Q25
	LR-MDS (REMARK) (monotherapy)					EMSCO MYELODYSPLASTIC SYNDROMES	Initial Ph II data in 2Q25
	Myelofibrosis (POTAMI-61) (mono and combo with ruxolitinib)						Initial Ph II data in 2Q25
	Solid Tumors (AMNYS-51)						Complete Ph I data & translational studies in 2024
MEN1703 (SEL24) (PIM/FLT3)	DLBCL (mono and combo with glofitamab)					MENARINI	Initiation of Ph II in 4Q24
SYNTHETIC LETHALITY							
RVU305 (PRMT5)	SOLID TUMORS						IND/CTA submission in 2H25
WRN	SOLID TUMORS						In lead optimization
NOVEL TARGETS	ONCOLOGY						
IMMUNO-ONCOLOGY							
STING & MULTI-TARGET IMMUNE MODULATION COLLABORATION	ONCOLOGY					BIONTECH	
STING ADC	ONCOLOGY					EXELIXIS	

Study start-up

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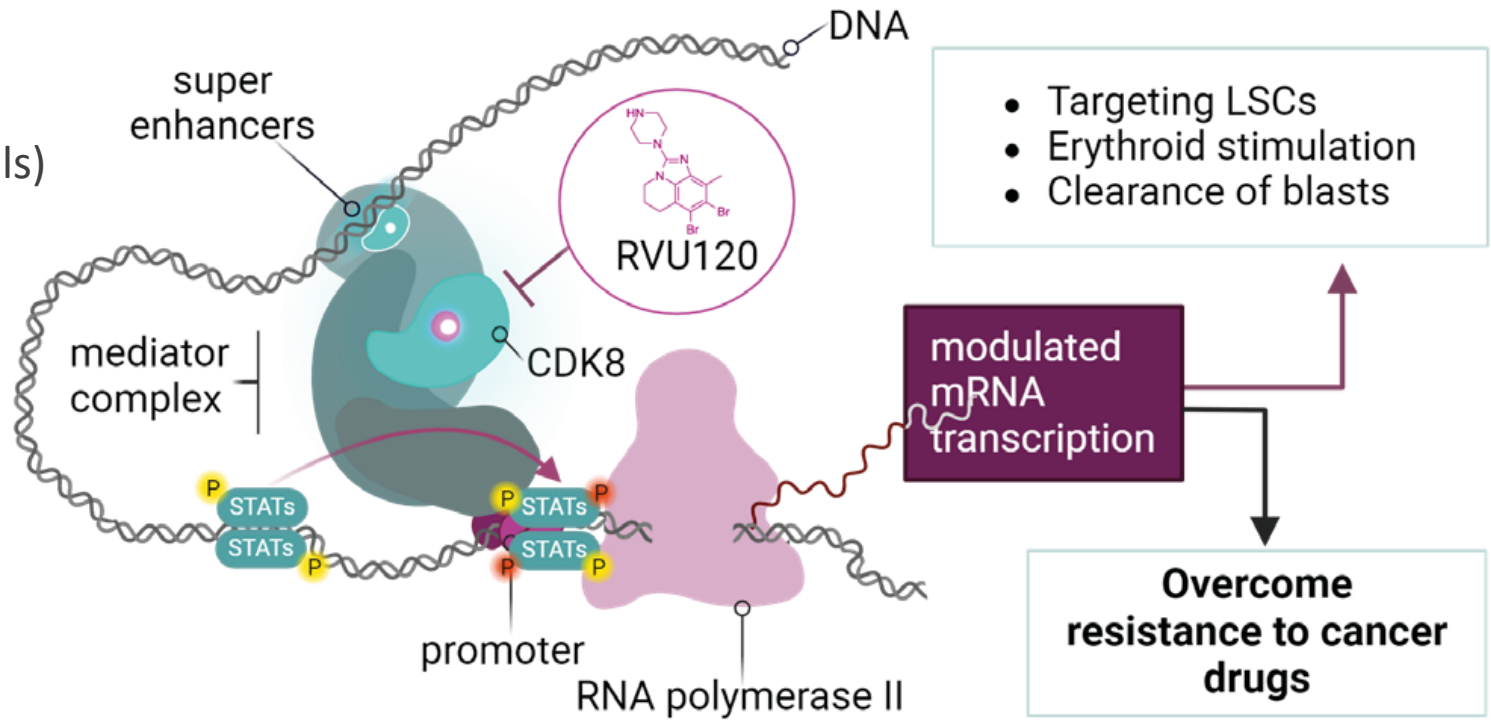
RVU120 is a clinical-stage, first-in-class, small molecule CDK8/19 kinase inhibitor developed and fully-owned by Ryvu

- high selectivity
- low risk of DDI (esp antifungals)
- easy to formulate
- orally bioavailable
- favorable safety profile



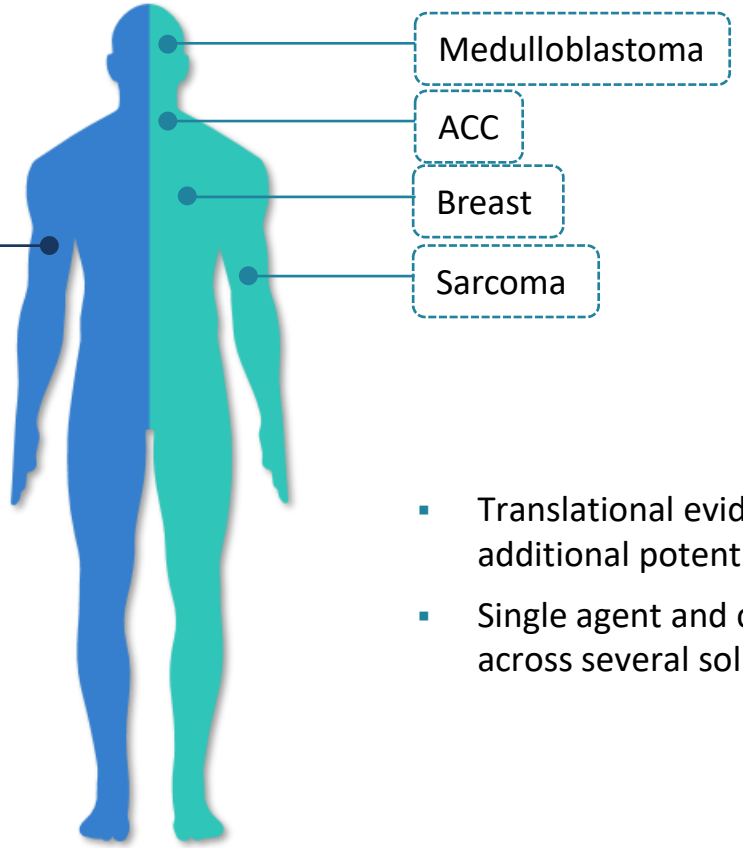
RVU120 is an innovative dual CDK8/19 inhibitor designed to target the expression of genes crucial for cancer cell survival and differentiation

RVU120: opportunities across a broad range of cancers

Blood Cancers & Disorders

AML
High-risk MDS
Low-risk MDS
Myelofibrosis (MF)
MDS/MPN overlap syndrome
NHL
Diamond-Blackfan Anemia

Solid Tumors



- **Signs of clinical activity in AML/HR-MDS**
- Broad potential across hematologic disorders
- Responder hypothesis in AML
  – unmet need with no approved therapies
- Synergy with standard-of-care in AML and MF
- **Next expected clinical data release – Q2 2025**

- Translational evidence in multiple tumor types, additional potential in combinations
- Single agent and combination potential across several solid tumors

RVU120 development plan is focused on hematological malignancies
Four Phase II studies ongoing

RVU120 Phase II development plan rationale: RIVER-51 clinical data

15 of 30 evaluable patients showed clinical benefit across dose levels

Clinical benefits

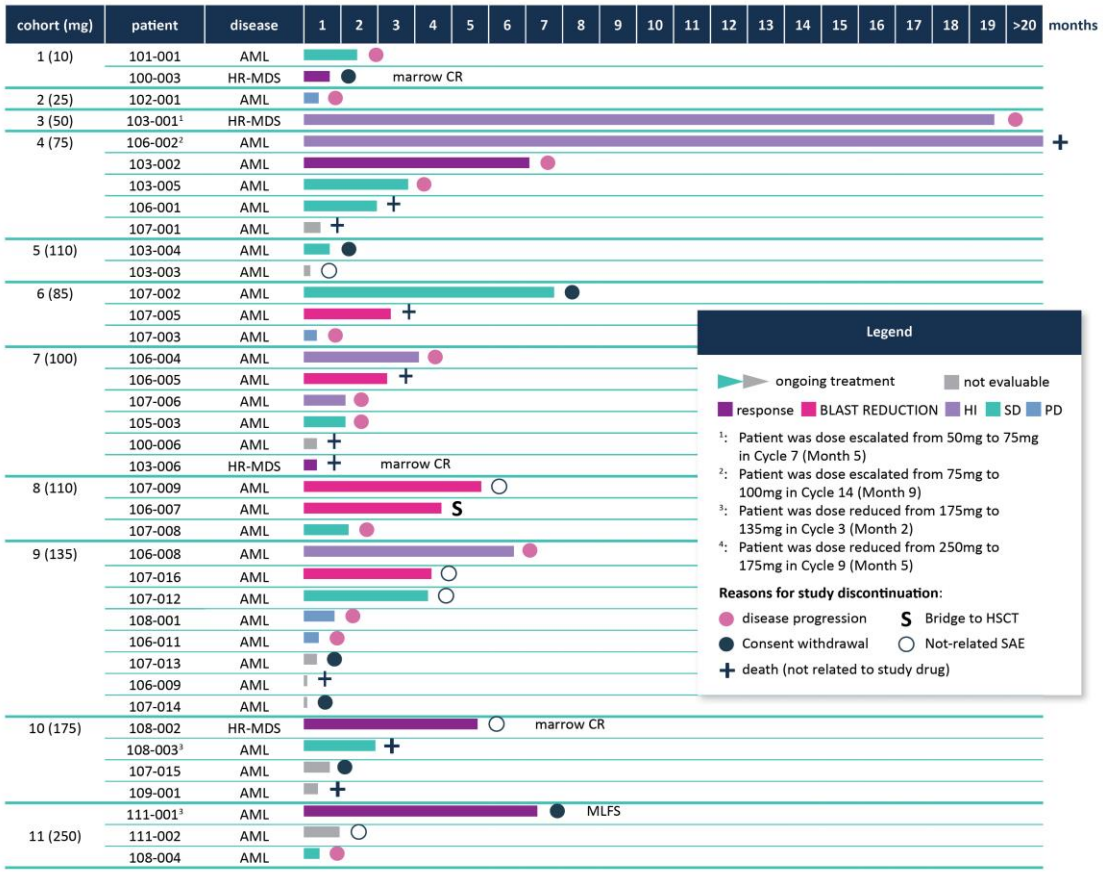
- **30 treated patients are evaluable for response (38 were treated in total)**
- **9 patients achieved clinically significant BM blast reduction**
- (including 1 CR, 1 MLFS, 3 marrow CRs)
- **5 patients achieved erythroid hematological improvement (HI-E),**
  4 of those became transfusion-independent,
  of which 2 normalized also their Grade 3 thrombocytopenia

NPM1 and DNMT3A mutations

- An **NPM1 mutation** was identified in 2 pts – **one patient achieved a CR**, the other experienced an unrelated SAE in cycle 2 and progressed
- Three additional patients had a **DNMT3A mutation** without NPM1 mutation and achieved **significant blast reductions, long-term disease control, or hematologic improvement**

HR-MDS

- 4 pts with HR-MDS treated were failing 1-5 prior lines of treatment
- **3 of these pts had >10 % blasts at baseline, all of them met the Cheson criterion of marrow CR during treatment with RVU120**



Favorable safety profile
Target engagement levels between 50-70% at a dose of 250 mg – selected for Phase II development

Data generated in RIVER-51 study support further development of RVU120 in AML, HR-MDS, LR-MDS and MF

Significant blast reductions

- Confirmed CR in NPM1/DNMT3A AML patient
- Several patients with significant blast reduction

Transfusion independence

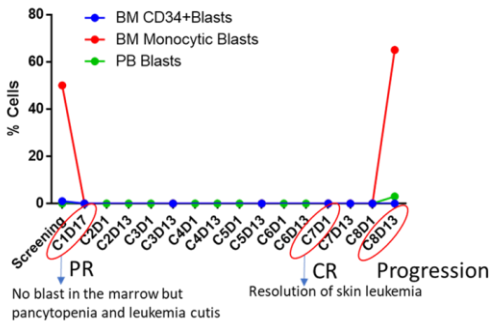
- >20% patients, (all with AML-MR or HR-MDS), showed hematological improvement, meeting Cheson criteria for erythroid response

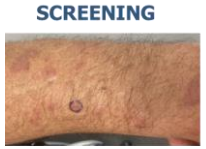
Improvement of BM architecture

- Signs of activity in secondary AML
  - reduction of fibrosis and hematologic impr.
- Supported by non-clinical data in MF/MDS models

P103-002 AML

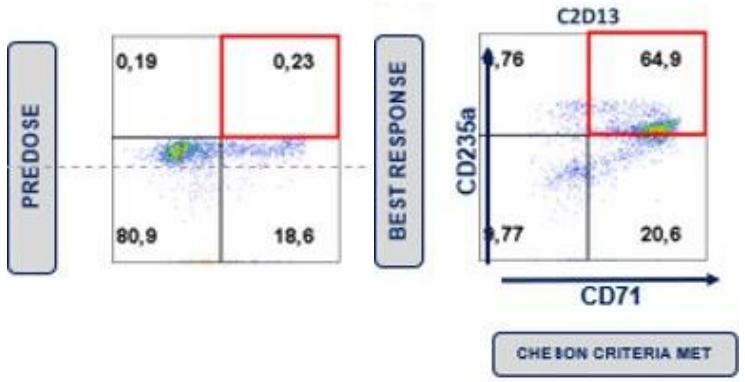
- NPM1, DNMT3A, FLT3-ITD.,NRAS
- 46,XX, 3 prior treatment lines
- 6U RBC/3 weeks and 6U Plts/4 weeks





P106-004 AML -MR

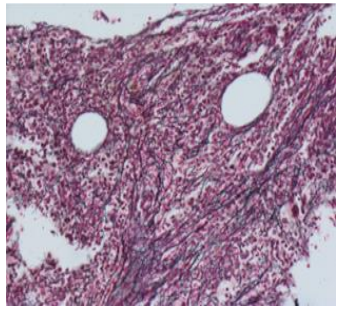
- Mutations: GATA2, RUNX1, SF3B1,TET2, WT1
- Karyotype: 47,XY,+21; 3 prior treatment lines
- 9U RBC/8 weeks; grade 4 Thrombocytopenia



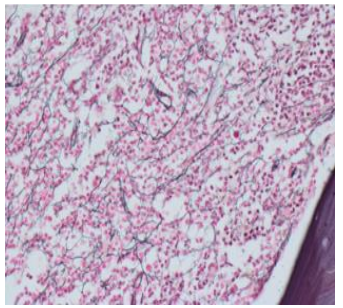
P108-002 HR-MDS

- Mutations: MPL, DNMT3A, U2AF1
- Karyotype: 46XY, add (4)(q21); 1 prior treatment line
- Best response: marrow CR

C2D13 fibrosis grade 3



C6D1 fibrosis grade 2

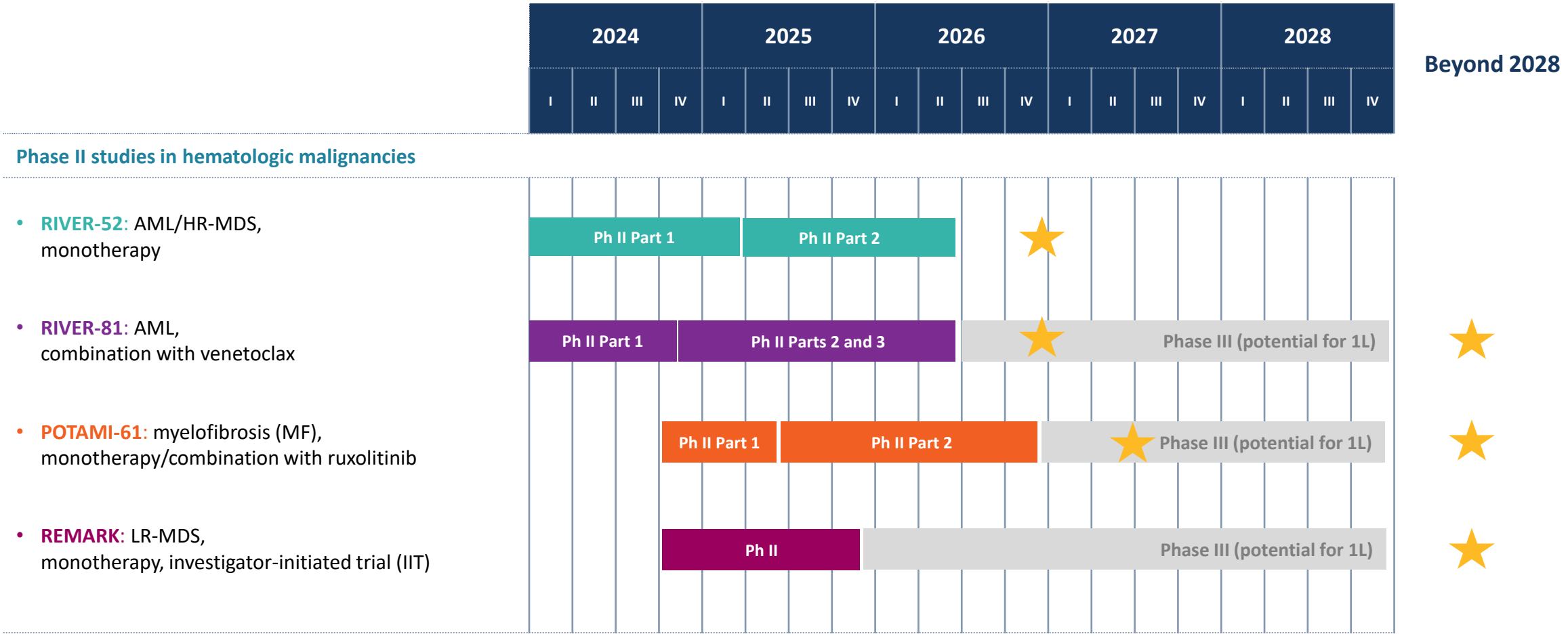


CR achieved end of C1 with persistent skin leukemia, resolved in C5

RBC-TI and Plt-TI on RVU120 treatment

Reduction of fibrosis grade and marrow CR

Current clinical development of RVU120 focuses on single agent trials in patients with AML, MDS, and MF and combinations in AML and MF



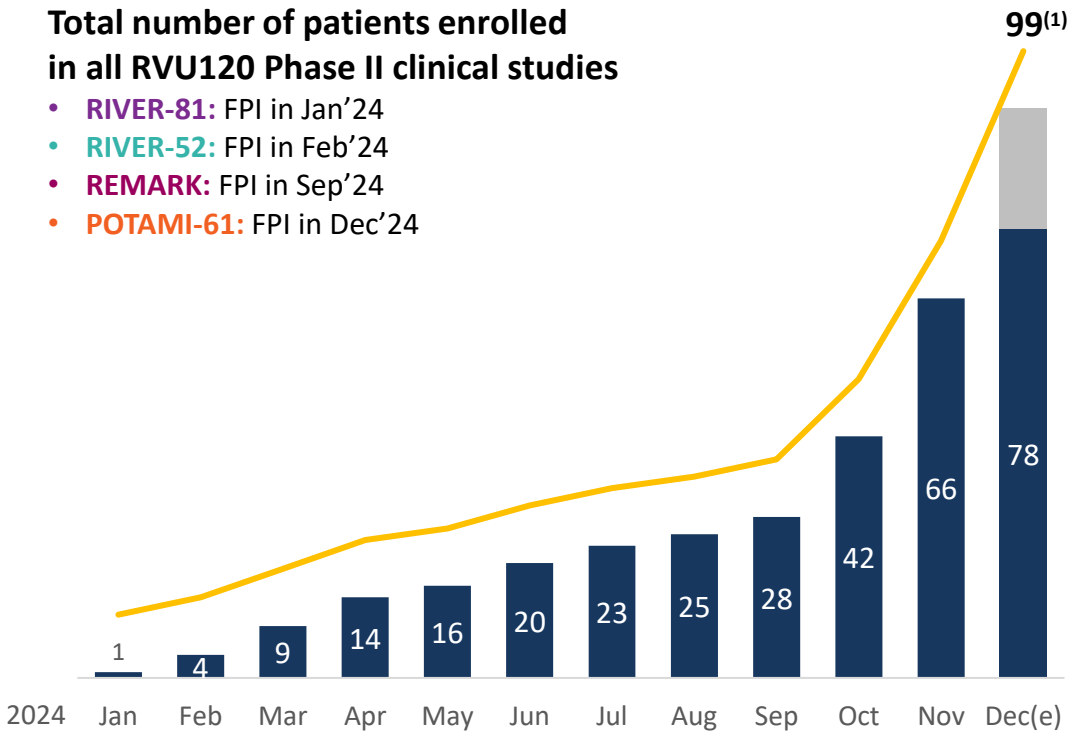
RVU120 Phase II studies progress and data update

Summary of enrollment

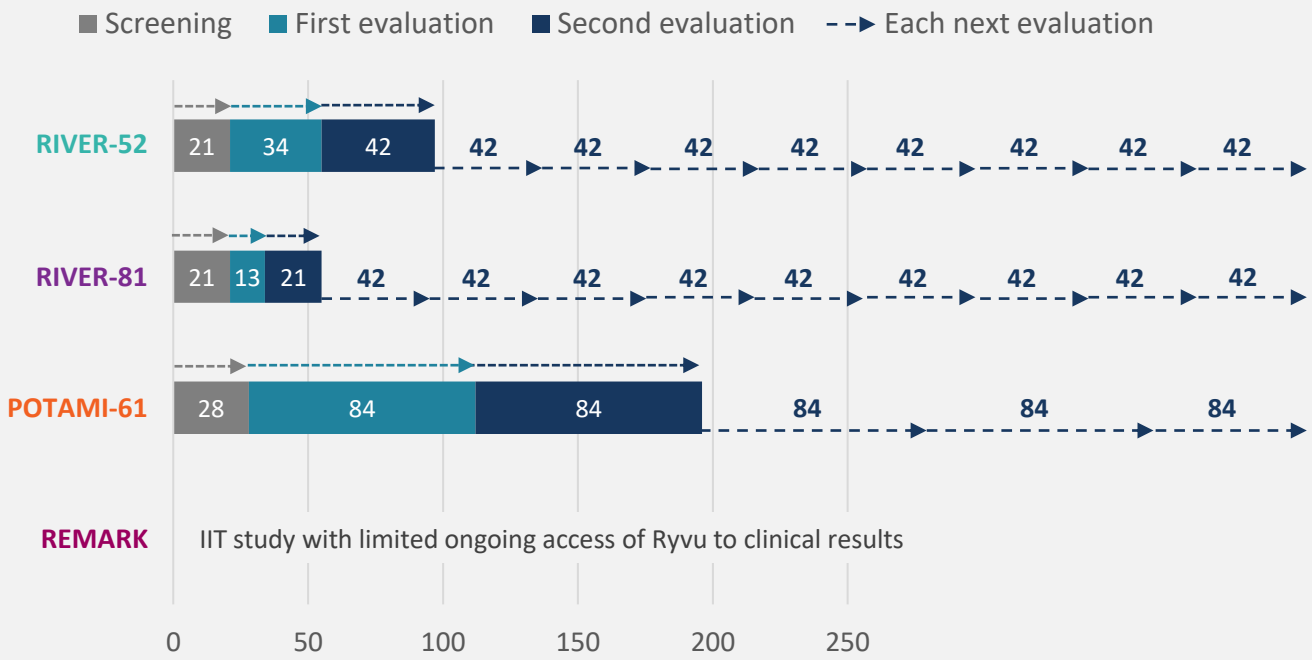
Active enrollment in all four Phase II studies

Total number of patients enrolled in all RVU120 Phase II clinical studies

- **RIVER-81:** FPI in Jan'24
- **RIVER-52:** FPI in Feb'24
- **REMARK:** FPI in Sep'24
- **POTAMI-61:** FPI in Dec'24



Time needed for screening and evaluating patients (days)



Note: Responses to targeted agents can occur up to 6 months after start of treatment

Expected number of patients enrolled in Q4 almost 3x higher than in Q1-Q3 combined

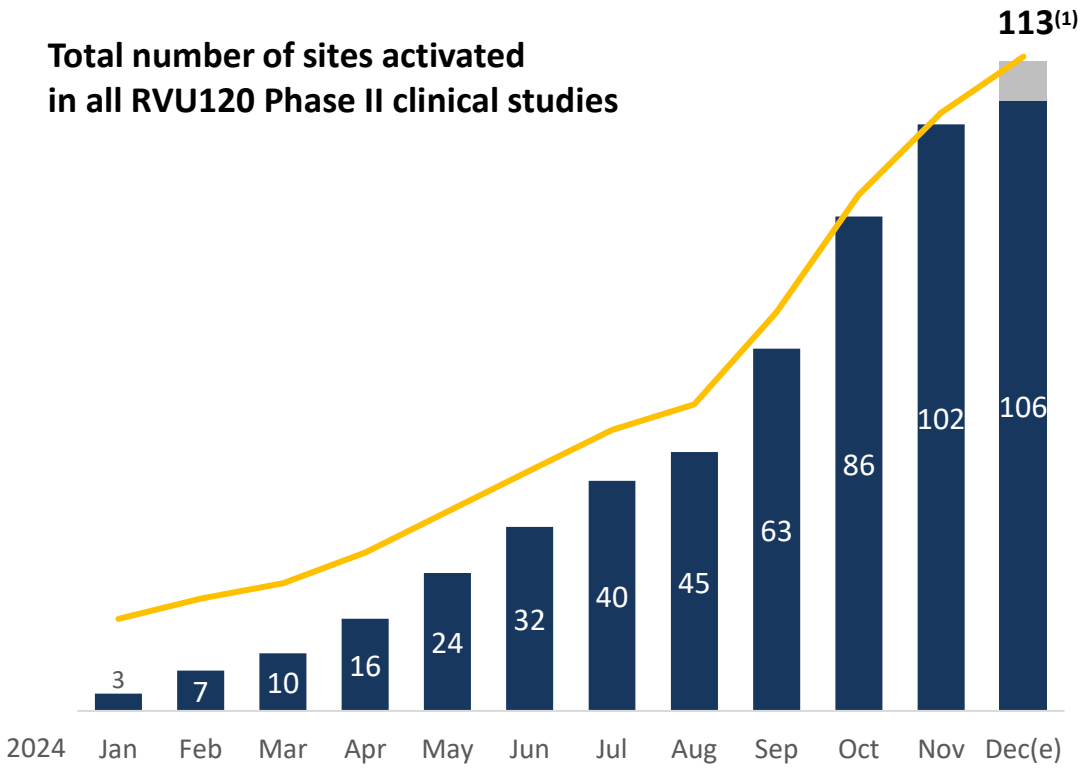
(1) expected as of December 31, 2024

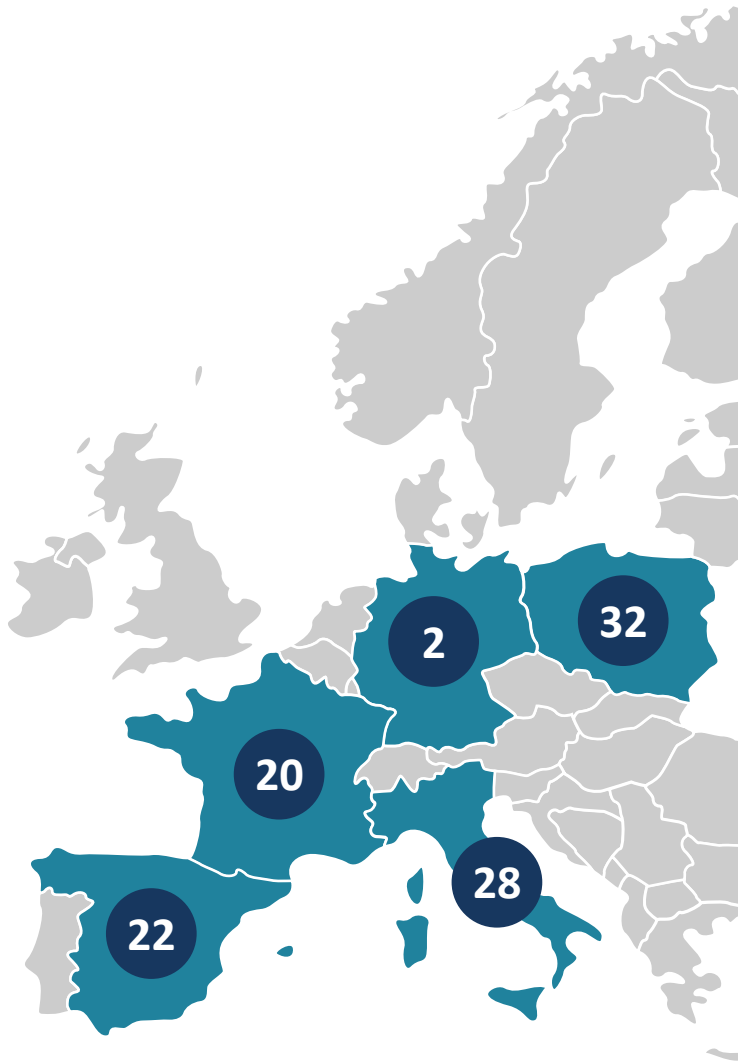
RVU120 Phase II studies progress and data update

Summary of site activations

150% increase in the number of activated sites from Sep to Dec 2024(1)

Total number of sites activated in all RVU120 Phase II clinical studies





Clinical program with a global footprint enabling accelerated enrollment

(1) expected as of December 31, 2024

RVU120 Phase II studies progress and data update

Studies summary

RIVER-52	**Increasing enrollment from Q4 2024**	• 1 of 2 evaluable NPM1+ pts with 50% blast reduction • Disease stabilizations and reductions of peripheral blasts observed in DNMT3A+ pts • Data from the first 10+ evaluable patients in Cohorts 2-4 expected in Q1 2025
RIVER-81	**Good enrollment and first data**	• Dose escalation completed with tolerable safety for the full combination doses • **1 complete remission (CR) in a difficult to treat ven-refractory population, eight patients at RVU120 250 mg had at least one evaluable post-baseline assessment** • Part 2 initiated; further development decision in H1 2025
POTAMI-61	**Robust enrollment expected**	• FPI on December 4, 2024; study in progress • First efficacy data expected in Q2 2025
REMARK	**Promising start of enrollment**	• FPI on September 18, 2024; study in progress • First efficacy data expected in Q2 2025

First signs of efficacy in Phase II; number of evaluable patients expected to increase in H1 2025

(1) Estimated enrollment for December 31, 2024

Commercial Opportunity for RVU120 in AML

Development of RVU120 towards earlier lines of therapy

RVU120 Path to Market		US Market Opportunity		
Relapsed/ Refractory AML	**RIVER-52**	Patients with AML harboring NPM1/DNMT3A mutations have few options in second- or third-line after failing menin inhibitors, chemo, ven and other treatment	**Mutation-driven**	**2k** 2L and 3L NPM1/DNMT3A patients US, 2030[2] → **$200M+** Total US market size: 3L[2]
	RIVER-81	High unmet medical need in patients failing first-line ven: nearly all ven patients relapse or become refractory with few treatment options	**Venetoclax-refractory**	**4k** Unfit venetoclax patients progressing to 2L US, 2030[2] → **$400M+** Total US market size: 2L ineligible[2]
Newly Diagnosed AML (Unfit)	• Strong Phase II combo data could support a Phase III registration study with approval as early as 2029 • A first-line doublet or triplet could be an efficacious and safe alternative to ven+aza and triplet combos for patients unfit/ineligible for intensive chemo		**20k** Newly diagnosed AML cases US, 2030[1] → **12k** Patients ineligible for intensive induction US, 2030[2] → **$1.2B+** Total US market size: 1L ineligible[2]	

Initial combo opportunity in r/r AML could expand into a significantly larger opportunity in front-line AML

(1) PharmaIntelligence, AML Epi Datapack, July 2023. (2) Datamonitor AML Patient-based Forecast Model, Dec 2024.

RIVER-52 Phase II

RVU120 monotherapy
in r/r AML and HR-MDS patients

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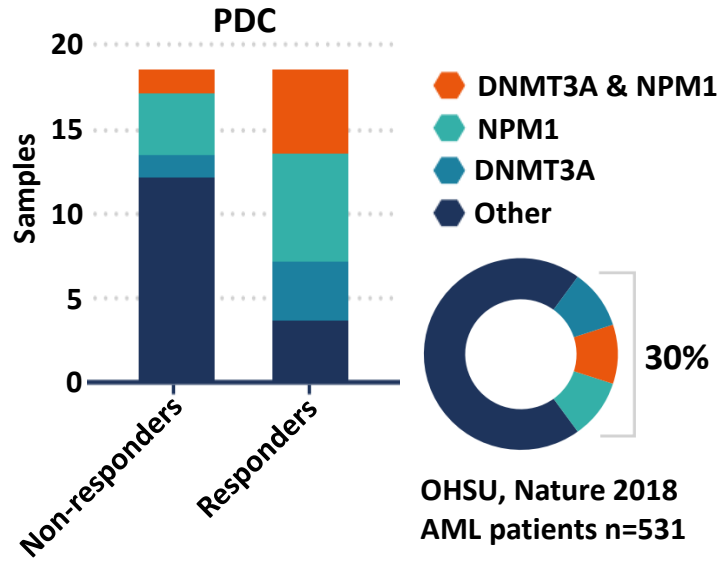
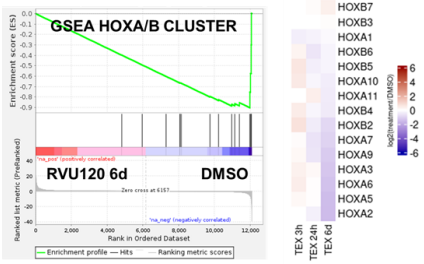
RIVER-52 Nonclinical Results and Signals of RVU120 Efficacy from Phase 1 (RIVER-51) Provide Rationale for Phase 2 study in NPM1 and DNMT3A Mutant Patients

- **Differential efficacy of RVU120 in AML models**:
  - In vitro screening of AML patient-derived cells revealed differential efficacy of RVU120 and other CDK8 inhibitors in NPM1 and/or DNMT3A mutants
  - RVU120 as monotherapy demonstrated high efficacy in NPM1 or DNMT3A-mutated patient-derived xenografts
- **Transcriptomic profiling provides mechanistic rationale:**
  Transcriptomic profiling indicated RVU120 represses MEIS1/HOXA/B gene expression programs, highly enriched in AML positive for NPM1 and DNMT3A mutations
- **Clinical Activity in Phase I:**
  One of two NPM1 mutant patients recruited in Phase I achieved complete remission (CR); transcriptomic profiling demonstrated repression of MEIS1/HOXA/B genes, consistent with nonclinical findings

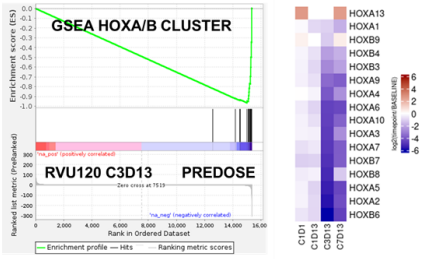


RVU120 downregulates homeobox cluster genes in TEX CD34+ leukemic cells and in AML patient 103-002 that achieved a complete remission

Preclinical data (TEX CD34+ cells)



Clinical data (patient 103-002):



RIVER-52 Phase II study with RVU120 as a single agent in AML/HR-MDS

RVU120 monotherapy

STUDY DESIGN

- Primary endpoints:
  - Rate of CR, CRh, CRi, with and without MRD, and DoR
- Secondary endpoints:
  - Transfusion independence, Progression-free survival, Relapse-free survival (RFS), Overall survival
- For Part 2: including PRO and HRQoL change from baseline
- Population: relapsed/ refractory AML or HR-MDS with no alternative treatment
- Estimated enrollment: **~40-140 patients**
- Up to **80 clinical sites** planned globally

PART 1 (N = ~40 pts)

Genetically defined and disease specific cohorts:

- Pts with NPM1-mutated AML
- Pts with DNMT3a-mutated AML
- Pts with HR-MDS

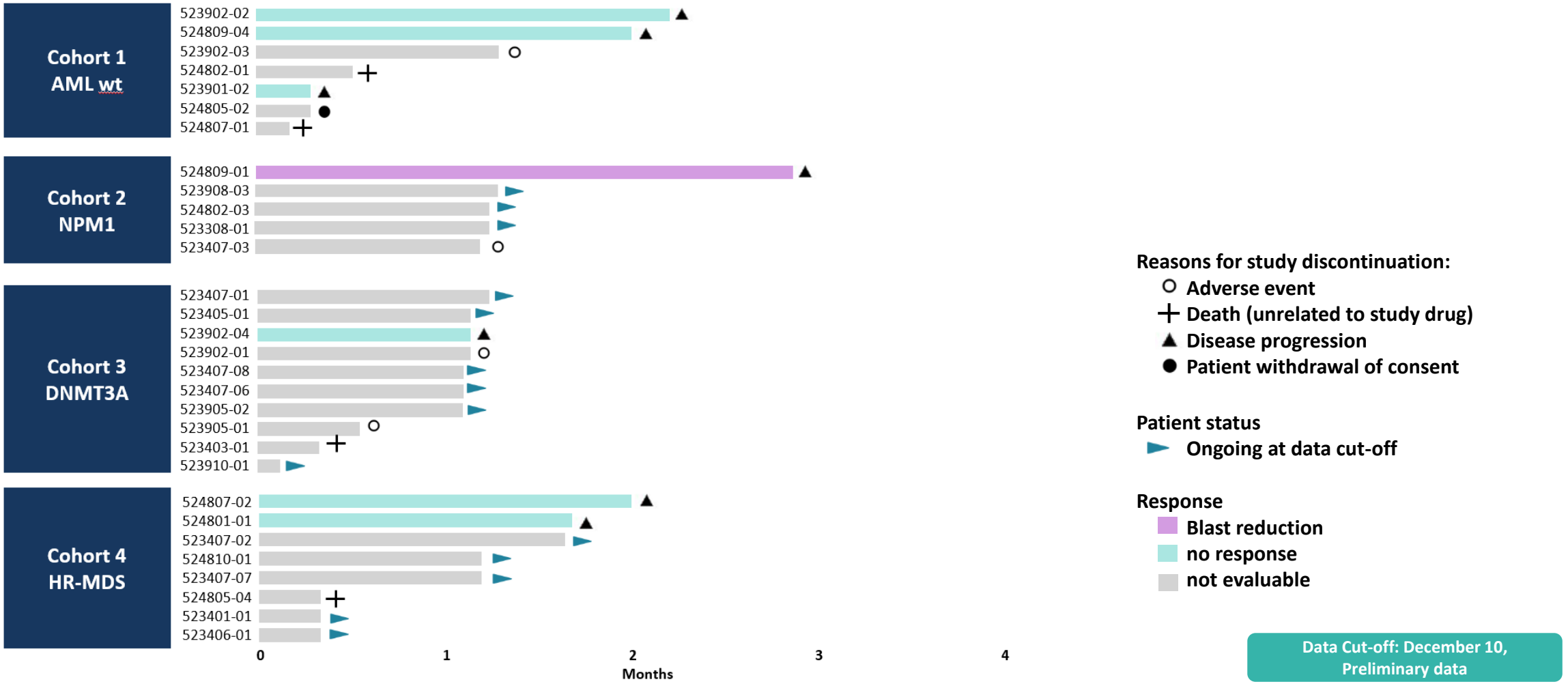
Clinical Benefit
(CR/CRh/CRi/HI)
in any of the cohorts

PART 2 (N = ~100 pts)

Confirmatory Cohort
Simon 2-stage design
Pts selected based on Part 1 outcome

Results from the ongoing Part 1 will determine potential launch of Part 2

RIVER-52 Swimmer Plot : 14 ongoing patients out of 30 enrolled overall



Data Cut-off: December 10, Preliminary data

No new safety signal was identified
Systemic exposure of RVU120 following oral dosing of 250 mg QOD was confirmed to be consistent with previous studies
Data is immature for the interpretation of efficacy

RIVER-52 RVU120 appears to have a good safety profile, with the notable absence of QTc prolongation and differentiation syndrome

Agent (#pts)	Revumenib (N=94)	Ziftomenib (N=83)	RVU120 (N=20)
Trial	Phase 1/2 (AUGMENT-101)	Phase 1/1b (KOMET-001)	Phase 2 (RIVER-52)
Company	Syndax	Kura	Ryvu
DLT	Ph 1 QTc Pr	Gr 3 Pneumonia Gr 4/5 DS	No
DS (all)	**26 (28%)**	**12 (15%)**	**0 (0%)**
DS (≥ Gr3)	15 (16%)	10 (12%)	0 (0%)
Neutropenia (≥ Gr3)	27 (29%)	7 (8%)	2 (10%)
Febrile Neutropenia (≥ Gr3)	36 (38%)	18 (22%)	3 (15%)
Thrombocytopenia(≥ Gr3)	20 (21%)	5 (6%)	3 (15%)
Anemia	22 (21%)	20 (24%)	2 (10%)
QTc prolongation (any)	**24 (25%)**	**0 (0%)**	**1 (5%)**
QTc prolongation (≥ Gr3)	13 (14%)	0 (0%)	0 (0%)
Transaminitis	27 (29%)	16 (19%)	1 (5%)
Sepsis	11 (12%)	15 (18%)	1 (5%)

Data cut-off 01 Nov 2024

RIVER-52 Patient 524809-01 – Cohort 2 (NPM1+)

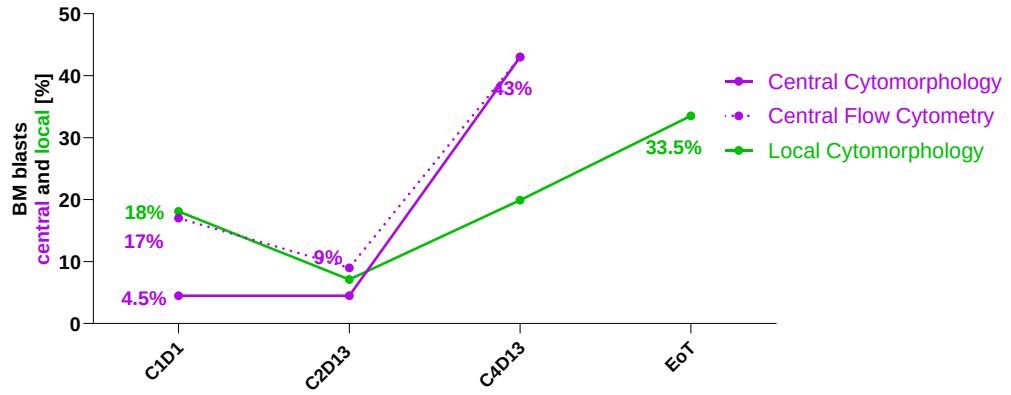
C1D1 15-May-2024

EoT 12-Sep-2024

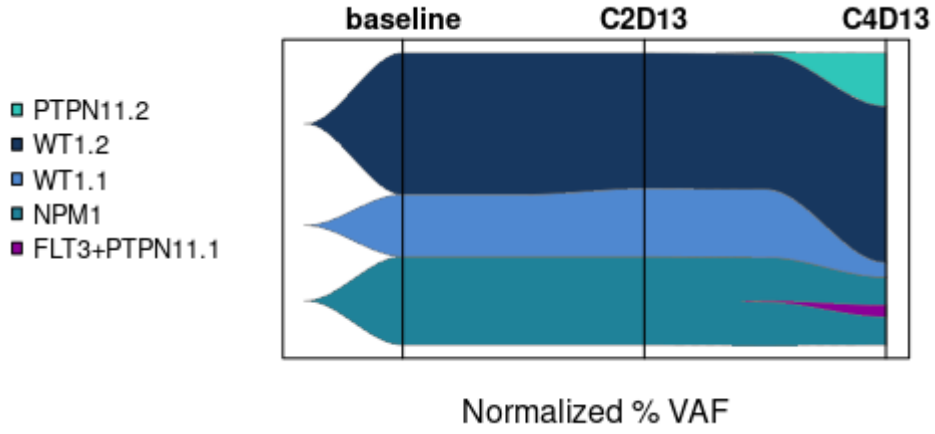
Patient history

- 59yo Female, ECOG 1
- Comorbidities: degenerative spine disease with musculoskeletal and connective tissue disorders
- **AML with NPM1 mutation, May 2022**
  - Previous treatment: cladribine, daunorubicin, cytarabine (May-Sep 2022): CR
- 4 completed cycles of RVU120
  - SAEs Anemia/Fatigue

Bone Marrow

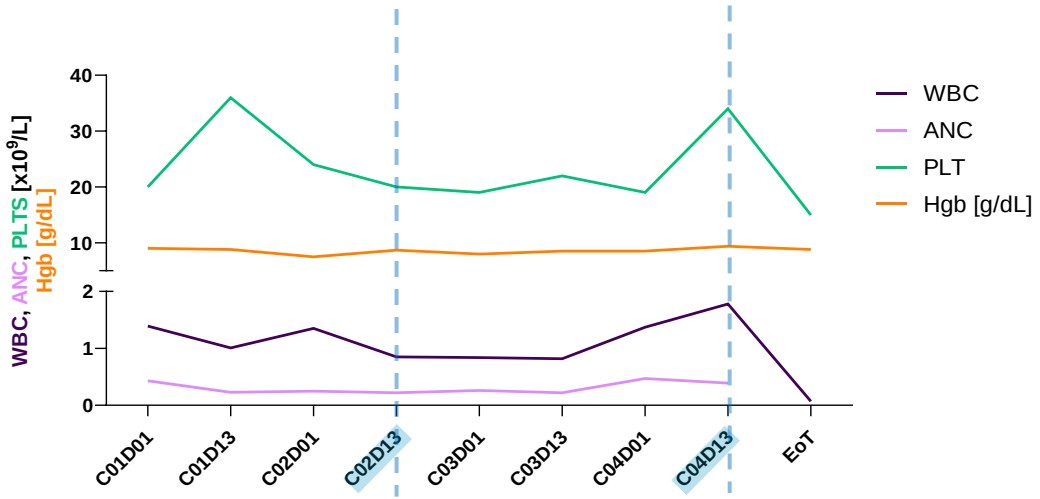


NGS



WT1.1 – c.1110dup; WT1.2 – c.1249+2T>C; PTPN11.1 – c.766_768delinsAGGGTG; PTPN11.2 – c.854T>C

Hematology



An initial reduction of blasts of > 50% could be detected in this patient that has a highly heterogenic disease

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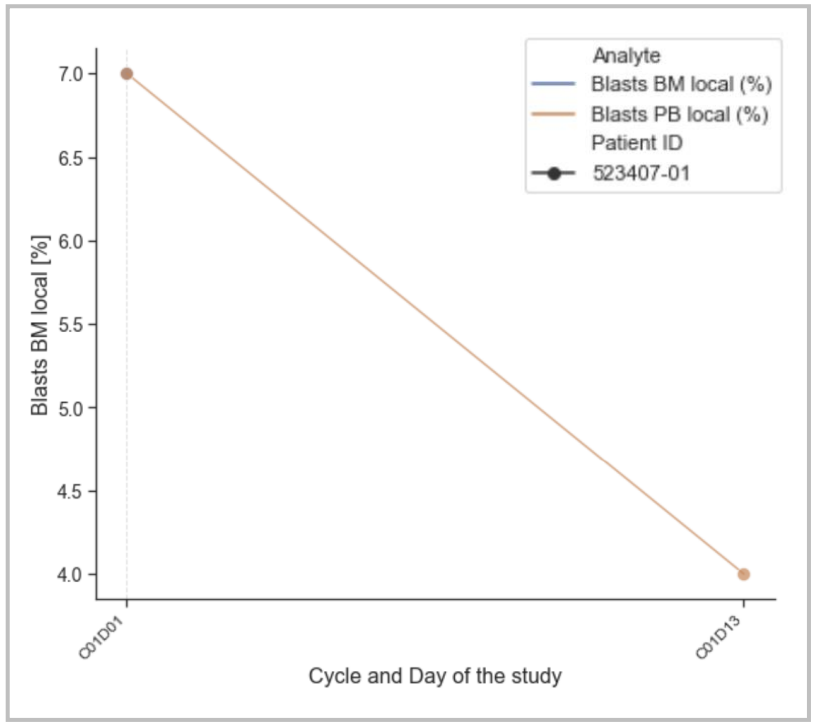
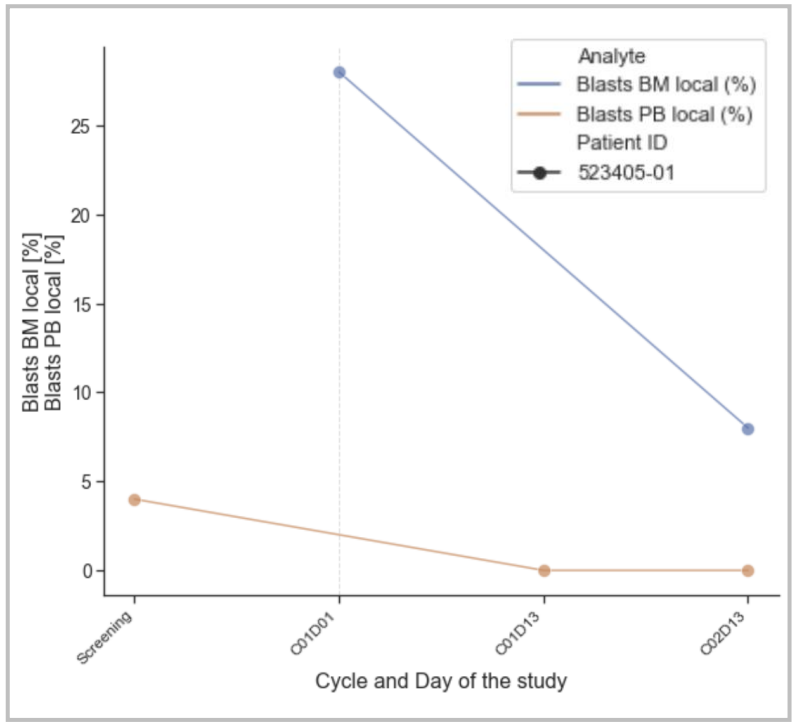
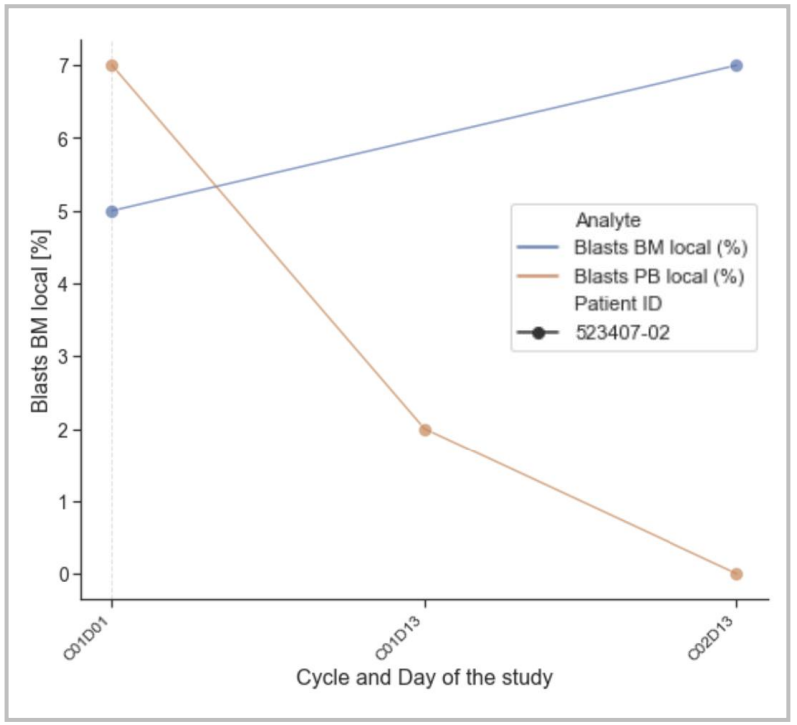
RIVER-52 Although not meeting objective response criteria, preliminary data in additional patients showed reduction of blasts with multiple patients ongoing

Patients with DNMT3A mutated AML





Patient with HR-MDS



The patients are ongoing on RVU120, and the treatment outcome has still to be assessed at later time points

RIVER-52 Enrollment increasing with the activation of new sites, to yield preliminary data in H1 2025

31 patients enrolled, and **42 sites activated** (as of Dec 11, 2024)

PART1

Cohort 1 (AML WT)

- Discontinued,
  data used to strengthen RVU120 safety database

Cohort 2 (AML NPM1+)

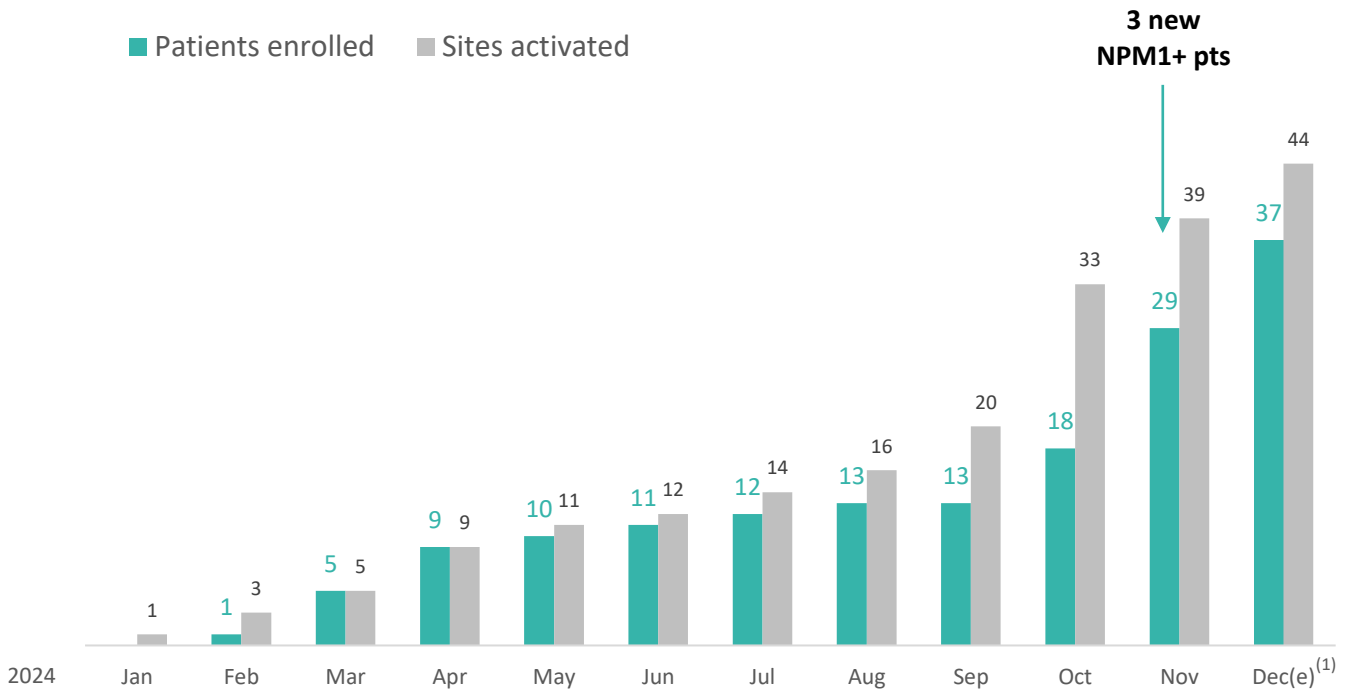
- Enrollment improved after initiation of new sites in Spain and France in Q4 2024

Cohort 3 (AML DNMT3A+)

- Enrollment in line with the expectations

Cohort 4 (HR-MDS)

- Enrollment in line with the expectations



- 42 out of 44 sites planned for this year have already been activated
- Data from the first 10+ patients in Cohorts 3-4 (DNMT3A+, HR-MDS) are expected in Q1 2025
- Data from the first 10+ patients in Cohort 2 (NPM1+) are expected in Q2 2025

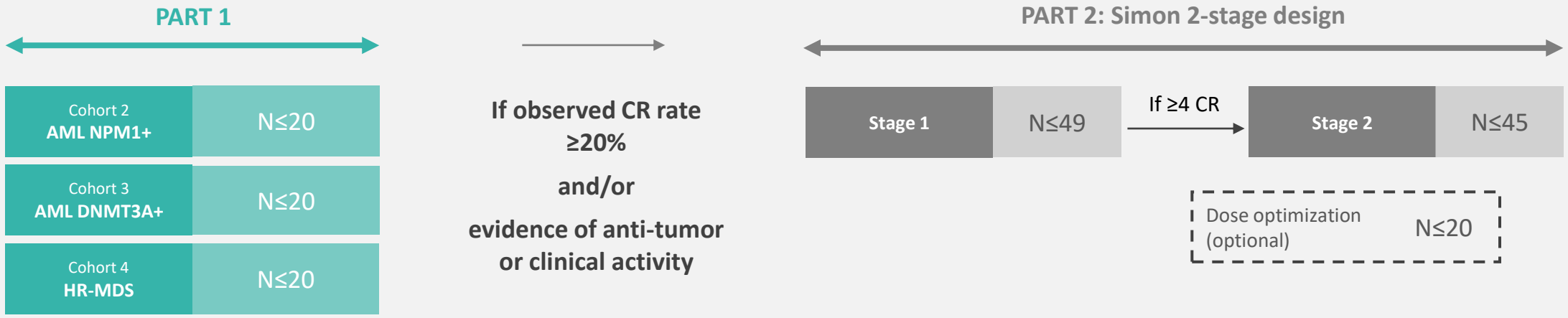
(1) expected as of December 31, 2024

RIVER-52 Summary

Phase II study with RVU120 as a single agent in AML/HR-MDS

- The available patient data are still immature for evaluation of efficacy
- 1 of 2 evaluable patients in Cohort 2 (AML NPM1+) with 50% blast reduction
- Significantly improved enrollment in Cohort 2 from Q4 2024
- Preliminary data expected in H1 2025

Study/risk management



RIVER-81 Phase II

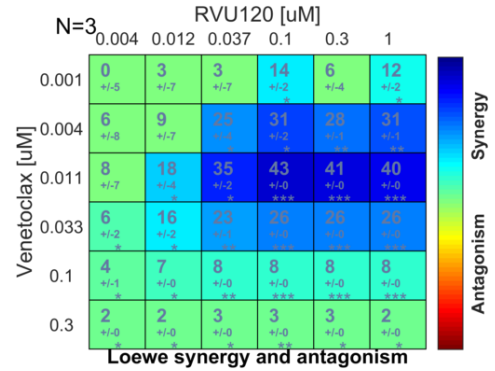
RVU120 combination with VEN
in patients with r/r AML

RIVER-81 Strong nonclinical evidence for synergy between RVU120 and venetoclax providing rationale for a Phase II study in venetoclax refractory patients

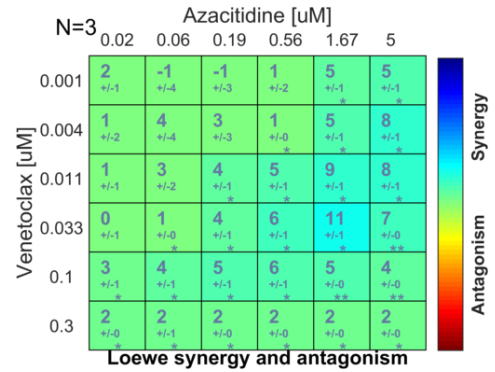
- **True Synergy and Superiority:**
  - RVU120 + ven demonstrates synergy across multiple AML cell lines and superiority over ven + aza
- **Remissions in Animal Studies:**
  - RVU120 + ven achieves remissions in animal models at doses that allow hematological recovery
- **Mechanism of Synergy:**
  - MCL-1 is a known mediator of ven resistance. RVU120 induces caspase-dependent degradation of MCL-1
  - MCL-1 inhibitors were tested in this setting, but prohibitive cardiotoxicity prevented further development
  - The safety profile of RVU120 allows exploration of this concept
  - Effectiveness on Leukemic Stem Cells (LSCs)

MV4-11

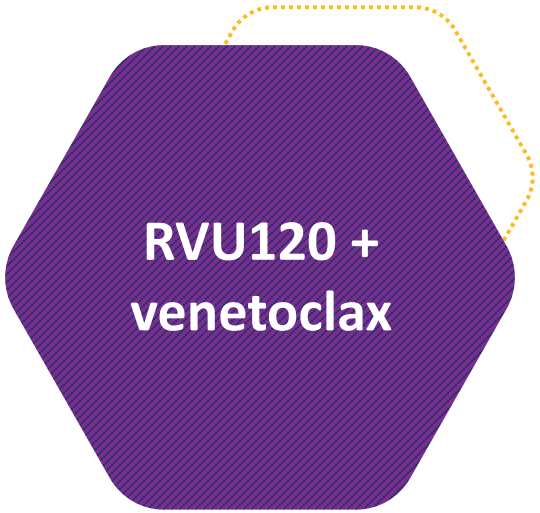
RVU120 + VEN



AZA + VEN



RIVER-81 Phase II study testing RVU120 in combination with venetoclax in ven-refractory patients with AML



STUDY DESIGN

- Primary endpoints:
  - Rate of CR, CRh, CRi, with and without MRD, and DoR
- Secondary endpoints: Transfusion independence, PFS, RFS, OS
- For Part 2: including PRO and HRQoL change from baseline
- Population: r/r ven-failed AML, no alternative treatments
- Estimated enrollment: **~35-97 patients**(1)
- Up to **50 clinical sites** planned globally

MEDICAL RESEARCH AGENCY

RIVER-81 is supported in part by a €13.3M grant from the Polish Medical Research Agency (ABM)

PART 1 (N = 17 pts)

Dose finding in patients with r/r AML after failing a venetoclax-based regimen

PART 2 (N = ~39 pts)

Expansion Cohort at selected doses of RVU120 and venetoclax
(Simon 2-stage design + optional enrichment cohort)

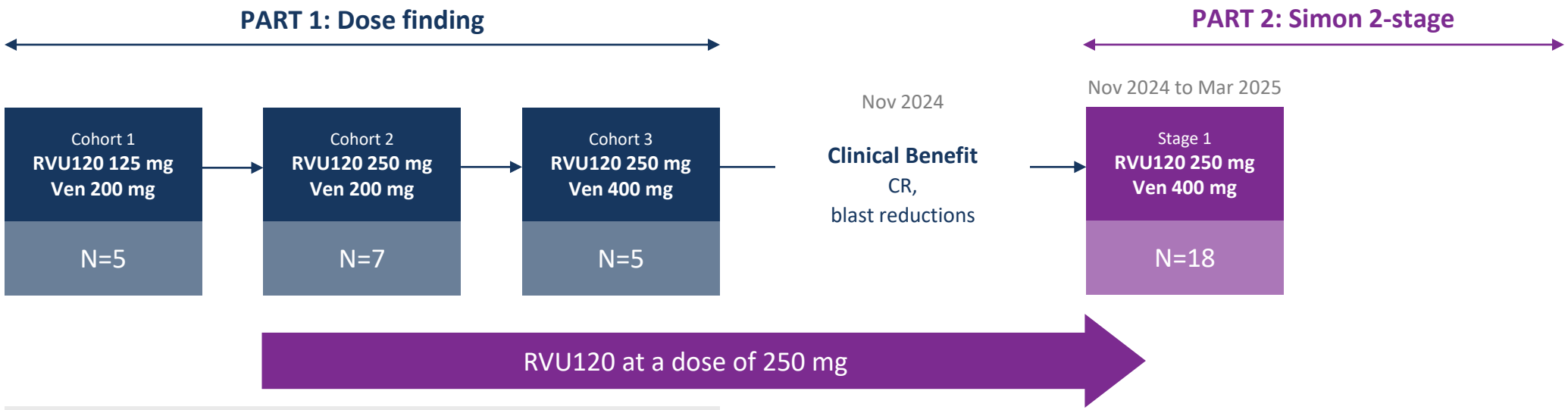
PART 3 (N = ~41 pts)

Confirmatory Cohort at doses of RVU120 and venetoclax as in PART 2

(1) 35 patients for: Part 1 (N=17 pts) and Stage 1 of Part 2 (N=18 pts); 97 patients for: complete planned enrollment into Parts 1, 2 and 3, including optional additional enrichment cohort.

RIVER-81

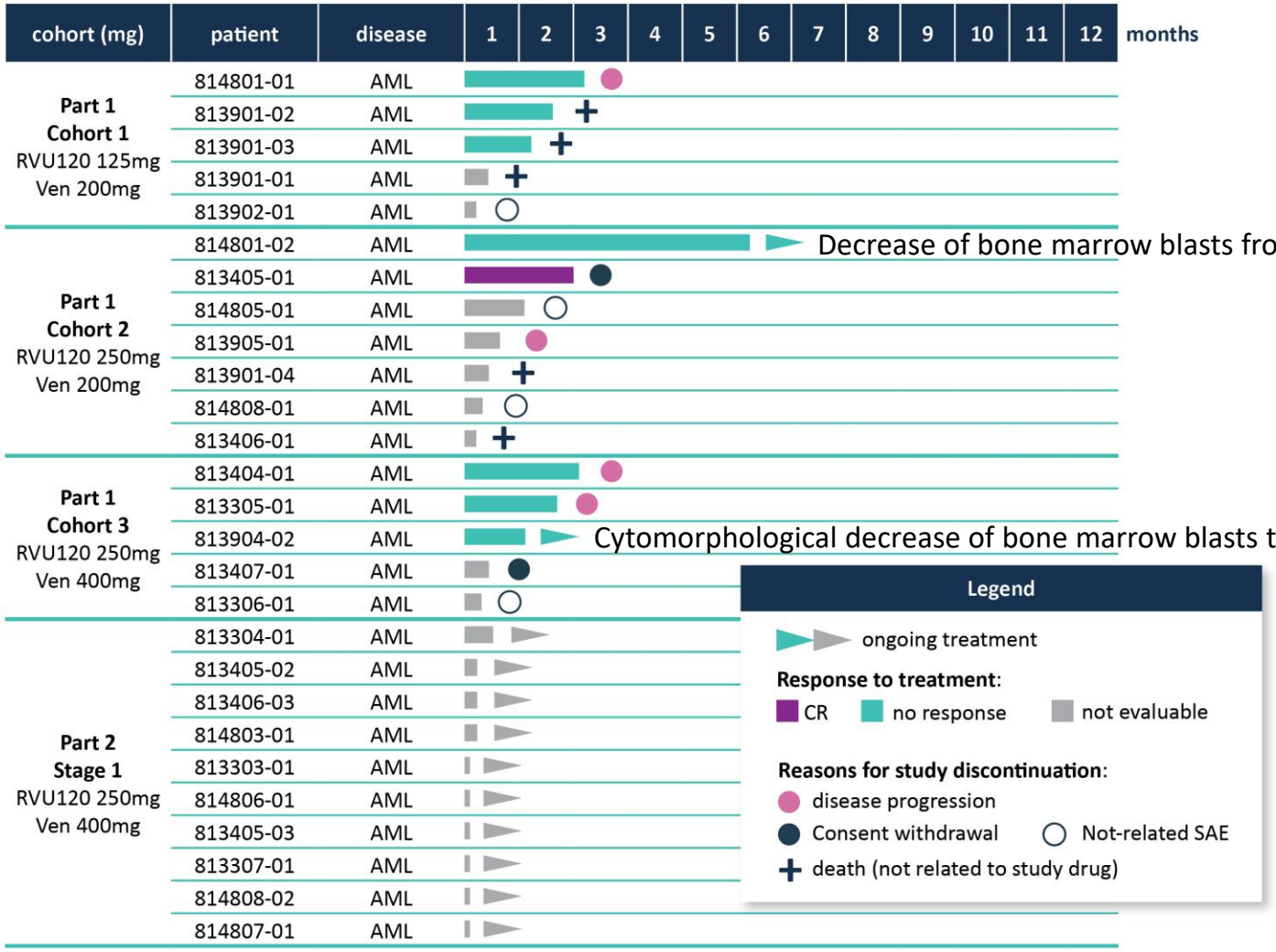
PART 1 (dose escalation) has been completed, the study is currently enrolling into PART 2 at the highest dose from PART 1



- Dose escalation successfully completed, no DLT was observed
- No altered exposure when dosed in combination with venetoclax
- Maximal anticipated RVU120 + ven combination dose (250 mg + 400 mg) achieved
- Confirmed potential for RVU120 + ven doublet and possible triplet combinations in the future

Enrollment in Part 2 initiated based on the observed safety and the early signs of efficacy of the combination
11 of 18 patients have already been treated in Stage 1 of Part 2

RIVER-81 One patient achieved a CR in a difficult to treat ven-refractory population



Data Cut-off: December 10, Preliminary data

Eight patients treated with RVU120 at a dose of 250 mg (RP2D) had at least one evaluable post-baseline assessment

RIVER-81 Patient 813405-01 – Cohort 2 (RVU120 250 mg + Ven 200 mg)

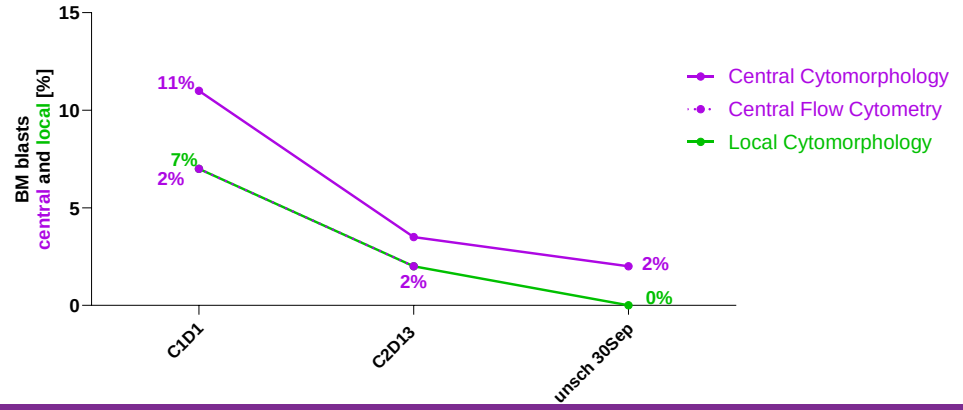
C1D1 04-Jul-2024

EoS 10-Oct-2024

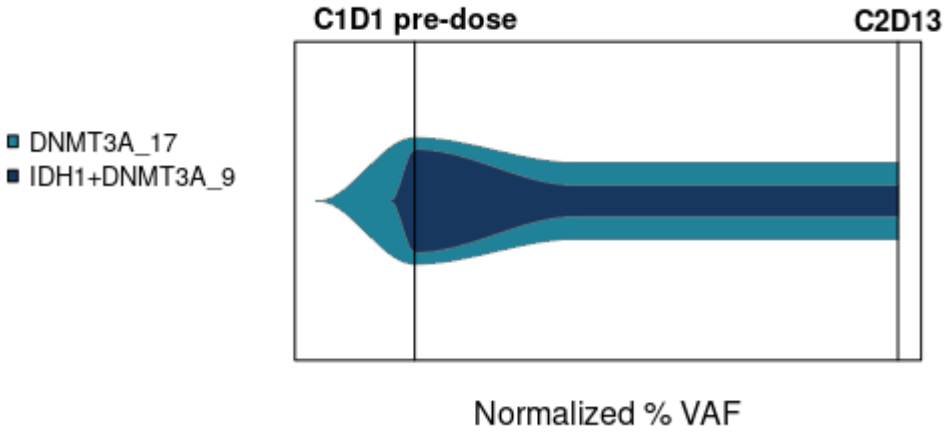
Patient history

- 82yo Female, ECOG 2 (C2D1)
- AML with myelodysplasia-related changes Oct-2022
  - Previous treatment: venetoclax plus azacitidine (Oct-2022 to Mar-2024)
- C1D1: 4-Jul-2024
  - 250 mg RVU120 + 200 mg Ven
- CR declared on C3D7 (27-Aug-2024); last drug administration on 2-Sep-2024; patient withdrew consent on 10-Oct-2024

Bone Marrow

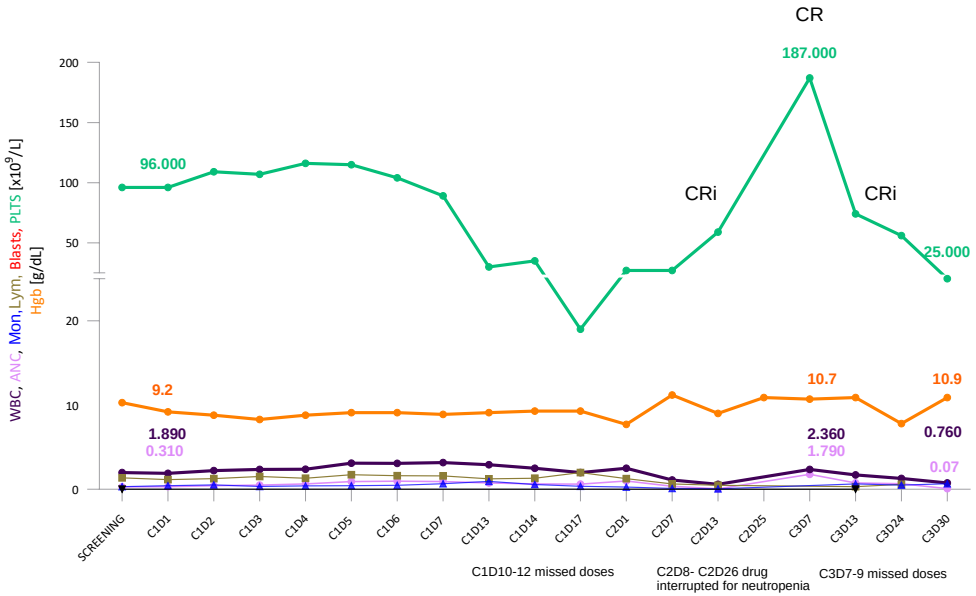


NGS



DNMT3A_17 – c.2063G>A ; DNMT3A_9 – c.1064del; IDH1 – c.394C>G

Hematology



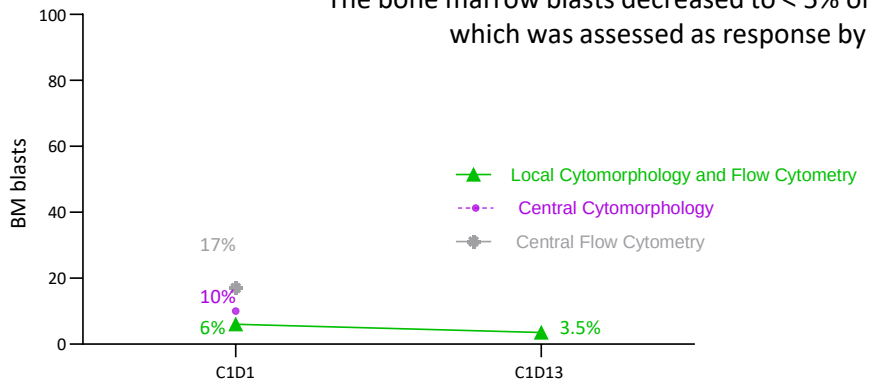
RIVER-81 Patient 813904-02 – Cohort 3 (RVU120 250 mg + Ven 400 mg)

Patient history

- 74yo Female, ECOG 1
- Comorbidities: type 2 diabetes mellitus, appedicectomy, tonsillectomy, hysterectomy
- AML with myelodysplasia-related on Apr-2023, del5q31 and 17p13 (TP53)
  - Previous treatment: venetoclax and azacitidine (Apr-2023 to Aug-2024)
- C1D1: 30-Oct-2024
  - 250 mg RVU120 + 400 mg Ven
- Completed 2 cycles of treatment

Bone Marrow

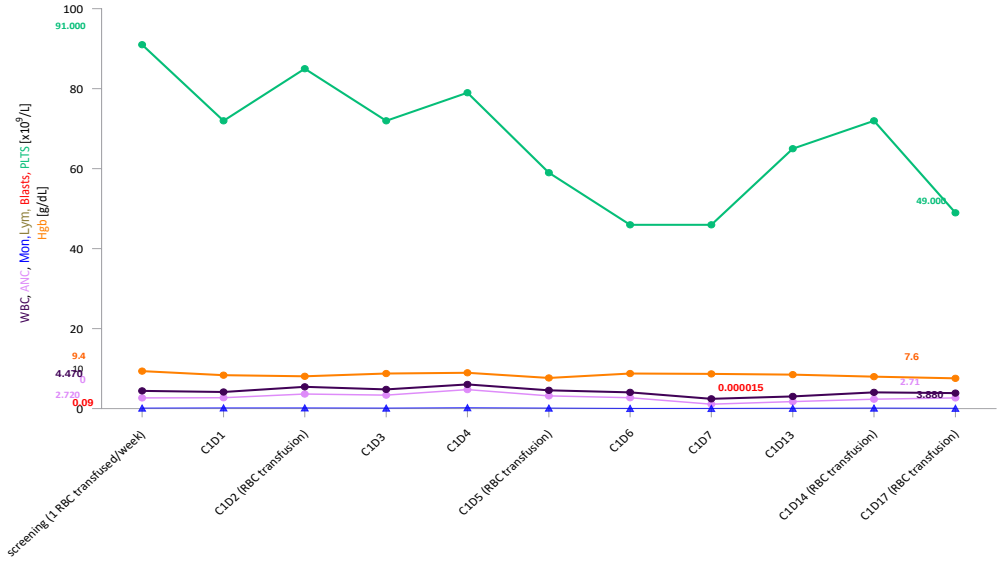
The bone marrow blasts decreased to < 5% on one timepoint, which was assessed as response by the investigator



NGS

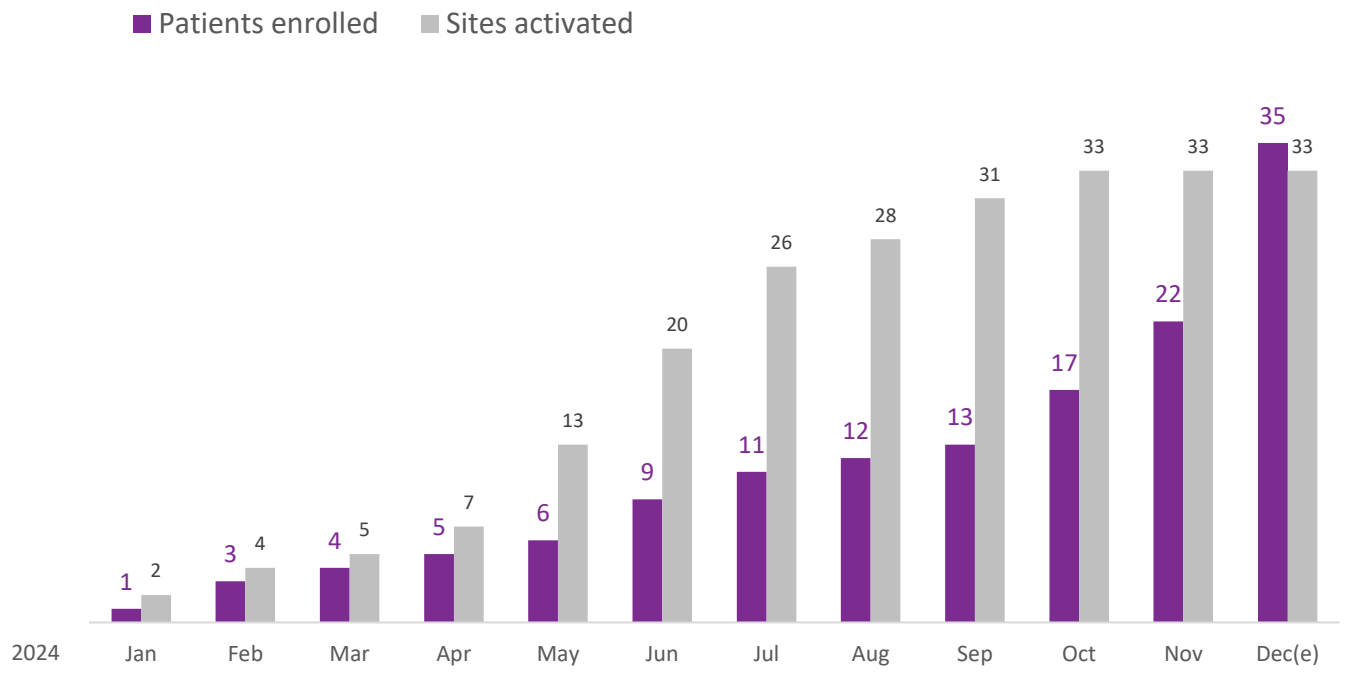
TIER	MUTATION	% VAF
TIER 1	**ASXL1** *c.1913_1914del*	36%
	U2AF1 *c.470A>C*	35%
	CUX1 *c.2983C>T*	9%
	STAG2 *c.3277+1G>C*	8%
	TP53 *c.814G>A*	25%
	c.524G>A	10%
	c.577C>T	2%
TIER 2	**TP53** *c.434T>G*	6%
	c.650T>G	5%

Hematology



RIVER-81 All 33 clinical sites expected for this year have already been activated. Enrollment for Part 2 is ongoing at a high rate.

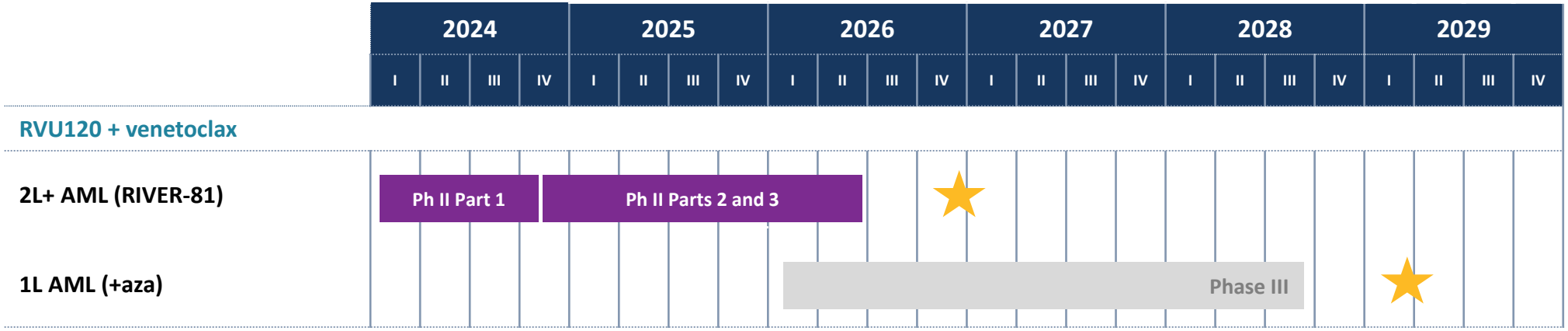
28 patients enrolled, and **33 sites activated** (as of Dec 11, 2024)



- Dose escalation in Part 1 successfully completed
- Enrollment in Part 2 initiated: 11 patients already treated, a total of 18 patients planned for Stage 1 of Part 2

RIVER-81 Potential for accelerated approval in r/r AML and upside path to 1L combo

- Early signs of efficacy for RVU120 + ven in r/r AML (1 CR and 1 blast reduction)
- **Relapsed/Refractory (2L+)**: opportunity to resensitize patients to venetoclax treatment
  – ven rechallenge is not routinely done currently
- **Newly diagnosed (1L)**: Potential to move with combo into 1L to tap into larger commercial opportunity



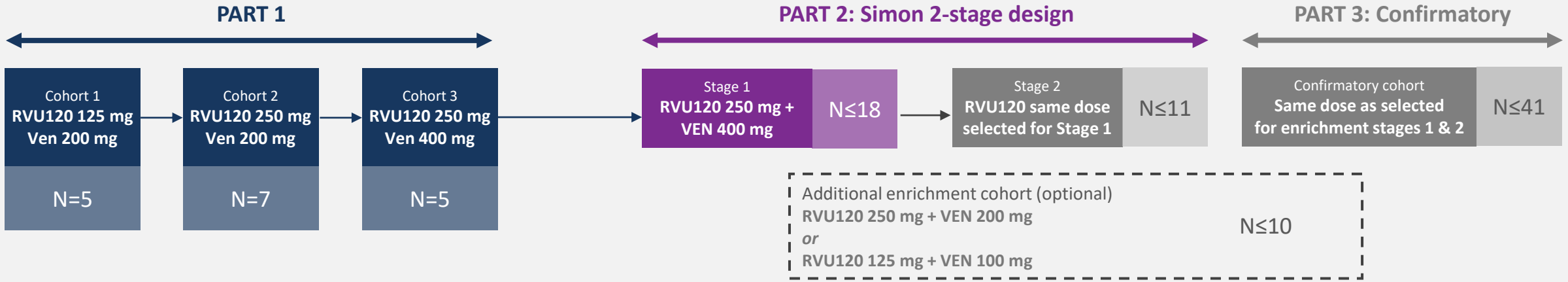
Approval process in selected regions

RIVER-81 Summary

Phase II study testing RVU120 in combination with venetoclax in AML

- **Part 1 (dose escalation) completed; safety profile confirmed**
- **One patient in Part 1 achieved a CR**
- **Part 2 initiated – 11 patients treated** (as of December 11, 2024)
- **Next data release expected in H1 2025**

Study/risk management



RIVER-52

RIVER-81

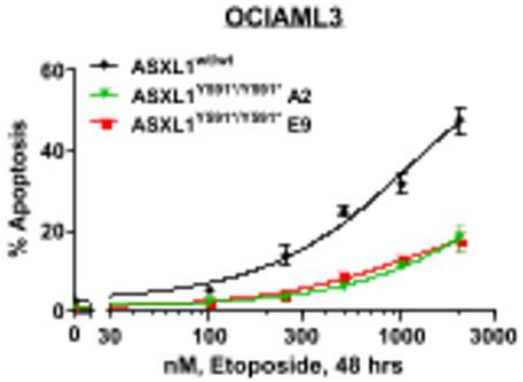
An increasing volume of academic research confirms the interest in CDK8 inhibition and RVU120 in AML

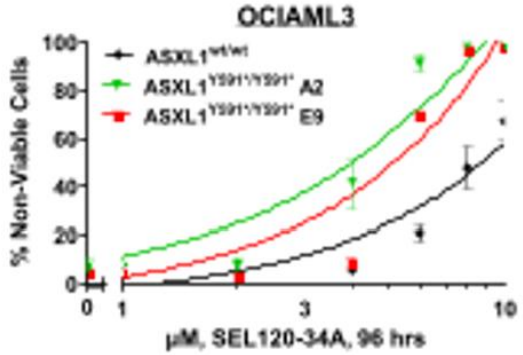
ASXL1 mutations in AML are associated with a distinct epigenetic state which highlights vulnerabilities to specific epigenetic-targeted agents

Christopher Peter Mill, PhD, BA[1], Warren C. Fiskus, BSc, PhD[1], Christine Birdwell, PhD[1], John A. Davis[1], Kaberi Das, PhD[1], Hanxi Hou[1], Surbhi Sharma, PhD[1], Koji Sasaki, MD[1], Sanam Loghavi, MD[2], Tapan M. Kadia, MD[1], Naval Daver, MD[1], Courtney D. DiNardo, MD, MSc[1], Lu Wang, PhD[3] and Kapil N. Bhalla, MD[1]

[1]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Hematopathology, University of Texas MD Anderson Cancer Center, Houston, TX; [3]Department of Biochemistry and Molecular Genetics, Northwestern University, Chicago, IL

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center





Conclusions

1. Developed two isogenic knock-in (KI) models of mtASXL1 Y591* into the AML cell lines OCI-AML3 and UCSD-AML1 which exhibited elevated expression of truncated ASXL1, BAP1, and reduced H2AK119Ub histone mark.
2. ASXL1/BAP1 stabilization caused increased expression of c-Myc protein in OCI-AML3 and UCSD-AML1 mtASXL1 KI cells.
3. We observed reduced H2AK119Ub at H3K27Ac-marked chromatin on Wnt/β-catenin pathway genes in OCI-AML3 mtASXL1 KI that are involved in stem cell signaling.
4. KI of mtASXL1 in OCI-AML3 cells increased G_0/G_1 with a concomitant reduction in S and G_2/M phases of the cell-cycle.
5. Compared to parental cells, OCI-AML3 mtASXL1 KI cells exhibited reduced sensitivity to chemotherapeutics. These cells were also more sensitive to epigenetically targeted agents.
6. Treatment with NEO2734/EP31670 reduced permissive chromatin marks, mRNA, and protein of c-Myc, c-Myb, and PU.1.
7. Treatment with SEL120-34A/RVU120 reduced active chromatin marks in the mtASXL1 expressing AML cells. This was associated with reduced protein expression of BAP1, MEIS1 and HOXA9.
8. In vitro co-treatment with NEO2734 or pelabresib and SEL120-34A induced synergistic apoptosis in mtASXL1-expressing cells. In vivo treatment with NEO2734, pelabresib, or SEL120-34A, significantly reduced AML burden in NSG mice engrafted with OCI-AML3 mtASXL1 cells.
9. Collectively these findings highlight previously uncharacterized biologic effects of the presence of mtASXL1 in isogenic models and support the rationale for further evaluating AML therapies incorporating BETi, HAT-BETi or inhibitor of mediator kinase.

723 CDK8 Inhibition Represses Monocyte-like Gene Expression in Acute Myeloid Leukemia Cells and Antagonizes In Vivo Resistance to FLT3 Inhibition

Program: Oral and Poster Abstracts
Type: Oral
Session: 604. Molecular Pharmacology and Drug Resistance: Myeloid Neoplasms: Resistance to Standard and Novel Therapies
Hematology Disease Topics & Pathways:
Research, Acute Myeloid Malignancies, AML, Combination therapy, Apoptosis, Translational Research, Diseases, Treatment Considerations, Myeloid Malignancies, Biological Processes

Monday, December 9, 2024: 11:00 AM

Timothy T. Ferng, MD[1], *Samantha M. Pintar, BA*[2*], *Vanessa E. Kennedy, MD*[3], *Shaheen Kabir, PhD*[1*], *Theodore C. Tarver III, BS*[2*], *Veronica Steri, PhD*[4*], *Paul Phojanakong, BA*[4*], *Juwita Hübner, MD*[5*], *Carolina E. Morales, BS*[5*], *Jose M. Rivera*[6*], *Aaron C. Logan, MD, PhD*[7], *Benjamin Braun, MD, PhD*[5*], *Elliot Stieglitz, MD, PhD*[6], *Luke A. Gilbert, PhD*[1*] *and Catherine C. Smith, MD*[8]

[1]*Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA*
[2]*Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA*
[3]*Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University School of Medicine, Palo Alto, CA*
[4]*Preclinical Therapeutics Core, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA*
[5]*Department of Pediatrics, Benioff Children's Hospital, University of California San Francisco, San Francisco, CA*
[6]*Division of Hematology-Oncology, Dept. of Pediatrics, University of California San Francisco Benioff Children's Hospital, San Francisco, CA*
[7]*Department of Medicine, Division of Hematology and Oncology, University of California, San Francisco, San Francisco, CA*
[8]*Department of Medicine, Division of Hematology/Oncology, University of California, San Francisco, San Francisco, CA*

RYVU THERAPEUTICS

POTAMI-61 Phase II

RVU120 as a single agent
and in combination with ruxolitinib
in patients with myelofibrosis (MF)

RYVU THERAPEUTICS

POTAMI-61 RVU120 validated preclinically as a drug candidate in MF

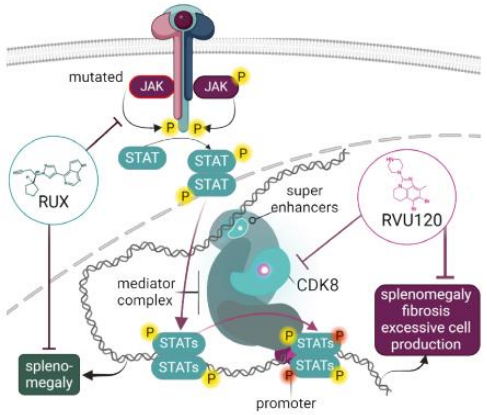
Opportunity in myelofibrosis

- Growing market with many patients undiagnosed or not treated due to lack of treatment options
- Long durations of therapy and unmet medical need, for example, in patients with severe cytopenias

RVU120 in myelofibrosis

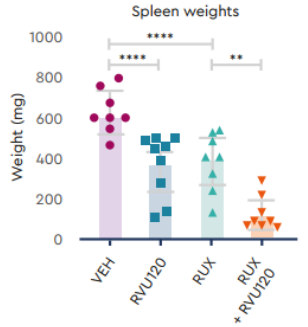
- CDK8 kinase is an important player in MPN pathogenesis, and RVU120 disrupts the downstream signaling events, mitigating MPN symptoms
- In preclinical studies, RVU120 effectively reduced splenomegaly, bone marrow fibrosis, and abnormal blood cell production. RVU120 has also demonstrated synergy in combination with JAK inhibitors
- RVU120 has erythroid stimulating activity and demonstrated a favorable safety profile on normal hematopoiesis, making it a potential candidate for broad clinical use in treating MPNs

Mechanism of RVU120 in MF



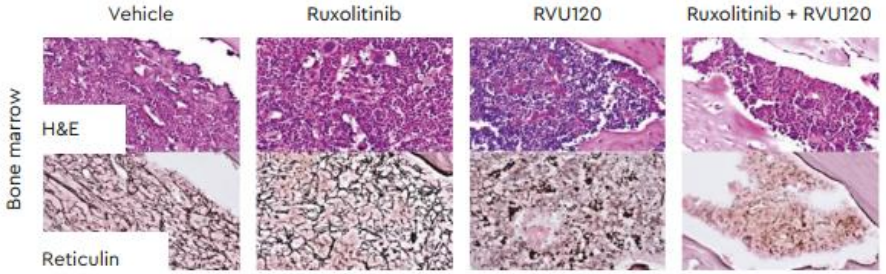
RVU120 reduces splenomegaly

RVU120 as a monotherapy and in combination with ruxolitinib reduces splenomegaly in a MPLW515L mouse model of MPN

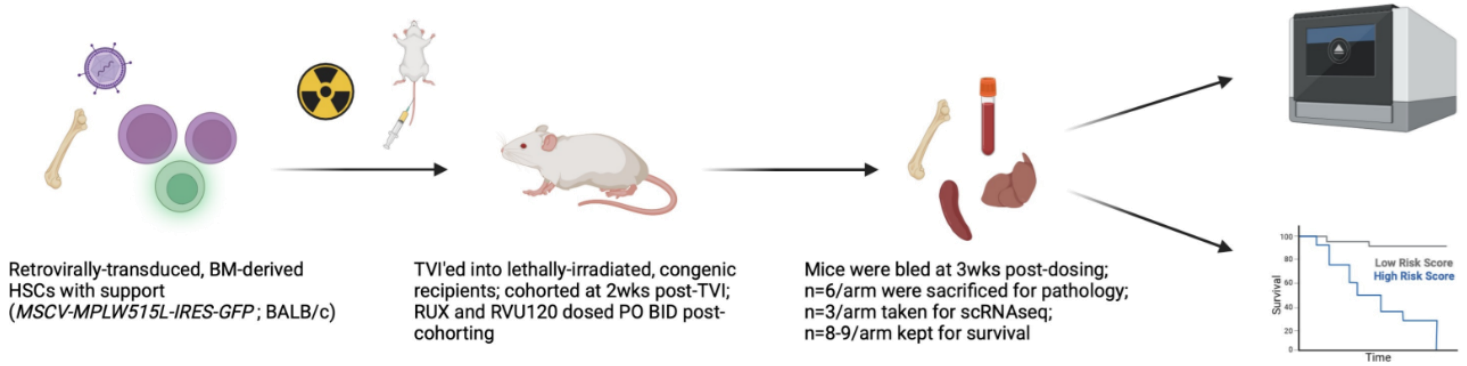


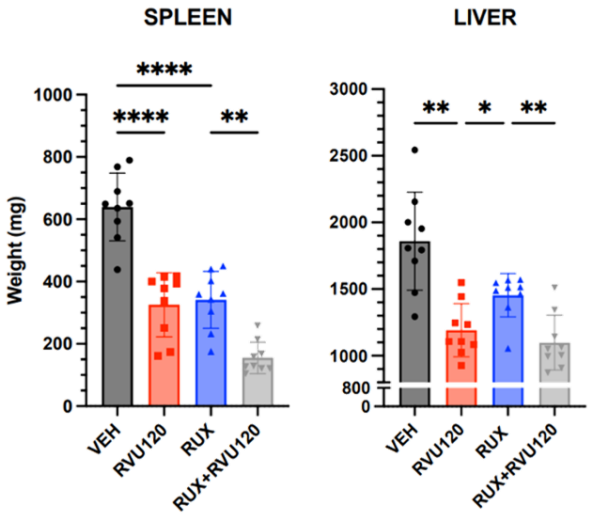
RVU120 reduces bone marrow fibrosis

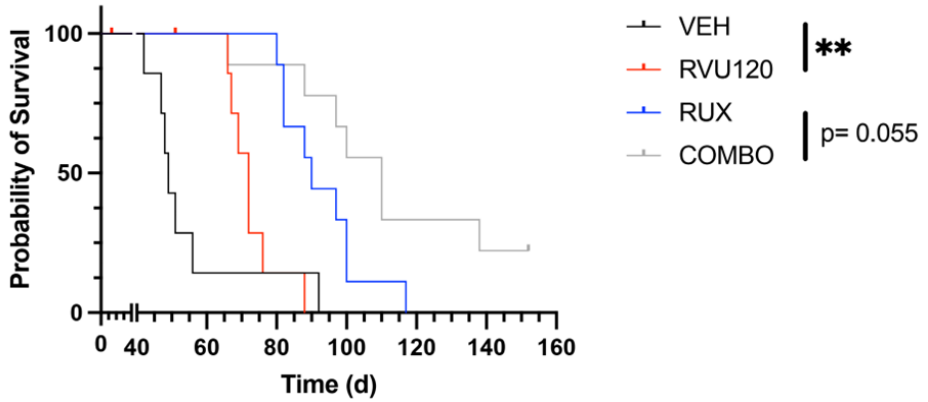
RVU120 as a monotherapy and in combination with ruxolitinib reduces bone marrow fibrosis while also increasing trilineage hematopoiesis in a MPLW515L mouse model



POTAMI-61 RVU120 attenuates MPN phenotypes relevant for accepted clinical endpoints, e.g., spleen volume reduction and survival





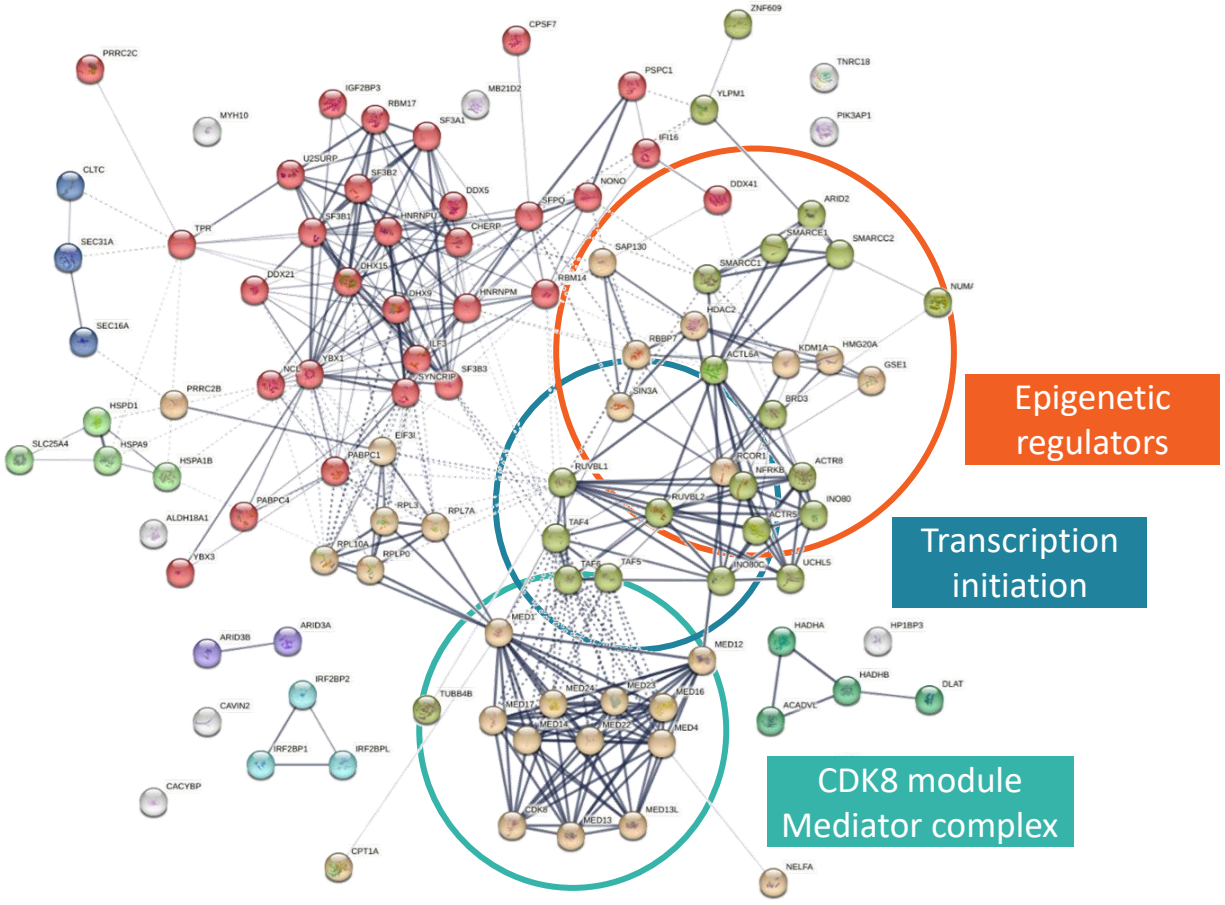


Memorial Sloan Kettering Cancer Center

RYVU THERAPEUTICS

POTAMI-61 Validated synergy with SoC and advanced experimental therapies

CDK8 interactome in SET2 JAK V617F cells



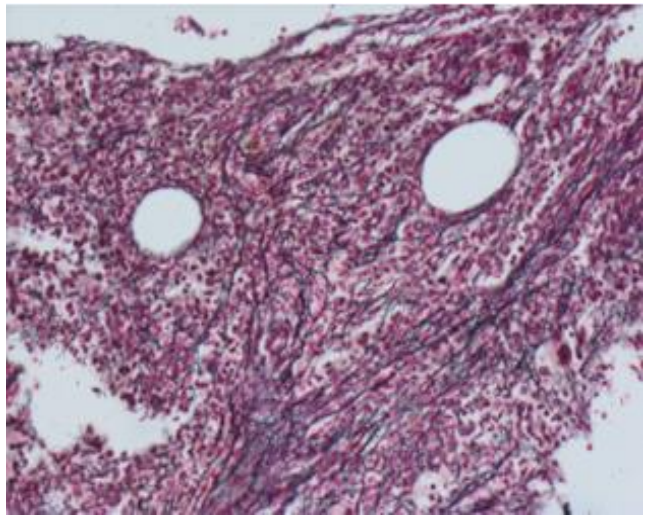
Synergistic interactions of RVU120 in SET2 JAK V617F cells

Compound	Target	SET2 WT		SET2 RUXO-Persistant	
		EC50 [µM]	Combination effect	EC50 [µM]	Combination effect
RVU120	CDK8/19	2.99-4.44		>5	
Ruxolitinib	JAK1/JAK2	0.11	synergy	0.28	synergy
Momelotinib	JAK1/JAK2	0.71	synergy	1.15	synergy
Pacritinib	JAK2, IRAK1	0.36	synergy	0.65	slight synergy
Pelabresib	BET	0.65	synergy	0.80	slight synergy
Navitoclax	BCL2	0.20	no synergy	0.28	no synergy
TP-3654	PIM	3.88	no synergy	4.68	no synergy
Navtemadlin	MDM2	>10	no synergy	>10	no synergy
Bomedemstat	LSD1	>10	no synergy	>10	no synergy
INF alpha		893.7 IU/ml	no synergy	>10^5 IU/ml	no synergy

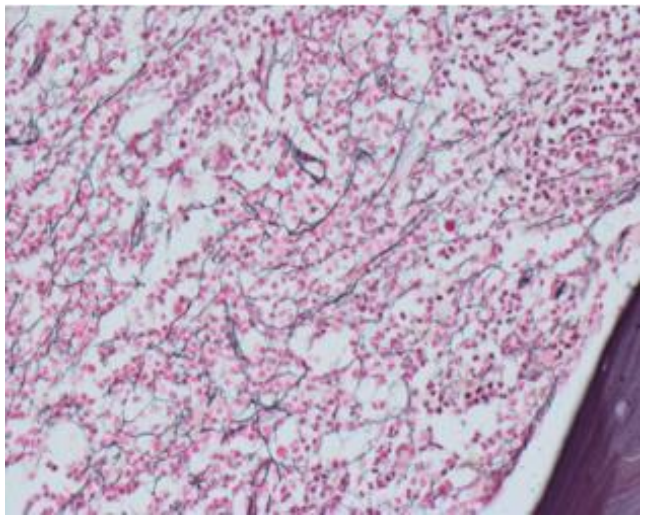
POTAMI-61 Clinical evidence (Phase I in AML) of activity on bone marrow fibrosis

Patient with MDS and bone marrow (BM) fibrosis showed clinical evidence of activity:
achieved marrow CR and BM fibrosis reduced from G3 to G2 on C6D1 biopsy

C2D13 fibrosis grade 3



C6D1 fibrosis grade 2



POTAMI-61 Phase II study of RVU120 in myelofibrosis (MF) as mono and combo – first patient dosed in December 2024

STUDY DESIGN

- **Population:**
  - Primary or secondary MF; intermediate or high-risk MF per DIPSS;
    Cohort 1) previously treated with or ineligible for JAK inhibitor and Cohort 2) suboptimal response to RUX
  - Important: patients with thrombocytopenia can be included in Cohort 1
- **Primary endpoints:** spleen volume reduction at 24 weeks
- **Secondary endpoints**: DoR, leukemic transformation, hematologic improvement, BM fibrosis reduction, PFS and OS
- Estimated enrollment: **~20-230 patients**(1)
- Up to **50 clinical sites** planned globally
- Status as of December 11, 2024: **first patient dosed, 5 patients in screening, 12 sites activated** (17 sites planned by year-end)

Part A (N = ~20 pts)

Cohort 1
(Mono RUX-ineligible or RUX-failed)

Cohort 2
(RUX add-on)

Part B (N = ~210 pts)

Expansion of Cohort 1 or 2

Cohort 3
(Frontline)

Initial opportunity in second line treatment with potential to move into frontline therapy

(1) ~20 patients in Part A, ~210 patients in Parts B

REMARK Phase II

RVU120 as a single agent
in patients with lower-risk myelodysplastic syndrome (LR-MDS)

REMARK RVU120 validated preclinically as a drug candidate in LR-MDS

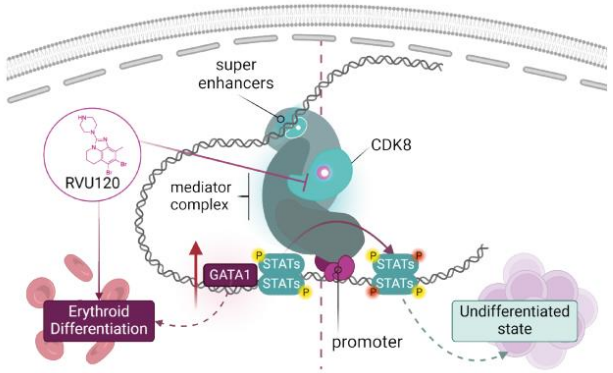
Opportunity in LR-MDS

- A high unmet medical need remains in low-risk MDS (LR-MDS) after failure of available therapies
- Transfusion burden remains high for patients with LR-MDS, resulting a poor quality of life

RVU120 in LR-MDS

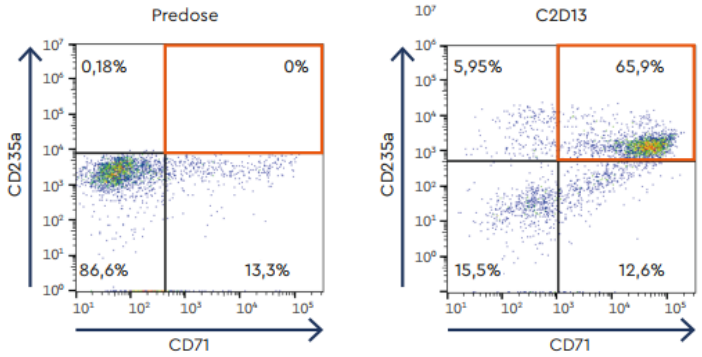
- MDS pathogenesis is influenced by gene expression alterations that hinder the maturation of hematopoietic cells.
- When aberrant stem cells from MDS patients are treated with RVU120, it triggers erythroid gene expression programs orchestrated by STAT5 and GATA1.
- Importantly, RVU120's activity does not lead to significant toxicity in the hematopoietic system. As a result, RVU120 emerges as a promising drug candidate for treating transfusion-dependent MDS patients.

Mechanism of RVU120 in LR-MDS



Clinical evidence of erythropoiesis demonstrated with RVU120

Several patients with AML and HR-MDS showed signs of hematological improvement, including an erythroid response in the RIVER-51 study. Induction of erythropoiesis was confirmed by flow cytometry.



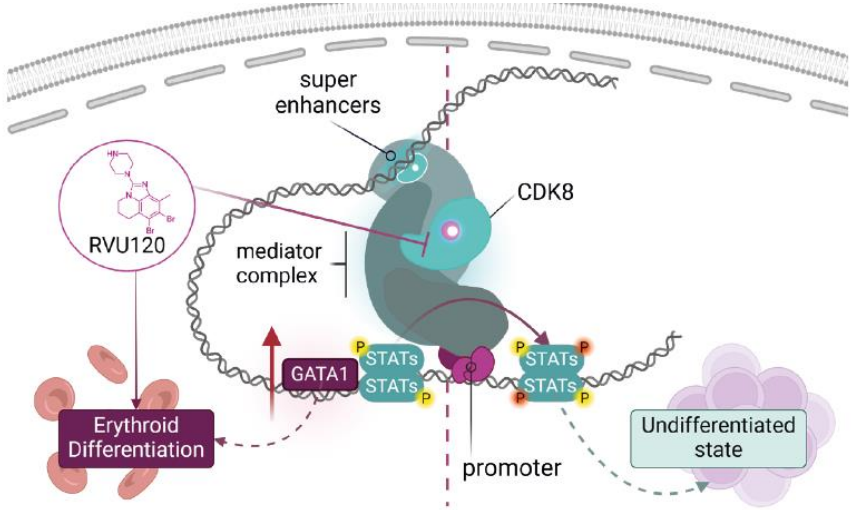
REMARK RVU120 has strong erythroid-stimulating activity in nonclinical anemia models and selected patients with AML/HR-MDS in Phase I (RIVER-51), providing the rationale for the Phase II clinical study in patients with LR-MDS

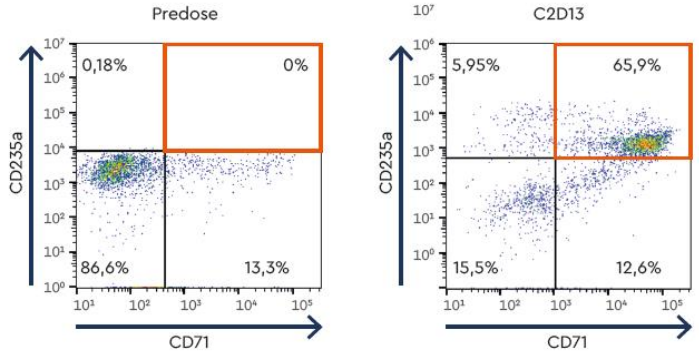
Nonclinical rationale

- Treatment of transformed CD34+ cells with RVU120 results in erythroid lineage commitment
- Isolated CD34+ cells derived from MDS and Diamond-Blackfan anemia patients differentiate into erythrocytes in the presence of RVU120
- Increased red blood cell count and hemoglobin levels were observed in animal studies
- Transcriptomic and chromatin studies identified that RVU120 can enhance GATA1-dependent transcription and reduce the expression of pro-inflammatory genes in MDS cells

Related clinical observations

- 4 AML/HR-MDS patients treated with RVU120 in Phase I showed hematological improvement
- An increase in reticulocytes was also observed in patients with solid tumors





REMARK RVU120 in LR-MDS – IIT conducted by Prof. Uwe Platzbecker and the EMSCO network

STUDY DESIGN

- Population:
  - Patients with relapsed/refractory LR-MDS
- Primary endpoint:
  - Erythroid response (HI-E) according to IWG 2018 criteria after 8 cycles of treatment
- Secondary endpoint:
  - RBC transfusion independence
  - Hb improvement
  - Quality of life (QoL)
  - Disease progression according to IWG 2018 criteria
  - Mutational pattern and burden of selected genes and their influence on response

PHASE II

EXPLORATORY
RVU120 AS A SINGLE AGENT
Patients failing available options
Enrollment of ~40 patients planned

ONGOING ASSESSMENT OF PHASE II WILL DRIVE FURTHER DEVELOPMENT

IIT

- **First patient dosed in September 2024; 18 patients enrolled as of December 11, 2024**
- Study conducted as an Investigator Initiated Trial with **Prof. Uwe Platzbecker within EMSCO** (European Myelodysplastic Neoplasms Cooperative Group)

EMSCO MYELODYSPLASTIC SYNDROMES

UNIVERSITÄT LEIPZIG

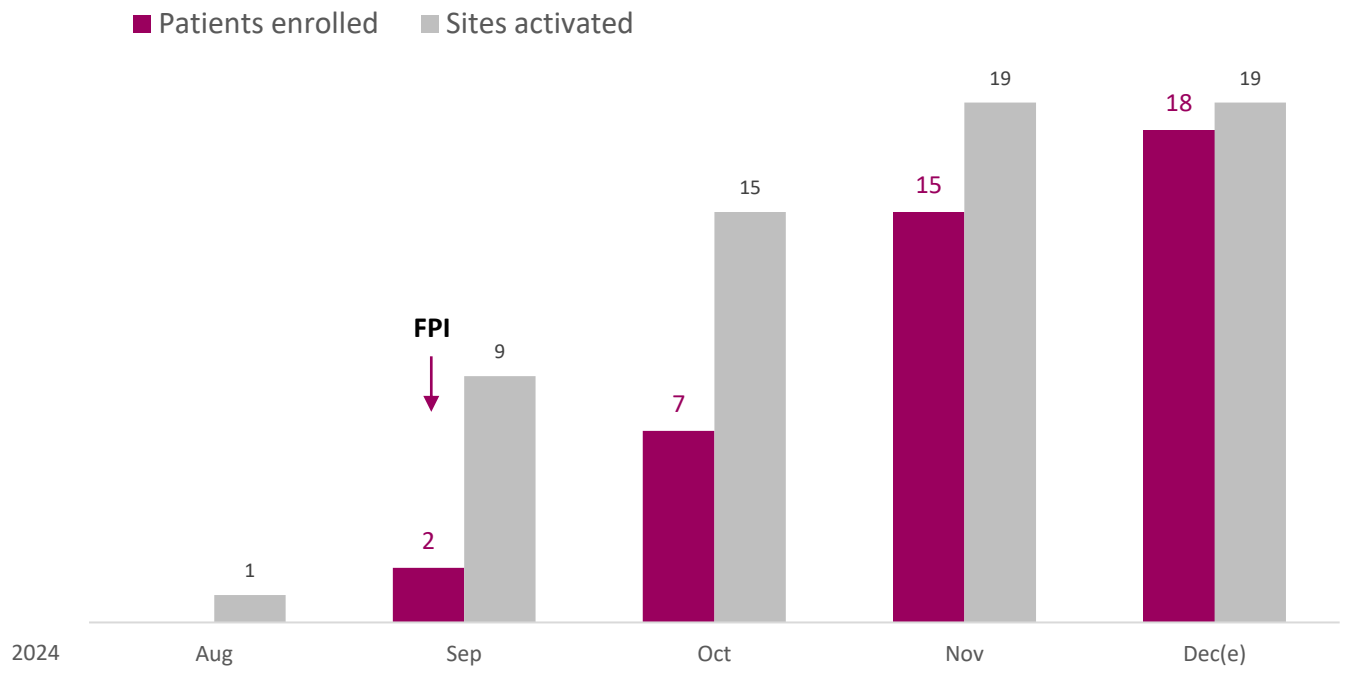
Prof. Uwe Platzbecker

- Co-founder and chairman of EMSCO and co-chairman of the European Hematology Association Scientific Working Group on MDS
- Primary focus on myelodysplastic syndromes (MDS) and its treatment
- Worked on trials assessing luspatercept (Reblozyl) and imetelstat in patients with LR-MDS

RYVU THERAPEUTICS

REMARK 19 of 24 sites planned for the study have already been activated. Efficient enrollment in the study supported by the EMSCO network.

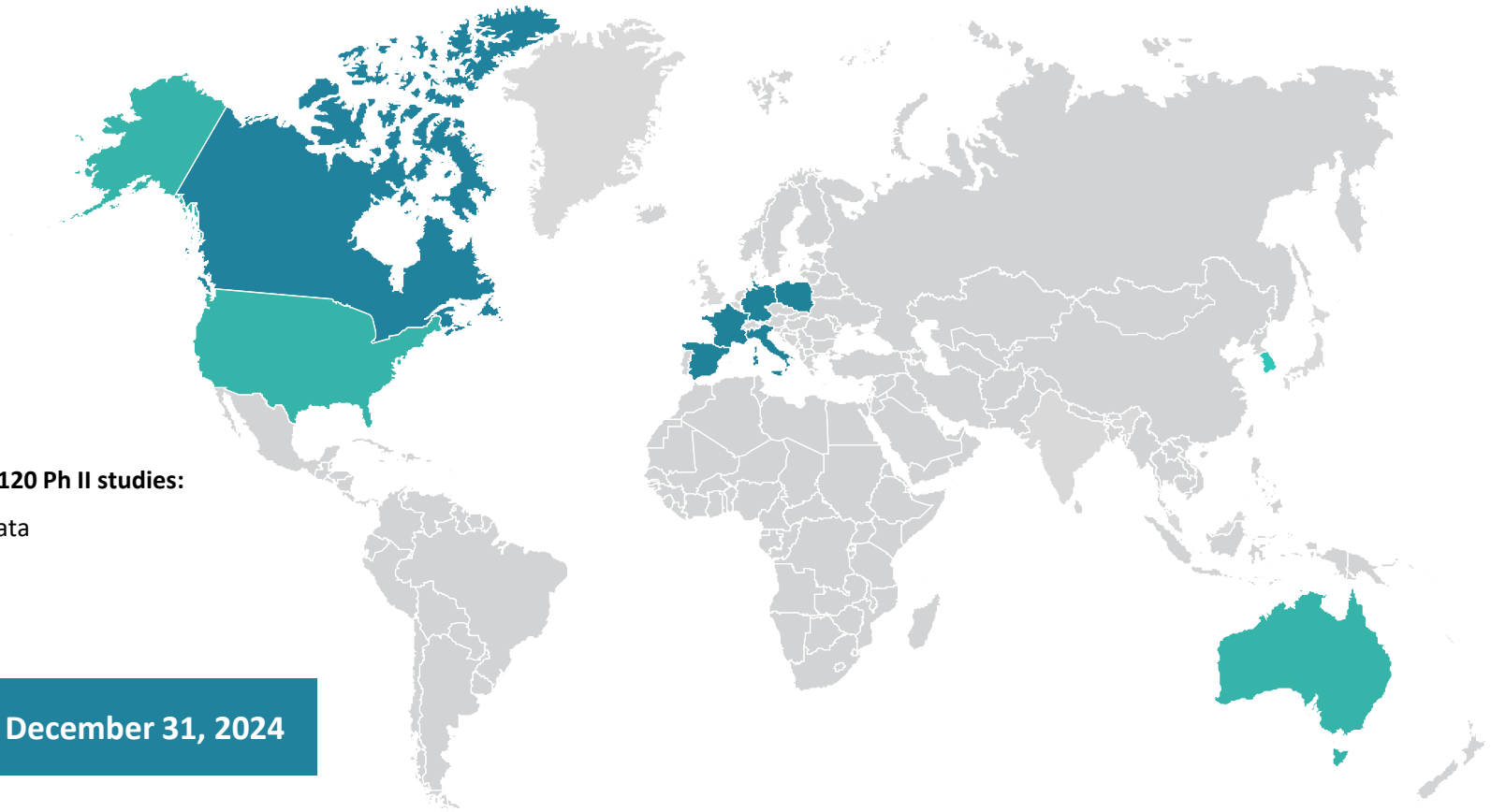
18 patients enrolled, and **19 sites activated** (as of Dec 11, 2024)



- **FPI on September 18, study progress in line with the schedule**
- Dosing optimization in progress – different tolerability/efficacy considerations in LR-MDS vs. AML
- Initial study results expected in Q2 2025 (due to 16-week observation period needed)

RVU120 Outlook

RVU120 Phase II clinical development with a global footprint



Planned locations for RVU120 Ph II studies:

- Part 1: exploratory data
- Part 2: expansion

Global site locations and patient population

Global CROs and clinical vendors

Regulatory authorities worldwide

Expected status as of December 31, 2024

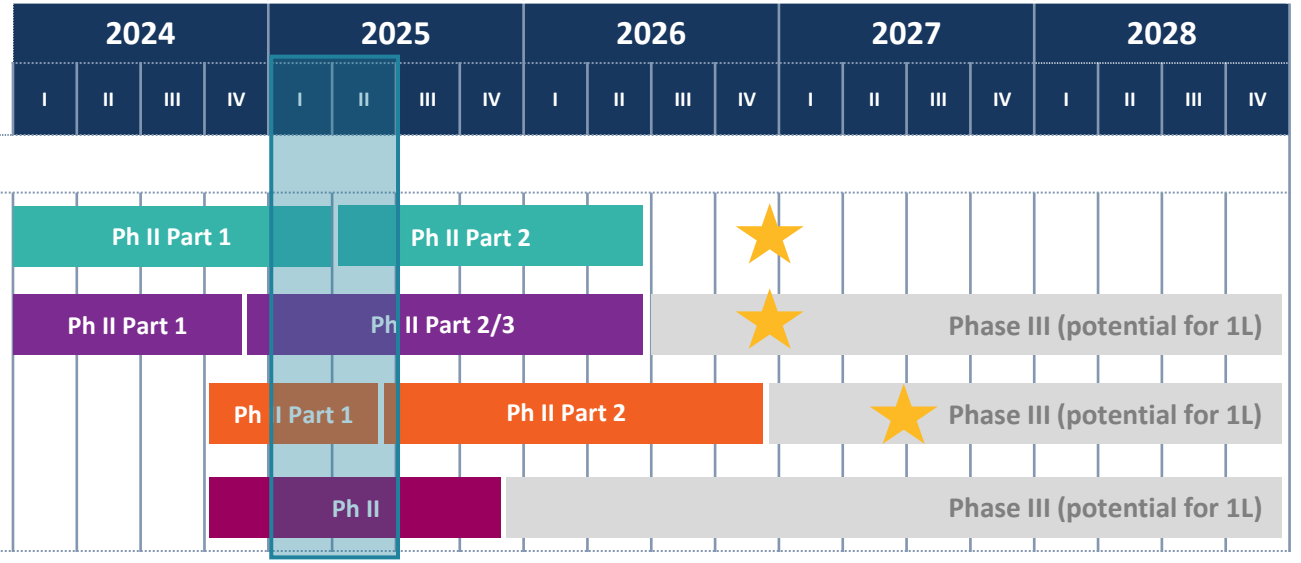
Number of Ph II clinical trials initiated in 2024	**Number of countries** across studies	**Number of activated clinical sites** globally	**Number of patients** enrolled	**Number of clinical vendors** managed	**Number of internal Ryvu team members** in Clinical Development and Translational teams
4	6	110+	~100	20+	80+

RVU120

Robust program progress without budget overruns allows for pre-planned program review and focusing on the best paths to approvals in H1 2025

Planned Ph II studies in hematologic malignancies

- **RIVER-52**: AML/HR-MDS, monotherapy
- **RIVER-81**: AML, combination with venetoclax
- **POTAMI-61**: myelofibrosis (MF), monotherapy/combination with ruxolitinib
- **REMARK**: LR-MDS, monotherapy, investigator-initiated trial (IIT)



Approval process in selected regions

In H1 2025 Ryvu expects to have:

- RIVER-52 / Part 1 completed (10+ evaluable patients in all three AML/NPM1+, AML/DNMT3A+ and HR-MDS cohorts)
- RIVER-81 / Part 2 Stage 1 completed (30+ evaluable patients in RVU 250 mg + ven cohorts)
- REMARK and POTAMI-61 / first efficacy data

which will allow the pre-planned program review to focus on the most promising development paths

All studies are in-line with the originally planned budgets. Q1 2026 cash runway remains unchanged.

RVU120 Market potential in hematological malignancies

AML (Acute Myeloid Leukemia)

- The most common, highly aggressive type of acute leukemia occurring in adults; unfavorable outcomes for most patients[1]
- Annual incidence in the US at ~20,800 with an est. 11,220 deaths in the US in 2024[2]
- **Venclexta (venetoclax) sales estimated to exceed USD 3.5 bn in 2025[3]**
- **Kura licensed rights to ziftomenib to Kyowa Kirin for USD 330M upfront and USD 1.2 bn total milestones in Nov 2024**
  - Phase III asset
  - Part of a global collaboration

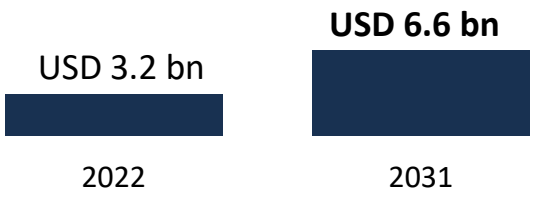
MDS (Myelodysplastic Syndrome)

- Disease leading to bone marrow damage, classified as cancer
- Growing market due to faster diagnosis of the disease and potential new therapies
- US incident cases expected to increase from 36,000 in 2018 to 46,000 in 2028[4]
- **Reblozyl (luspatercept) projected peak sales of USD 3.2 bn by 2029[5]**
- **Rytelo (imetelstat) projected peak sales of USD 1.2 bn[6]**

MF (Myelofibrosis)

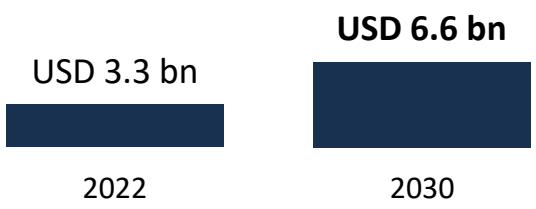
- MF is a bone marrow disease characterized by JAK mutations; often leads to severe anemia
- Chronic disease with long duration of therapy; US prevalence is est. to be ~13,000 patients[7]
- **Jakafi (ruxolitinib) sales in 2023 – USD 2.6 bn**
- **Morphosys acquired by Novartis for EUR 2.7 bn in Feb 2024**
  – primary asset is Phase III MF drug pelabresib

Global AML Market [4]



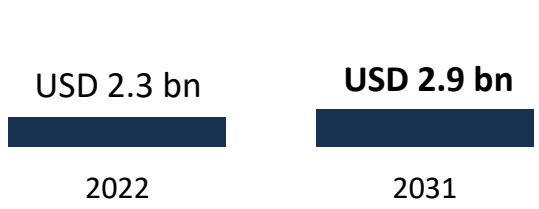
8.5% CAGR (2022-2031)

Global MDS Market [4]



9.3% CAGR (2022-2030)

Global MF Market [7]



2.6% CAGR (2022-2031)

1. Mayo Clinic 2. cancer.org January 2024 3. Biomedtracker 5 March 2023 4. GlobalData forecast 5. Goldman Sachs forecast 6. Coherent Insights

RVU120 Summary / Q&A

All studies on-track, efficacy analysis in H1 2025

RVU120 Phase II Progress

RIVER-52 — **Next data in Q2 2025**

- 1 of 2 evaluable NPM1+ pts with 50% blast reduction
- 1 of 3 evaluable DNMT3A+ pts with disease stabilization
- Data from the first 10+ evaluable patients in Cohorts 2-4 expected in H1 2025

RIVER-81 — **Next data in Q2 2025**

- Part 1 (combo dose escalation) completed – safety confirmed
- One patient in Part 1 achieved a CR
- Part 2 initiated; further development decision in H1 2025

POTAMI-61 — **Enrollment ongoing; initial data in Q2 2025**

- First patient dosed in Dec'24
- Initial efficacy data expected in Q2 2025

REMARK — **Enrollment ongoing; initial data in Q2 2025**

- First patient dosed in Sep'24
- Initial efficacy data expected in Q2 2025

RVU120 program summary

- Successful launch of all 4 Phase II studies: RIVER-52, RIVER-81, POTAMI-61, REMARK
- Global clinical program with accelerating enrollment
- Strong interest from the investigator community
- Safety profile potentially better than in most drugs used in AML
- Encouraging early signs of efficacy in Phase II
- Numerous data readouts expected in 2025
- No budget overruns with cash runway still to Q1 2026

Next steps and upcoming newsflow

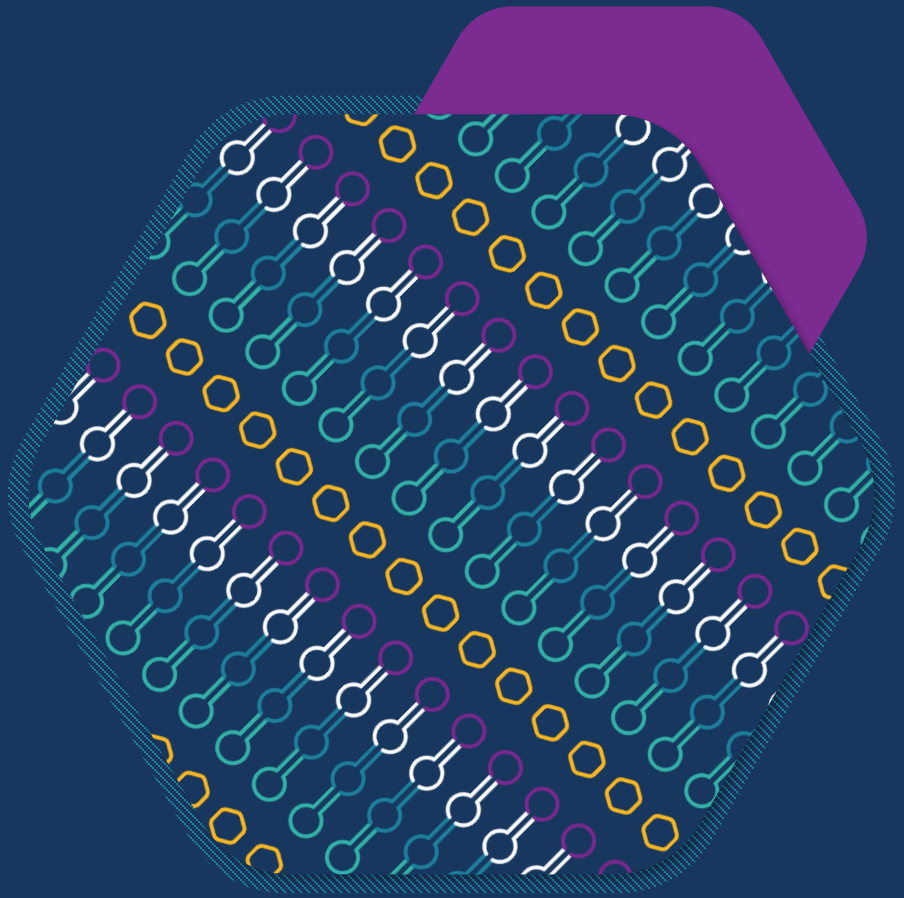
H1 2025 — **RVU120 development plan review based on:**

- Ongoing data analysis
- Updated competitive analysis
- KOL feedback

Q2 2025 — **RVU120 Phase II data update: RIVER-52, RIVER-81, POTAMI-61, REMARK**

RYUU THERAPEUTICS

Thank you



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