RYVU THERAPEUTICS

Developing therapeutics
at the forefront of oncology

Corporate Presentation

October 2024

Note on the presentation and forward-looking statements

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

FIRST-IN-CLASS CLINICAL PIPELINE

RVU120

- First-in-class, wholly-owned, oral **CDK8/19** inhibitor
- Three Ph II studies ongoing in AML/HR-MDS (mono and combo) and LR-MDS; additional Ph II study to initiate in MF

MEN1703

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

SMALL MOLECULE DISCOVERY PLATFORM

SYNTHETIC LETHALITY
Wholly-owned

- **RVU305/PRMT5**: in IND-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

Team with a strong track record of clinical development and shareholder value creation

Pawel Przewiezlikowski, MSc, MBA
CEO and Founder

Krzysztof Brzozka, PhD, MBA
CSO

Hendrik Nogai, MD
CMO

Kamil Sitarz, PhD, MBA
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Vatnak Vat-Ho, MBA
CBO

Miika Ahdesmäki, PhD, MBA
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Justyna Zoltek, MSc
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Bartlomiej Konicki, MSc
Financial Director

Tomasz Rzymski, PhD, MBA
Director of Translational Medicine

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TADEUSZ WESOLOWSKI, *Ph.D*	

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	Initial Ph II data in 4Q24
	R/R AML (RIVER-81) (combination with venetoclax)						Initial Ph II data in 4Q24
	LR-MDS (REMARK) (monotherapy)					EMSCO MYELODYSPLASTIC SYNDROMES	Initial Ph II data in 2Q25
	Myelofibrosis (POTAMI-61) (monotherapy and combo)						Initial Ph II data in 2Q25
	Solid Tumors (AMNYS-51)						Complete Ph I data & Translational Studies in 2024
MEN1703 (SEL24) (PIM/FLT3)	DLBCL					MENARINI	Initiation of Ph II in 4Q25
SYNTHETIC LETHALITY							
RVU305 (PRMT5)	SOLID TUMORS						IND filing in H2 2025
WRN	SOLID TUMORS						Lead Optimization
NOVEL TARGETS	ONCOLOGY						
IMMUNO-ONCOLOGY							
STING & MULTI-TARGET IMMUNE MODULATION COLLABORATION	ONCOLOGY					BIONTECH	
STING ADC	ONCOLOGY					EXELIXIS	

Study start-up

RYVU THERAPEUTICS

RVU120:
First-in-Class CDK8/19 Inhibitor in Hematologic and Solid Tumor Malignancies

RYVU THERAPEUTICS

RVU120 is a fully-owned CDK8/19 inhibitor currently in Phase II

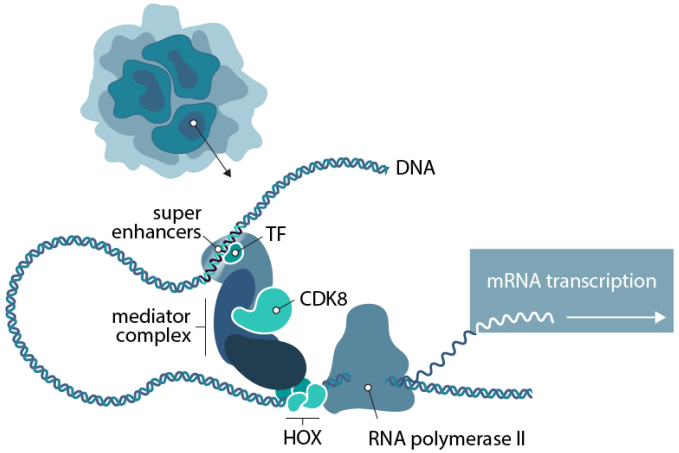
- First-in-class
- High potency

- High selectivity
- Low risk of DDI

- Easy to formulate
- Orally available

CDK8/19 mediator promotes AML growth

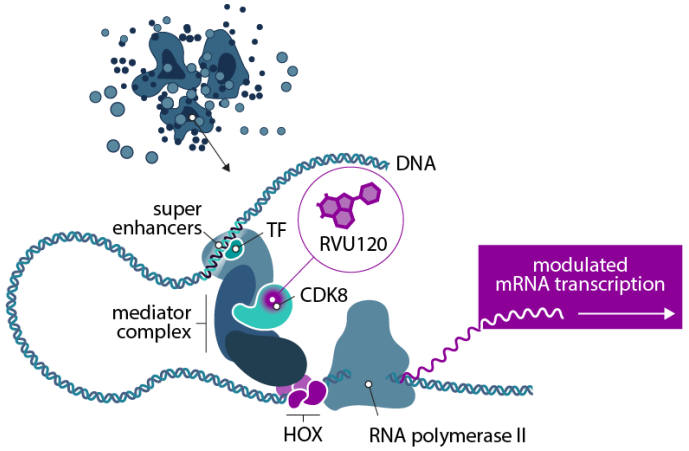
Viability of tumor cells



Maintenance of malignant stem cells
Suppression of differentiation

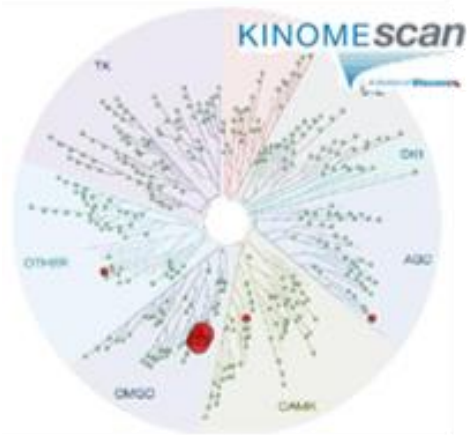
CDK8/19 inhibition by RVU120 triggers differentiation and apoptosis

Apoptosis of tumor cells



Apoptosis of malignant stem cells, incl. stem cells
Lineage Commitment

RVU120 is highly selective for CDK8/19

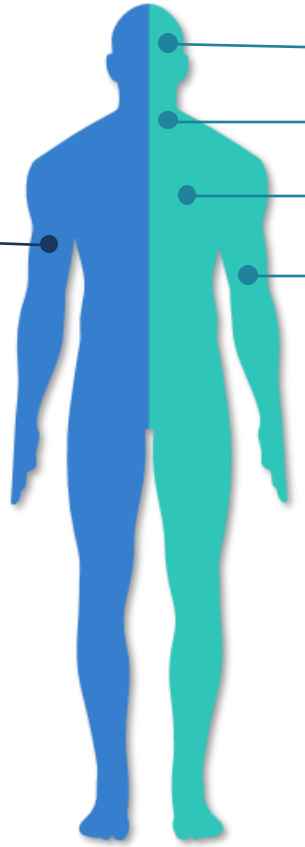


Current RVU120 development plan could lead to three accelerated approvals in 2026-2027

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

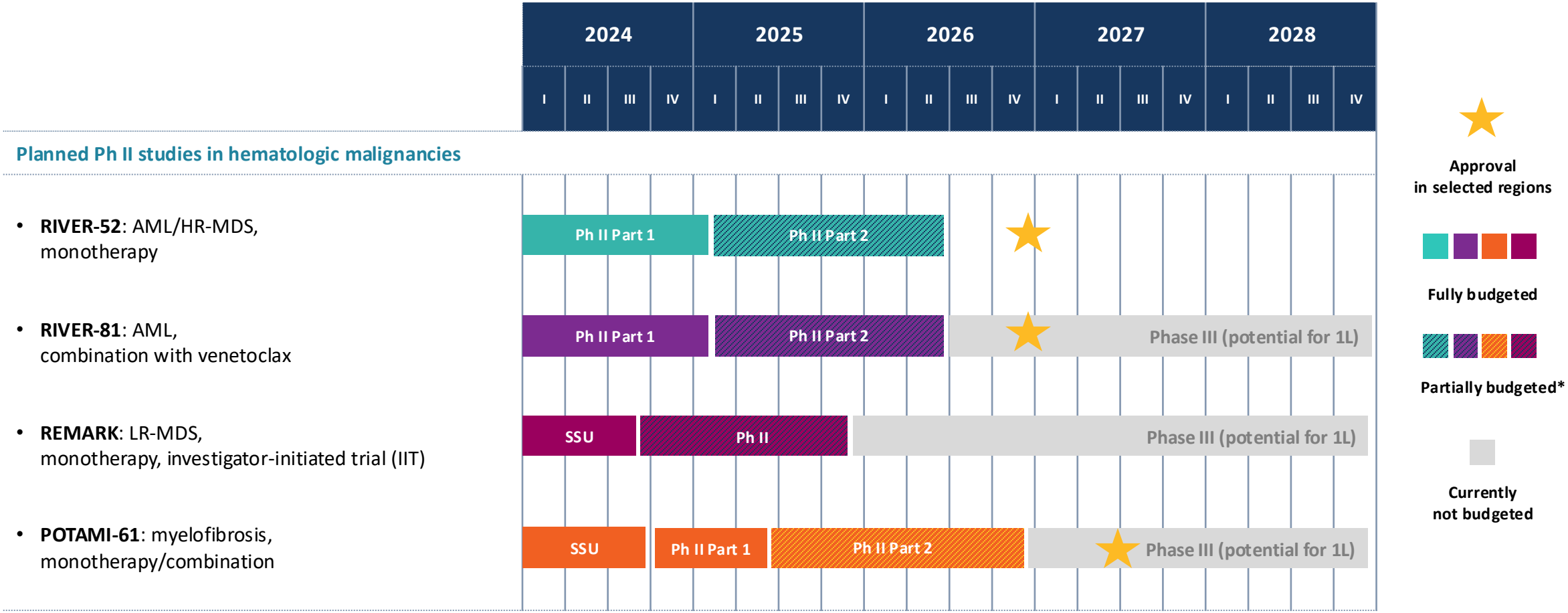
Medulloblastoma
ACC
Breast
Sarcoma

- **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 – Q4 2024**

- 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
Phase II studies ongoing

Clinical development of RVU120 focuses on hematologic malignancies, while translational research explores additional opportunities



Translational research is ongoing to support current clinical trials and to explore additional indications, including: medulloblastoma, sarcoma, TNBC, and other (undisclosed) indications

SSU = Study start-up

* budget allocation will prioritize RVU120 development scenarios based on the exploratory data from part 1.

RIVER-51 clinical update – EHA 2024: 15 of 30 evaluable patients showed clinical benefit

Clinical benefits

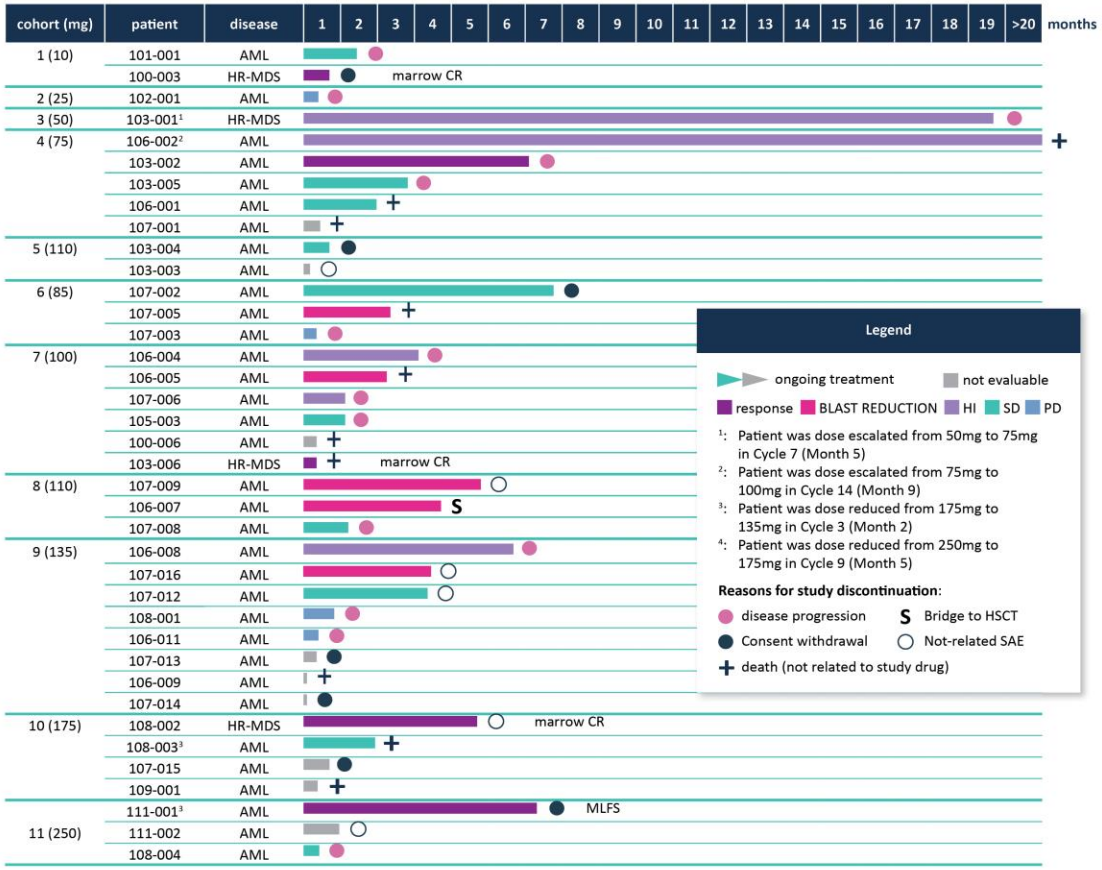
- **30 treated patients are evaluable for response (38 were treated in total)**
- **9 patients achieved clinically significant BM blast reduction**
  (including 1 CR, 1 MLFS, 3 marrow CRs)
- **5 patients achieved erythroid hematological improvement (HI-E),**
  4 of those became transfusion-independent,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

RIVER-51/52 – Confirmed safety at 250 mg dose

Data cut-off: May 17, 2023

- 13 pts from the Phase I/II received RVU120 at 250 mg EOD
- Gastrointestinal events are the most frequent
- Infectious complications are expected in this patient population
- The majority of AEs are of grade 1 or 2

Treatment Emergent Adverse Events (TEAE)	RVU120 (250 mg) from CLI120-001 and RIVER-52 trials Total number of pts dosed at 250 mg = 13	
	Any grade n of pts (%)	Grade 3-5 n of pts (%)
Nausea	3 (23)	1 (7)
Abdominal pain	3 (23)	1 (7)
Febrile neutropenia	2 (15)	2 (15)
Asthenia	2 (15)	1 (7)
Vomiting	1 (7)	-
Thrombocytopenia	1 (7)	1 (7)
Pneumonia	1 (7)	1 (7)
Hypokalemia	1 (7)	1 (7)

RVU120 is well tolerated at 250 mg dose
GI events are manageable with proper antiemetic premedication

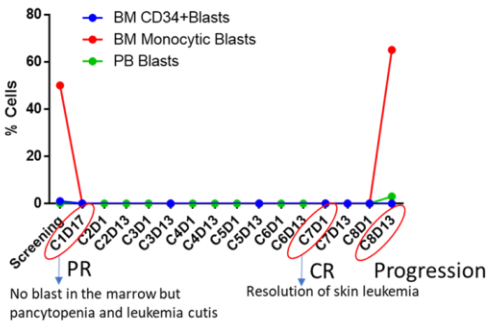
Data generated in RIVER-51 study support further development of RVU120 in AML, HR-MDS, LR-MDS and MF

Significant blast reductions

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

P103-002 AML

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



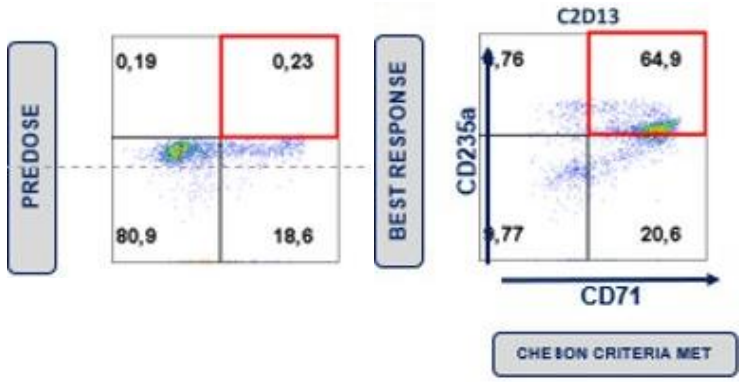
CR achieved end of C1 with persistent skin leukemia, resolved in C5

Transfusion independence

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

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



RBC-TI and Plt-TI on RVU120 treatment

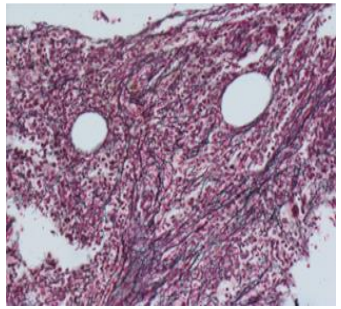
Improvement of BM architecture

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

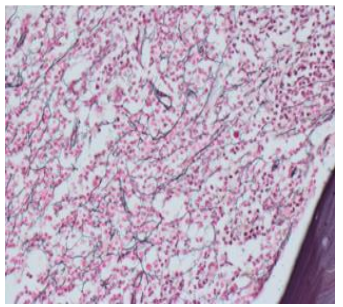
P108-002 HR-MDS

- 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



Reduction of fibrosis grade and marrow CR

RIVER-52 Phase II study with RVU120 as a single agent

Based on convincing translational rationale and clinical data, patients will be selected based on the disease features and genetic background

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: AML or HR-MDS with >10% blasts in BM and no alternative treatment
- Estimated enrolment: **140 patients in total**

PART 1

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

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

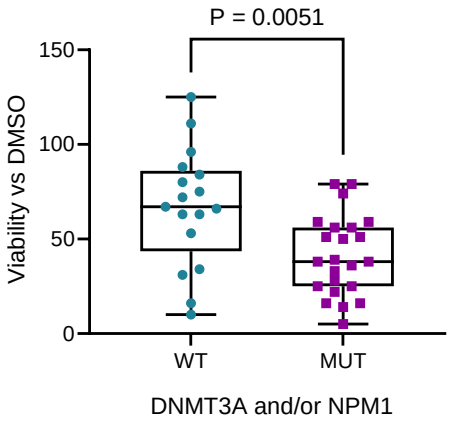
Ongoing assessment of Part 1 will drive selection of population for Part 2

DNMT3A and NPM1 are potential patient selection markers in AML

DNMT3A/NPM1 mutated AML is dependent on dysregulation of HOX genes

- **Low nM activity on CDK8/19**: RVU120 reduces the viability of AML PDCs, in particular those bearing recurrent DNMT3A and NPM1 mutations
- Open chromatin status of DNMT3A and NPM1 mutants makes cells more sensitive to transcriptional changes induced by RVU120
- RVU120 was shown to regulate expression of MEIS1 and homeobox (HOX) genes

Loss of viability with RVU120 treatment



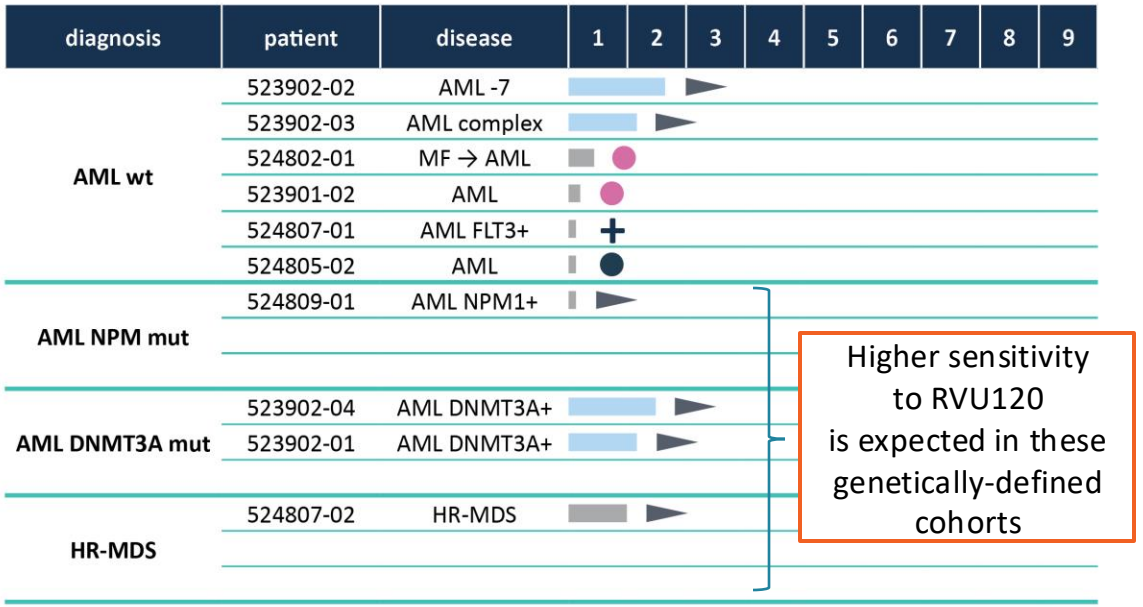
RIVER-52 – initial Phase II results

Data cut-off: May 17, 2023

- A total of 10 pts received RVU120 at 250 mg
- 6 pts are ongoing
- 4 pts were withdrawn (2 for PD, 1 for SAE unrelated to RVU120, 1 for withdrawal of consent)

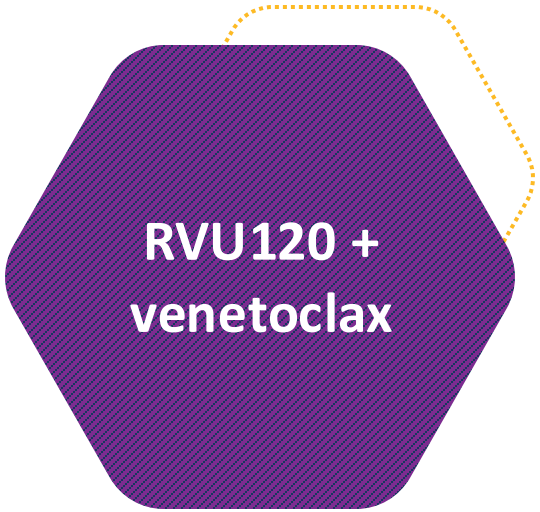
Outcomes

- 1 pt with AML harboring a DNMT3A mutation, showed a peripheral blast reduction on C1D13 and an increase of the hemoglobin level of 1 g/dl average in the first month of RVU120 treatment compared to the month prior to study entry.
- 2 ongoing pts, including a patient with AML harboring an NPM1 mutation and a patient with HR-MDS, were not yet assessed for response.



Enrollment and activation of additional sites are ongoing

RIVER-81 Phase II study testing RVU120 in combination with venetoclax



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
- Approx. **57-98 patients** planned
- 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

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

Clinical Benefit
CR/CRh/CRi, with and without MRD, and DoR

PART 2

Expansion Cohort at selected dose of RVU120 and venetoclax
Simon 2-stage design

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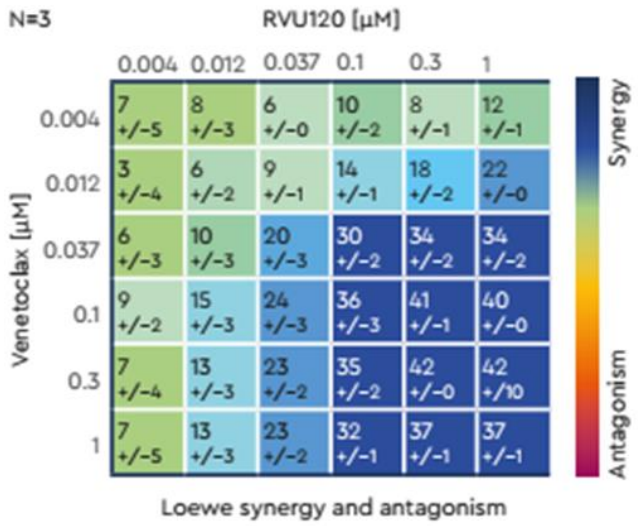
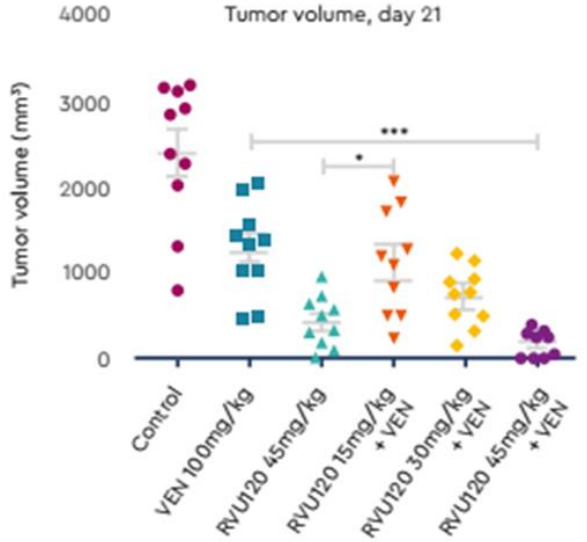
CDK8 inhibition by RVU120 synergizes with venetoclax in nonclinical AML models

Preclinical studies of RVU120 demonstrate robust anti-leukemic activity and synergy with VEN *in vitro* and *in vivo*

Loewe synergy matrix for KG-1 TP53mut AML cell line treated RVU120+VEN



MV4-11 MLL fusion AML xenografts model treated with RVU120 +VEN

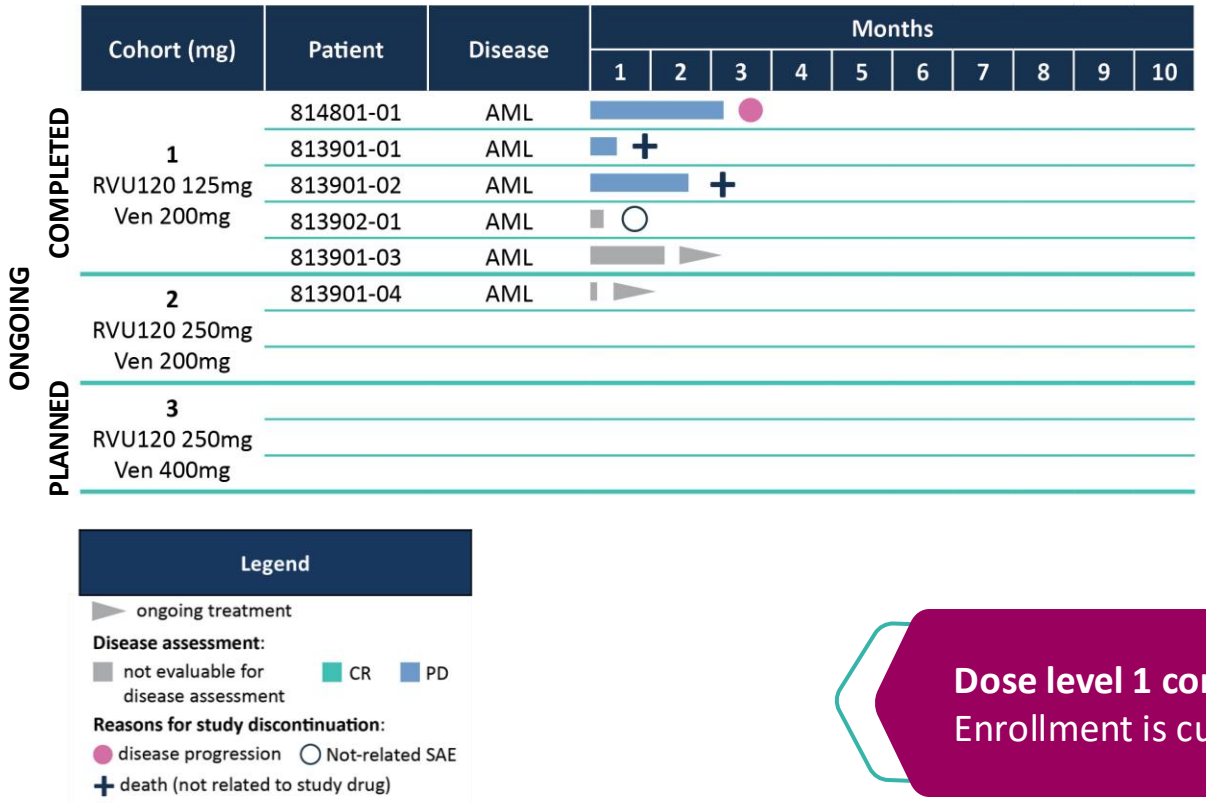


RVU120 Opportunity
Fast-to-market strategy as monotherapy in a potentially biomarker-selected population and broad opportunity in early lines of treatment in combination therapy

RIVER-81: Initial clinical safety of RVU120 with venetoclax

Dose level 1 (RVU120 125 mg + VEN 200 mg) completed

Initial clinical safety confirmed



Treatment Emergent Adverse Events (TEAEs) that occurred in more than 1 patient	RVU120 125 mg + Ven 200mg (Cohort 1)	
	Any grade n (%)	Grade 3-5 n (%)
Asthenia	3 (60)	1 (20)
Febrile neutropenia	2 (40)	2 (40)
Pneumonia	2 (40)	2 (40)

Dose level 1 completed
Enrollment is currently open for Cohort 2 (RVU120 250 mg + VEN 200 mg)

RVU120 – Validating efficacy in AML as monotherapy and combination

1. **RVU120 as a single agent showed clinical benefit in a heavily pretreated population with AML and HR-MDS in the Phase 1 trial. The strongest evidence of benefit was observed in patients with NPM1 and DNMT3A mutation, and in patients with HR-MDS**

2. Data in **RIVER-52** are immature for efficacy assessment in the target population.
Preliminary signs of clinical benefit have been observed in ongoing patients

3. Overall, the preclinical results support RVU120 as a candidate in a venetoclax relapsed/refractory and frontline AML setting in combination with VEN, countering therapeutic failure caused by persistent LSCs and MCL-1-mediated VEN resistance

4. **Initial data of the ongoing Phase II study RIVER-81 support the safety of the combination in patients with relapsed/refractory AML**

5. **Anti-leukemic efficacy in patients will be assessed at higher doses**

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

STUDY DESIGN

- Population:
  - Relapsed/refractory low-risk MDS for the treatment of anemia in patients failing available options
  - Opportunity for the first-line (1L) setting
- Primary endpoint:
  - Erythroid response (HI-E) according to IWG 2018 criteria
- 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
- Study will be conducted as an Investigator Initiated Trial with **Prof. Uwe Platzbecker within EMSCO** (European Myelodysplastic Neoplasms Cooperative Group)
- Enrollment planned in approx. 25 sites in EU

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

RVU120 validated preclinically as a drug candidate in LR-MDS

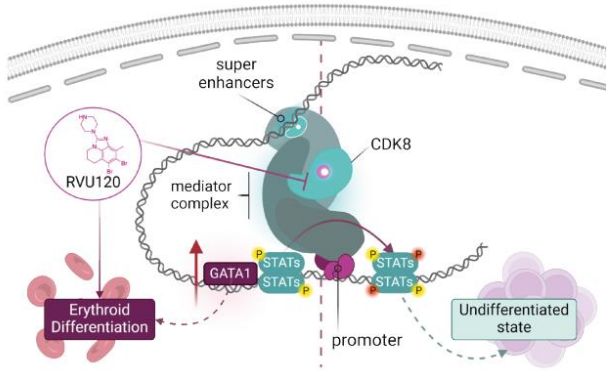
Opportunity in LR-MDS

- 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

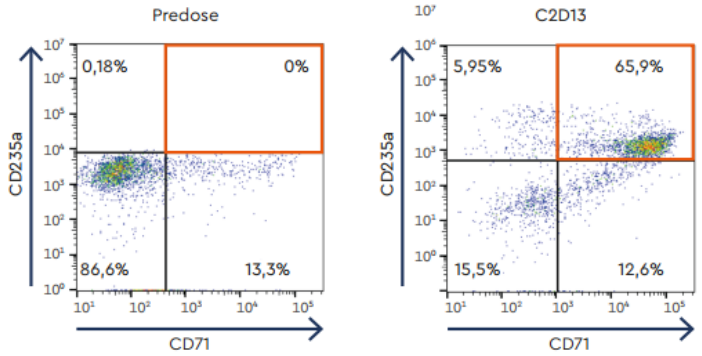
- MDS pathogenesis is influenced by gene expression alterations that hinder the maturation of hematopoietic cells.
- When aberrant stem cells from MDS patients are treated with RVU120, it triggers erythroid gene expression programs orchestrated by STAT5 and GATA1.
- Importantly, RVU120's activity does 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.



POTAMI-61 Phase II study of RVU120 in myelofibrosis (MF) as mono and combo

Study design

- **Population:**
  - Ultimate opportunity in the first line in combination with a JAK inhibitor
  - Starting point in the second line primary or secondary MF; intermediate or high-risk MF per DIPSS;
    (1) previously treated with or (2) ineligible for JAK inhibitor and patients with (3) suboptimal response to RUX
  - Important: patients with thrombocytopenia can be included in RVU120's trials
- **Primary endpoints** spleen volume reduction [SVR35] 24wks;
- **Secondary endpoints**: DoR, leukemic transformation, Hi, BM fibrosis reduction, PFS and OS
- Approx. 20-120 patients planned
- Up to 60 clinical sites planned globally; first patient expected to be dosed in Q4 2024

PART 1 (~20 patients)

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

Cohort 2
(RUX add-on)

PART 2

Expansion of Cohort 1 or 2

Cohort 3
(Frontline)

RVU120 validated preclinically as a drug candidate in MF

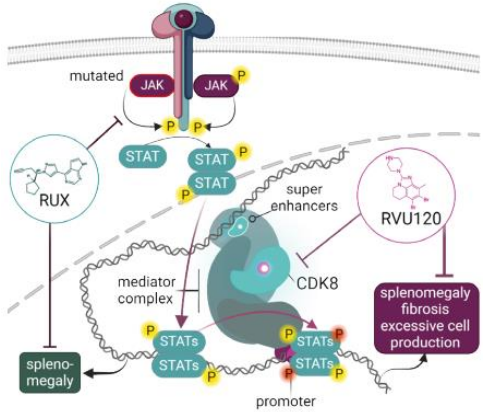
Opportunity in myelofibrosis

- 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 anemia

RVU120 in myelofibrosis

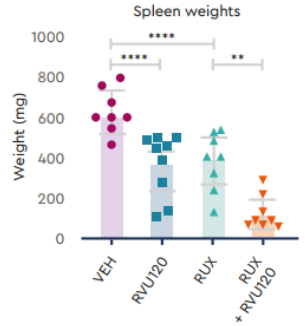
- CDK8 kinase is an important player in MPN pathogenesis, and RVU120 disrupts the downstream signaling events, mitigating MPN symptoms.
- In preclinical studies, RVU120 effectively reduced splenomegaly, bone marrow fibrosis, and abnormal blood cell production. RVU120 has also demonstrated synergy in 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



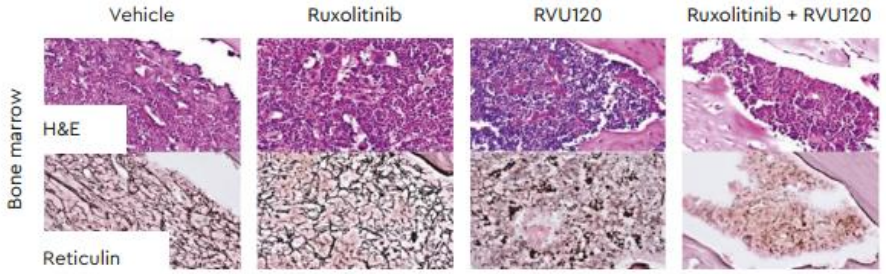
RVU120 reduces splenomegaly

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

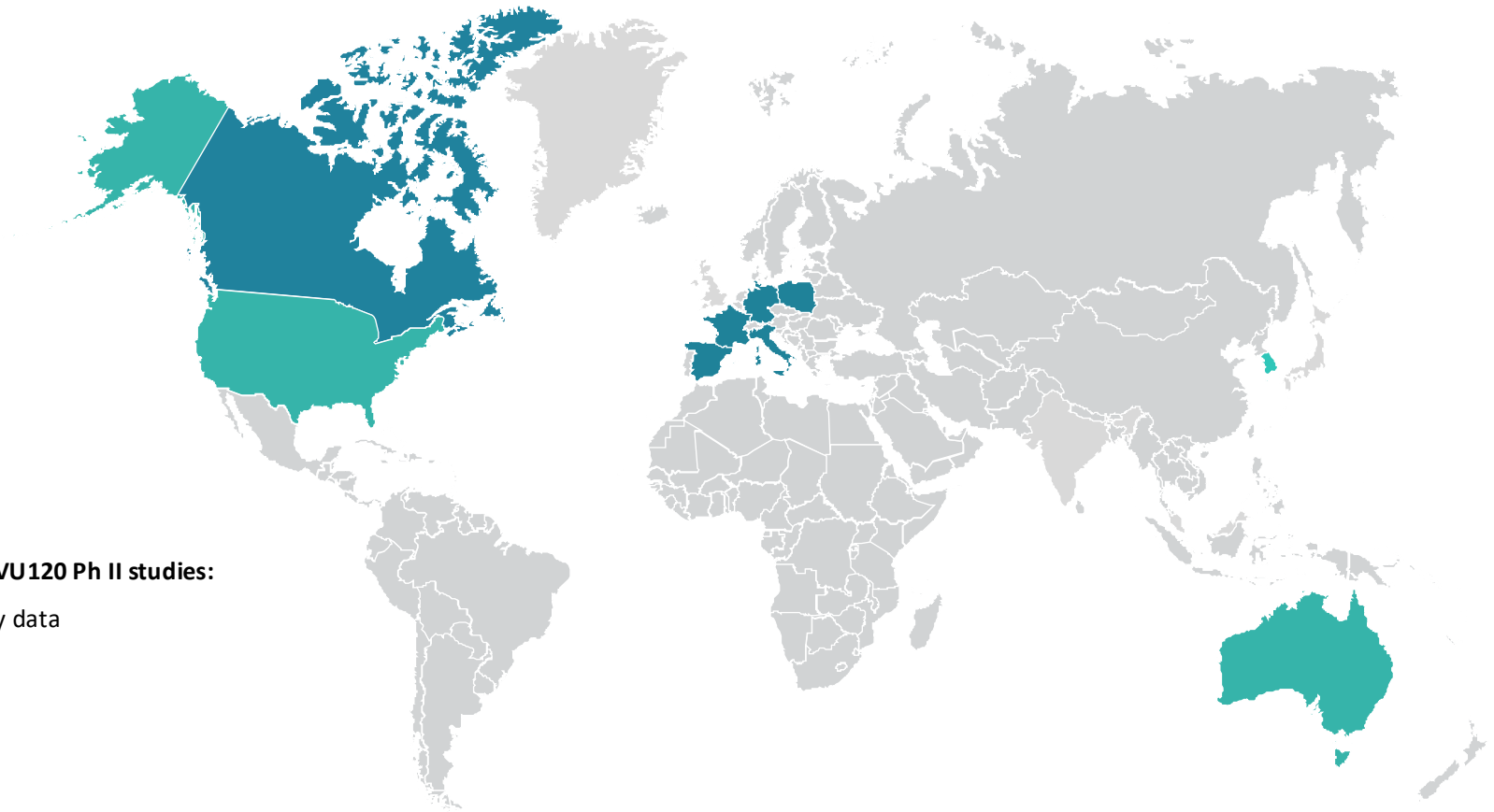


RVU120 reduces bone marrow fibrosis

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



Phase II clinical development of RVU120 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

Number of Ph II clinical trials initiating in 2024	**Number of countries** across studies	**Number of clinical sites** globally	**Number of patients** to be enrolled	**Number of clinical vendors** to be managed	**Number of internal Ryvu team members** in Clinical Development and Translational teams
4	10+	170+	270+	30+	70+

Ryvu to present clinical and preclinical data on RVU120 throughout 2024 and 2025

EHA

Jun 2024

RIVER-51 & RIVER-52 clinical data *#EHA-6466*

- ***RVU120, a first-in-class CDK8 inhibitor for the treatment of relapsed/refractory AML and high-risk MDS: preliminary results from two ongoing studies.***

Chraniuk Dominik, et al.

RIVER-81 clinical data *#EHA-6720*

- ***Synergistic Potential of RVU120, a first-in-class CDK8/CDK19 inhibitor, with venetoclax in AML: Preclinical and Initial Clinical Insights.***

Pakulska Urszula, et al.

RVU120 potential in MPNs *#EHA-6982*

- ***CDK8/19 Inhibition: A Promising Therapeutic Strategy in Myeloproliferative Neoplasms, Alone or in Synergistic Combinations***

Zachary Zaroogian et al (Dr Raajit Rampal's group at MSKCC, NY)

Dec 2024

Anticipated RVU120 disclosures

- **RIVER-52: interim data from Part 1**
- **RIVER-81: Part 1 data and interim data from Part 2**
- **POTAMI-61 and REMARK: update on clinical study progress**

Jun 2025

Anticipated RVU120 disclosures

- **RIVER-52: Part 1 data and interim data from Part 2**
- **RIVER-81: Part 2 data**
- **POTAMI-61: Part 1 data**
- **REMARK: interim data**

RYVU THERAPEUTICS

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 estimated 11,220 deaths in the US in 2024[2]
- **Venclexta (venetoclax) sales estimated to exceed USD 3.5 bn in 2025[3]**

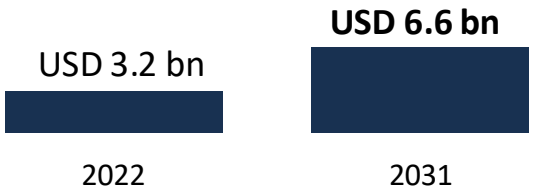
MDS (Myelodysplastic Syndrome)

- 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)

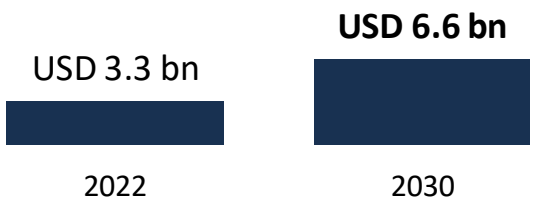
- MF is a bone marrow disease characterized by JAK mutations; often leads to severe anemia
- Chronic disease with long duration of therapy; US prevalence is estimated to be ~13,000 patients[7]
- **Morphosys acquired by Novartis for EUR 2.7 bn** in Feb 2024
  – primary asset is Phase 3 MF drug pelabresib

Global AML Market[4]



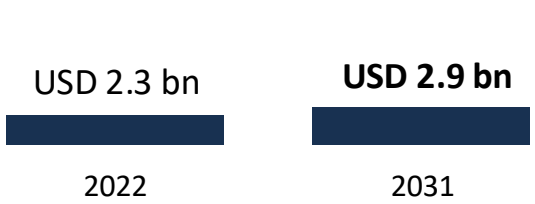
8.5% CAGR (2022-2031)

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

MEN1703 (SEL24): First-in-Class PIM/FLT3 Inhibitor

MEN1703 (SEL24)

Licensed to Menarini Group, currently in Phase II

PARTNERSHIP AGREEMENT WITH MENARINI GROUP (2017)

- EUR 4.8m upfront payment
- EUR 3.5m further milestone and translational research funding at Ryvu in 2017-2021
- Possible additional EUR 80m bio-dollar value + royalties
- Menarini conducts and funds all research and development costs

PROVEN SAFETY AND CLINICAL ACTIVITY

- Phase II clinical data (EHA2022) indicate efficacy in AML with IDH1/IDH2 gene mutations, similar to other drugs used as monotherapy
- Manageable safety profile
- Orphan drug designation (ODD) granted by FDA

Future directions

DLBCL

- Development to continue with the initiation of a **new Phase II** study in relapsed/refractory diffuse large B-cell lymphoma (DLBCL)

Future Opportunities

- Ongoing translational work supports potential development in other hematologic indications
- Development in AML to be deprioritized

Partnership

- As of September 2023, Ryvu has become Menarini's operational partner for Phase II execution
- The licensing partnership with Menarini remains unchanged, with Menarini funding all R&D. The total milestones and royalties due to Ryvu upon achievement of certain events remains unchanged

Initiating Phase II in DLBCL

MEN1703 PROFILE

- First-in-class dual PIM/FLT3 inhibitor with a unique mechanism of action
- Differentiated activity in cellular models compared to selective PIM inhibitors (broader activity profile)

CLINICAL STUDIES TO DATE

- H1 2017- H1 2021 Phase I dose escalation and cohort expansion in R/R AML – MTD of 125 mg established
- H2 2021 – H1 2023 Phase II in IDH+ R/R AML
- 73 patients dosed so far across all studies, including 48 at R2PD
- Manageable safety profile
  - No QTc prolongation, no differentiation syndrome, no gastrointestinal tox
  - No hematologic toxicity

PHASE II in DLBCL

- Phase II study to consist of two parts: Part 1 pilot cohorts to establish combination dose and monotherapy efficacy followed by Part 2 cohort expansion
- Study locations: USA, Europe
- Phase II study to be initiated in Q4 2024

Small Molecule Platform with Focus on Synthetic Lethality

RYVU THERAPEUTICS

RVU305: PRMT5 MTA-cooperative inhibitor in IND-enabling studies

RVU305/PRMT5i

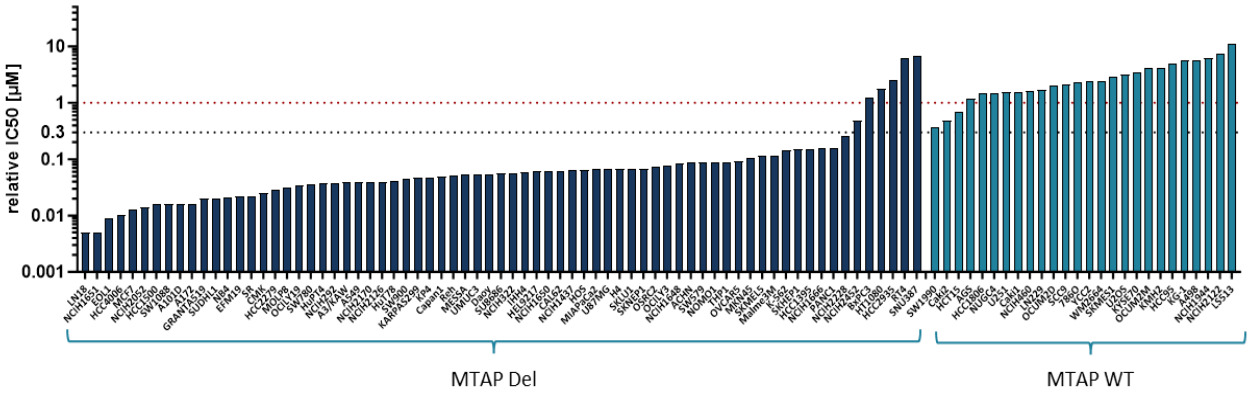
KEY RATIONALE and MOA	PRMT5 MTA-cooperative inhibitors exert synthetic lethal phenotype in MTAP deleted cells
NOVELTY	Best-in-class potential Focus on selectivity, potency and safety
TOP TUMOR INDICATIONS	MTAP deletions, up to 15% of all cancers, one of the largest genetically-defined population: pancreatic, lung, DLBCL, bladder, esophageal (by %: mesothelioma, GBM)
STATUS	File IND/CTA in H2 2025

RVU305 has best-in-class properties,
including favorable potency and selectivity vs. competitors

RVU305 demonstrates:

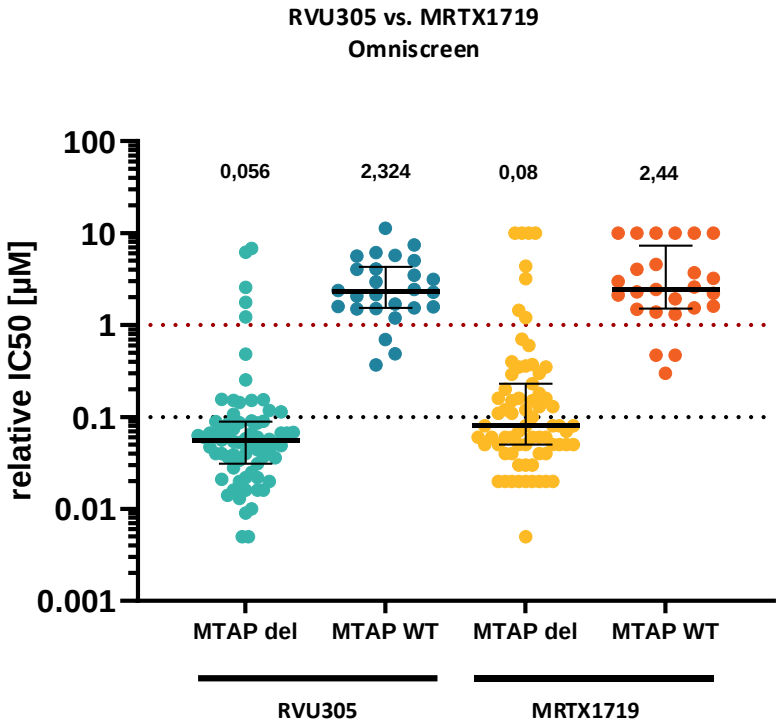
- robust **antiproliferative effect** on MTAP-deleted cell lines
- a good **safety window** for MTAP WT cells
- **superior selectivity** for MTAP del cell lines

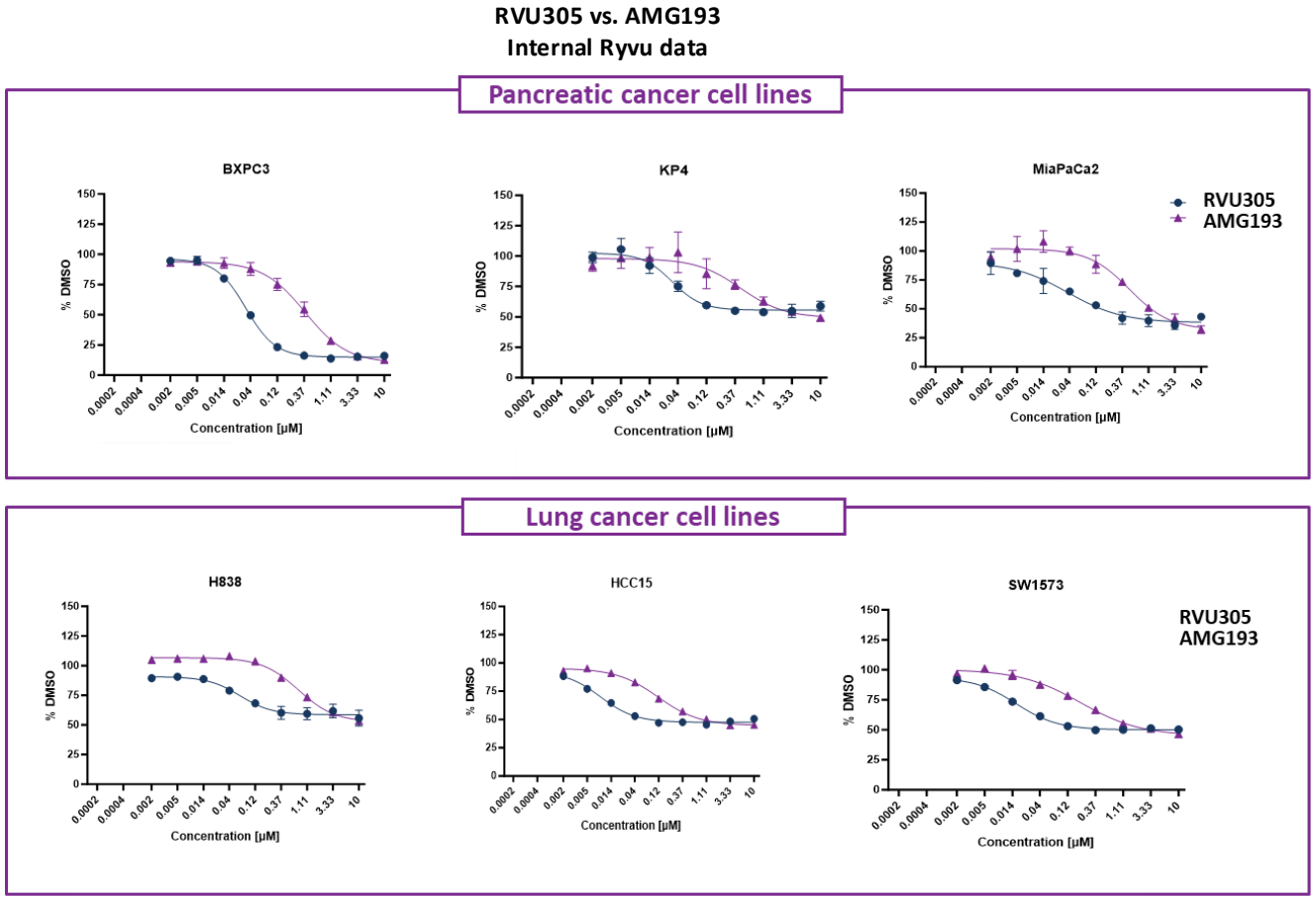
RVU305
Omniscreen results



Source: Radzimierski et al., AACR 2024.

RVU305 shows superior *in vitro* profile compared to competitors

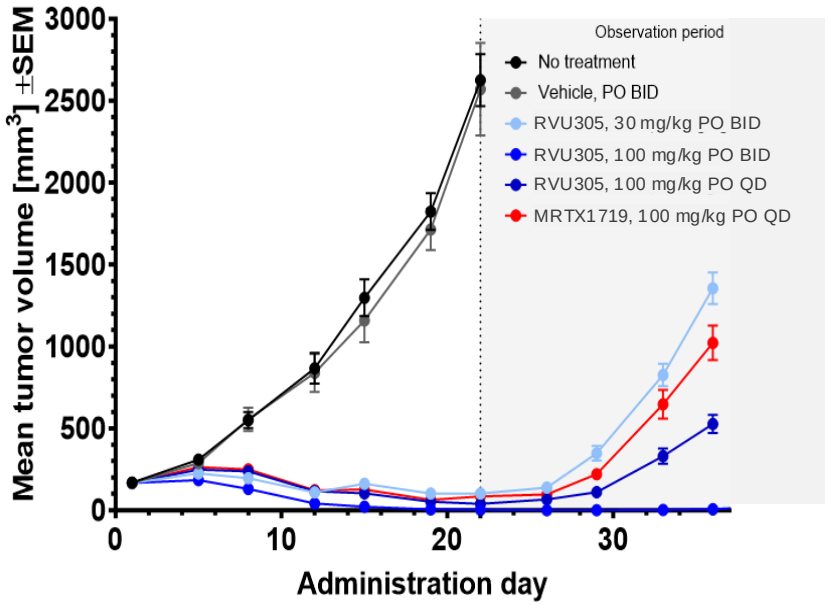




RVU305: advancing to IND filing with best-in-class properties

RVU305 has best-in-class properties,
including favorable *in vitro and in vivo* efficacy vs. competitors

Efficacy in MTAP del DoHH2 lymphoma CDX model



Tumor Growth Inhibition and Complete Remissions:

- RVU305 30 mg/kg BID : 103% TGI, 0/10 CR
- **RVU305 100 mg/kg BID : 107% TGI, 8/10 CR**
- **RVU305 100 mg/kg QD : 105% TGI, 0/10 CR**
- **MRTX1719 100 mg/kg QD : 103% TGI, 0/10 CR**

RVU305 has best-in-class potential based on robust multiparameter optimization

Superior preclinical properties

- **Antitumor efficacy and target engagement** achieved *in vivo* in responder CDX models
- **Antiproliferative activity** for MTAP-deleted cells *in vitro:* high potency and high efficacy in large cell line panel
- **Favorable PK profile** of Ryvu PRMT5 inhibitors demonstrated in PK studies in different species

Leading to differentiated clinical strategy:

- Ongoing translational work will support the selection of indications, patients, and therapeutic combination partners

RVU305 has best-in-class potential vs. clinical competitors

	MRTX1719	TNG908	TNG462	AMG193	RVU305
Potency [1]	+++	+	+++	++	+++
Viability fold shift MTAP KO/MTAP WT	+++	+	++	++	++++
Residence time	+++	+	ND	ND	+++
% of highly sensitive MTAP deleted cell lines in Omniscreen[2]	36%	ND	ND	ND	63%
Brain penetrance	-	+++	-	-	-
In vivo PK[3]	+	+	++	+++	+++
Potential for drug-drug interactions	+++	+	++	+++	+++
Expected target coverage at clinical dose and schedule[4]	++	+	+++	++	++++
Clinical safety	+++	ND	ND	+++	ND

1 Viability in vitro in MTAP del cell line model
2 Based on published data on MRTX1719 compared with Ryvu Omniscreen panel on RVU305
3 Overall murine PK profile including clearance
4 Based on the overall preclinical profile and simulations

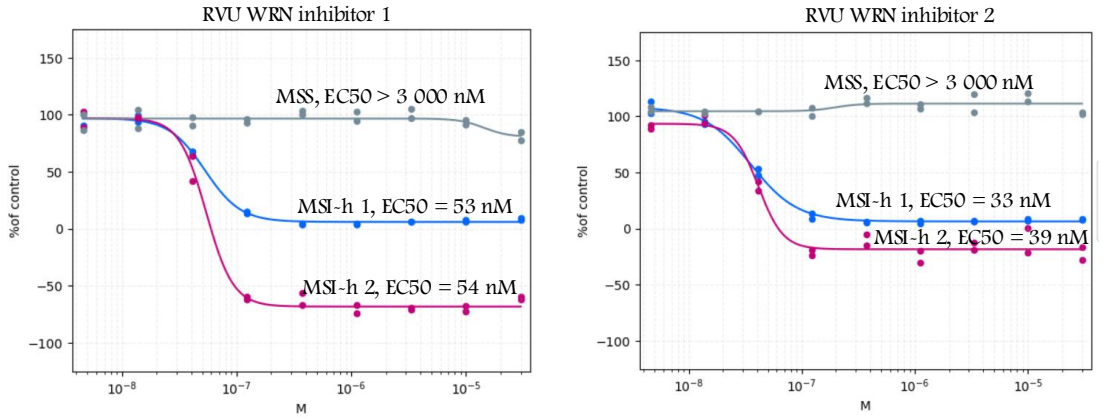
34

Werner Syndrome Helicase (WRN) inhibitors at Ryvu

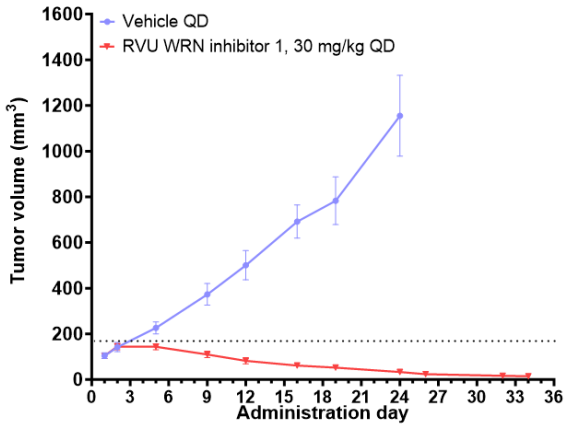
WRN Inhibitor Program at Ryvu

KEY RATIONALE and MOA	Synthetic lethality of WRN with microsatellite instability (MSI-high)
NOVELTY	Best-in-class potential Focus on selectivity, potency and safety
TOP TUMOR INDICATIONS	Tumor agnostic with MSI-high vulnerability (~10-30% of colorectal, endometrial, gastric, ovarian cancers)
STATUS	Lead Optimization

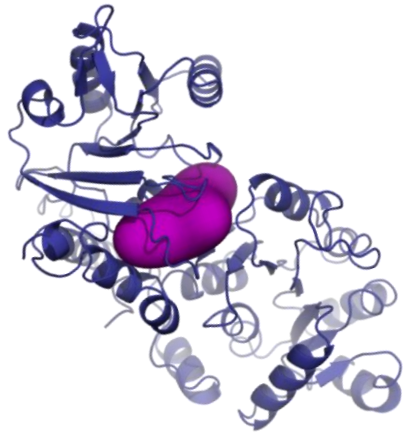
01 **Ryvu WRNi display specific nanomolar potency in viability assays in MSI-H cell lines, retaining excellent selectivity ratio against MSS cell lines**



02 **Ryvu WRNi induces a strong synthetic lethal phenotype in MSI-H xenograph CRC model**

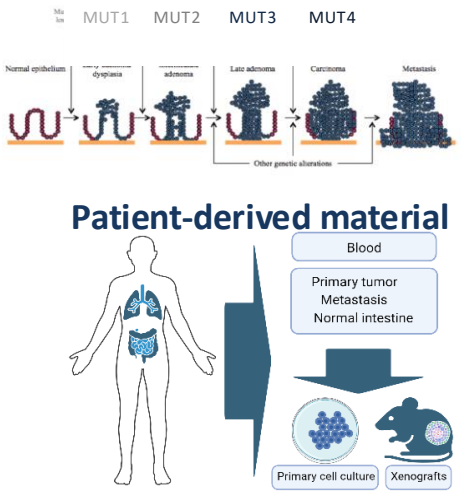


03 **X-Ray of WRN helicase with Ryvu ligand**

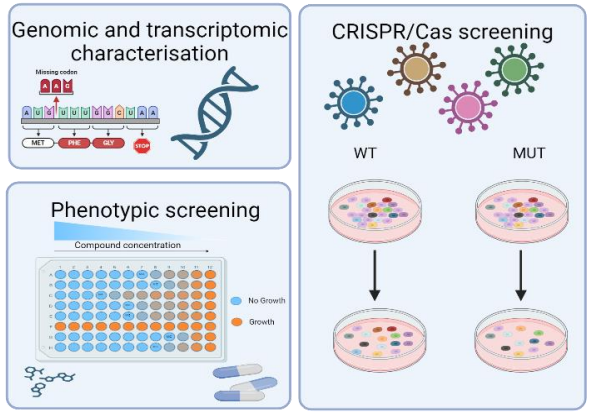


Accelerating ONCO Prime and Unveiling Novel Synthetic Lethal Targets

Modeling cancer progression



High Throughput Screenings

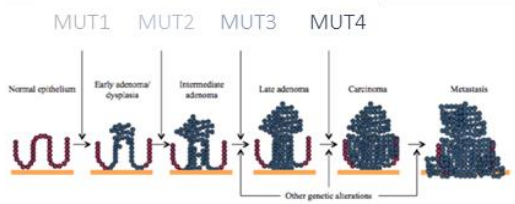
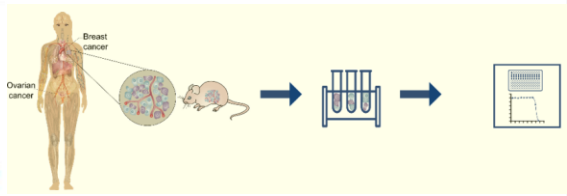


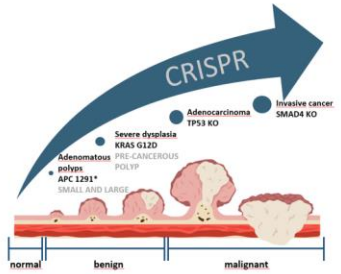
Novel Targets & Treatments

- Ryvu's OncoPrime platform has **broad potential to discover novel synthetic lethal targets** across a variety of tumor types – initial case study data presented in colorectal cancer
- Ryvu Target Discovery platform has identified **several novel targets** for **KRAS-driven tumors**
- Our approach allows exploring novel treatment strategies via phenotypic screening

Driving Novel Synthetic Lethal Target Discovery with Ryvu Therapeutics ONCO Prime Platform

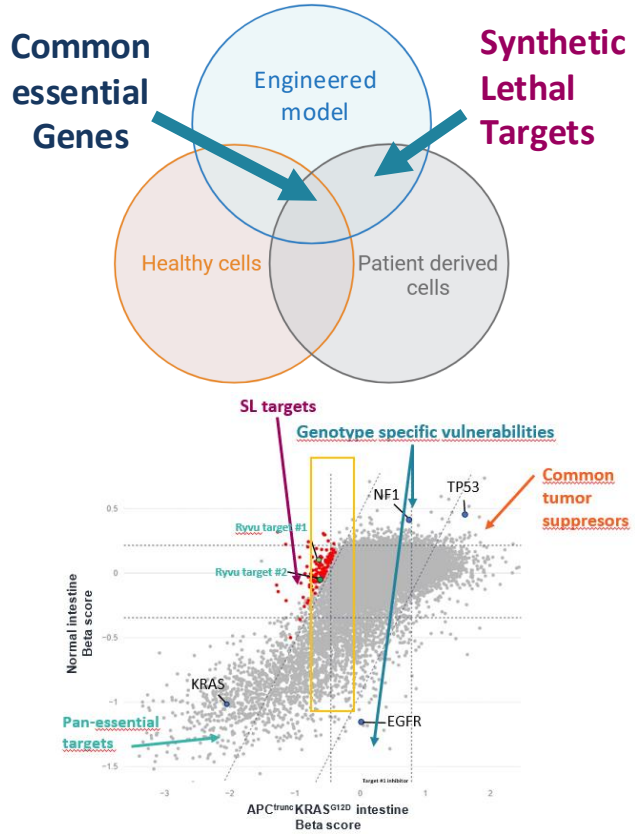
Ryvu's CRISPR-based target Discovery Platform

Engineered Model	Patient-Derived Cells (PDCs)
	
Isogenic Primary Cells Recreating the stages of tumor development	Tumor heterogeneity & relevant transcriptomic profile



Awarded PLN 26 million (~USD 6.6M) from Polish Agency for Enterprise Development[1]

Discovering Novel Synthetic Lethal Targets

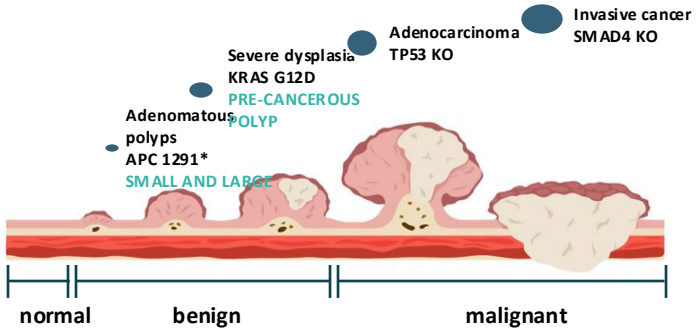


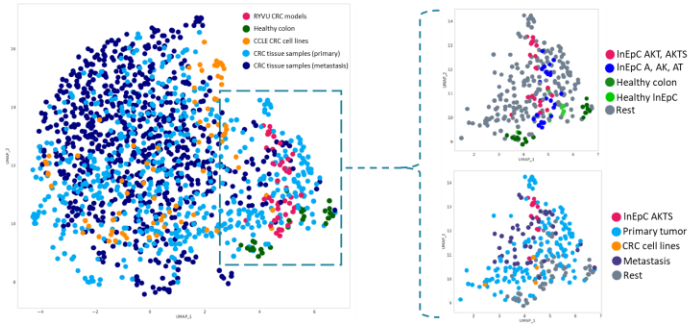
1 ONCO Prime is co-financed by the European Union under the Operational Programme European Funds for Modern Economy 2021-2027. Project title: "ONCO Prime: new possibilities for personalised anti-cancer therapy based on patient-derived primary cell cultures, omics characterisation, and functional assays". Grant Agreement no: FENG.01.01-IP.02-0095/23.

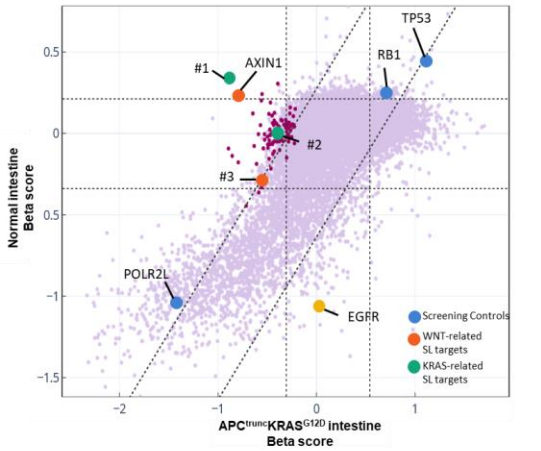
ONCO Prime: Broad potential to identify novel cancer targets – first data in KRAS-driven CRC

Ryvu's KRAS-mutated CRC tumor cells are representative of CRC patients

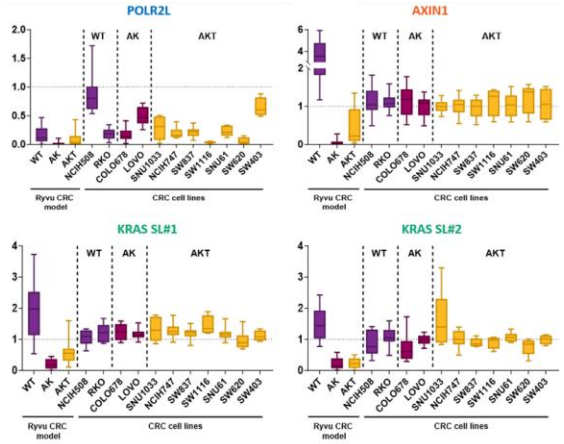
Screen of Ryvu cells yield synthetic lethal targets not seen in public data sets including DepMap







- Blue denotes internal screening controls (tumor suppresor and common essenial genes)
- Orange signifies synthetic lethal targets involved in WNT pathway regulation
- Green represents synthetic lethal targets involved in RAS pathway regulation.



ONCO Prime has broad applicability across all tumor types, and Ryvu is initiating the next set of tumor screens beyond CRC in the coming months

BioNTech and Ryvu: global collaboration to develop and commercialize immune modulation small molecule candidates

Largest-ever Ryvu deal: November 2022

1. Multi-target discovery collaboration on small molecule programs in immune modulation
2. STING agonist license as a monotherapy and in combinations

Partnership

- **Multi-target research collaboration**: Ryvu is conducting discovery and research activities to develop multiple small molecule programs targeting immune modulation in cancer and potentially other disease areas based on targets selected by BioNTech; BioNTech will hold exclusive worldwide development and commercialization rights.
- **STING agonist**: BioNTech receives a global, exclusive license to develop and commercialize Ryvu's STING agonist portfolio as standalone small molecules, including as monotherapy and in therapeutic combinations.

Key Financial Terms

- Ryvu received €40 million from BioNTech, comprised of €20 million in upfront cash and a €20 million equity investment
- All R&D funded by BioNTech
- Ryvu is eligible for R&D and commercial milestones, and low single-digit royalties on product sales

Exelixis and Ryvu: exclusive license agreement to develop novel STING agonist-based targeted cancer therapies

July 2022

1. Building STING-based antibody drug conjugates (ADCs)
2. Leveraging Ryvu's STING agonist portfolio and Exelixis's ADC technology

Partnership

- Exclusive license agreement to combine Ryvu's small molecule STING agonists and STING biology know-how with Exelixis' antibody engineering, antibody-drug conjugate (ADC) technologies and drug development expertise
- Ryvu retains global rights for the development and commercialization of standalone STING agonists (licensed to BioNTech)

Key Financial Terms

- $3M upfront cash; first milestone of $1M achieved in Q1 2023; second milestone of $2M achieved in Q1 2024
- Additionally, Ryvu is eligible to receive research funding, $2M in near-term research-based milestones, and a double-digit milestone at first development candidate selection
- In total, Ryvu is eligible to receive milestones of over $400 million plus tiered single-to-low double-digit royalties on annual net sales per product developed/commercialized

Corporate Progress

Financial Results: H1 2024

$ million	2023*	H1 YTD 2023*	H1 YTD 2024*
Revenues	**16.3**	**7.9**	**12.1**
Partnering	*11.2*	*5.5*	*9.3*
Grants	*4.9*	*2.3*	*2.8*
Total Costs**	**37.6**	**17.7**	**25.4**
Clinical Pipeline	*13.0*	*5.8*	*11.1*
Early Pipeline	*15.8*	*7.8*	*9.5*
G&A	*8.8*	*4.1*	*4.9*
EBIT**	**-21.3**	**-9.8**	**-13.3**
EBITDA**	**-18.7**	**-8.5**	**-11.9**
Net Results***	**-20.0**	**-9.4**	**-11.9**

Partnering revenues in H1 YTD 2024:
Exelixis ($2.0 million), BioNTech ($6.8 million recognized)

Cash position September 5, 2024†

$65.3M

Ryvu Employees

>300

Employees with PhD

~100

* Recalculated from PLN using 4.1823 PLN/USD, 4.2744 PLN/USD and 3.9979 PLN/USD – for 2023, H1 YTD 2023 and H1 YTD 2024, respectively
** Excluding the impact of the non-dilutive, cash-neutral Employee Incentive Scheme (of $2.0m, $1.4m and $0.6m in 2023, H1 YTD 2023 and H1 YTD 2024 respectively) and valuation of NodThera (+$0.9m (increase of costs) in 2023, +$0.5m in H1 YTD 2023, and 0,0m in H1 YTD 2024, respectively)
*** Excluding the impact of the non-dilutive, cash-neutral Employee Incentive Scheme (of $2.0m, $1.4m and $0.6m, in 2023, H1 YTD 2023 and H1 YTD 2024 respectively)
† Cash position includes all three tranches of EIB venture debt totaling EUR 22 million; the final tranche of EUR 6 million was received on 05 September 2024

Ryvu's Vision: from 2026, Ryvu will improve the lives of cancer patients worldwide

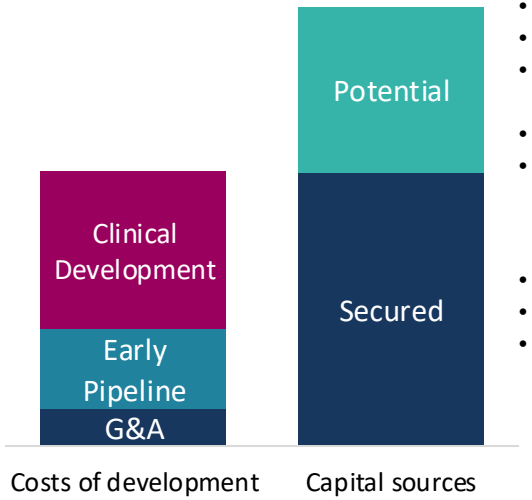
2024 KEY GOALS AND FINANCING

PIPELINE

- **RVU120 broad development (including potential fast-to-market strategy in AML/HR-MDS)**
- SEL24 (MEN1703) to start Phase II in DLBCL (with Menarini Group)
- **Advancement of one preclinical program into Phase I clinical trials**
- Strengthening of Synthetic Lethality Platform and acceleration in the early pipeline progress

BUSINESS

- **Achieving financial milestones in existing collaborations** (i.e. BioNTech, Exelixis, Menarini)
- **At least one new partnering deal per year**



- Research funding from existing R&D collaborations
- Milestones from existing R&D collaborations
- New grant funding
- New deals in the early pipeline
- RVU120 limited licensing (limited regions and/or co-development)
- NodThera exit
- Other

- Cash at hand + interest on cash
- EIB venture debt
- Existing grants

2024 – DEVELOPMENT PLAN KEY ASSUMPTIONS

- Accelerating the pipeline to deliver cancer therapeutics to patients
- Capital for development secured; potential additional non-dilutive sources
- Significant increase of the company's value
- Development strategy includes alternative, de-risking partnering scenarios

2024 – KEY ANTICIPATED EVENTS

- **Clinical data updates from RVU120 in Q4**
- New preclinical candidate in the early pipeline: achieved with RVU305

Ryvu equity summary

IPO on WSE **Corporate Split: Selvita and Ryvu**	Nov 2014 Oct 2019
Ticker: WSE	RVU
52-Week Range[1]	PLN 47.00 – 72.40
Average Daily Volume (YTD) [1]	3,154
Market cap[1]	PLN 1,235 M (USD 318M)
Shares outstanding	23.1 M
Cash[2]	USD 65.3M

Top Holders[3]		
1	Paweł Przewięźlikowski	18%
2	Allianz OFE	9.2%
3	BioNTech SE	8.3%
4	Nationale-Nederlanden OFE	7.9%
5	Tadeusz Wesolowski (incl. Augebit)	4.9%
6	PZU OFE	4.5%
7	Boguslaw Sieczkowski	4.0%
8	Allianz TFI	2.4%
9	Goldman Sachs TFI	2.1%
10	Norges Bank	2.1%
11	UNIQA OFE	1.8%
12	Generali OFE	1.5%

Analyst Coverage

ERSTE Group	mBank	NOBLE SECURITIES DOM MAKLERSKI	TRIGON DOM MAKLERSKI	ipopema	Bank Pekao Biuro Maklerskie	Santander Biuro Maklerskie
Vladimira Urbankova	Beata Szparaga-Waśniewska	Krzysztof Radojewski	Katarzyna Kosiorek	Łukasz Kosiarski	Marcin Górnik	Tomasz Krukowski

1. As of 10 September 2024 2. As of 05 September 2024 3. As of 29 Dec 2023

Thank you

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