



Developing therapeutics  
at the forefront of oncology

# Corporate Presentation

November 2024



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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

*Wholly-owned*

- First-in-class, 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

*Partnered*

- 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 Przewięźlikowski, MSc, MBA**  
CEO and Founder



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CSO



**Hendrik Nogai, MD**  
CMO



**Kamil Sitarz, PhD, MBA**  
COO



**Vatnak Vat-Ho, MBA**  
CBO



**Miika Ahdesmäki, PhD, MBA**  
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**Jakub Janowski, MSc**  
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**Bartłomiej Konicki, MSc**  
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**Tomasz Rzymiski, PhD, MBA**  
Director of Translational Medicine



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Director of HR



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# Broad pipeline addressing emerging targets in oncology

PROGRAM	INDICATION	DISCOVERY	PRECLINICAL	PHASE I	PHASE II	PARTNER	EXPECTED MILESTONES
<b>RVU120 (CDK8/19)</b>	R/R AML/HR-MDS (RIVER-52) (monotherapy)						Initial Ph II data in 4Q24
	R/R AML (RIVER-81) (combination with venetoclax)						Initial Ph II data in 4Q24
	LR-MDS (REMARK) (monotherapy)						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
<b>MEN1703 (SEL24) (PIM/FLT3)</b>	DLBCL						Initiation of Ph II in 4Q24
<b>SYNTHETIC LETHALITY</b>							
<b>RVU305 (PRMT5)</b>	SOLID TUMORS						IND/CTA submission in 2H25
<b>WRN</b>	SOLID TUMORS						In lead optimization
<b>NOVEL TARGETS</b>	ONCOLOGY						
<b>IMMUNO-ONCOLOGY</b>							
<b>STING &amp; MULTI-TARGET IMMUNE MODULATION COLLABORATION</b>	ONCOLOGY						
<b>STING ADC</b>	ONCOLOGY						

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



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

- First-in-class
- High potency

- High selectivity
- Low risk of DDI

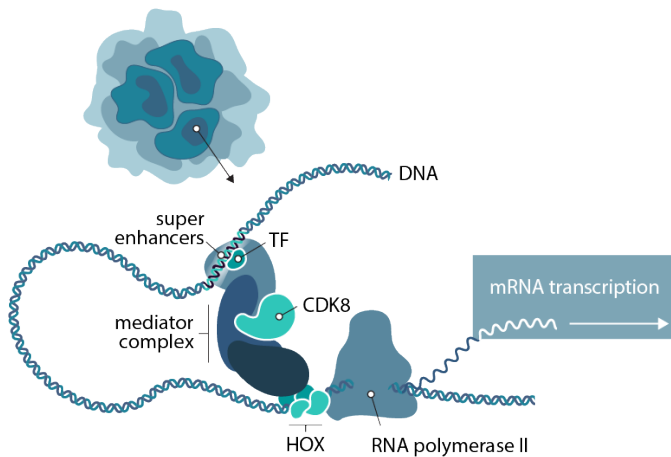
- Easy to formulate
- Orally available

CDK8/19 mediator promotes AML growth

CDK8/19 inhibition by RVU120 triggers differentiation and apoptosis

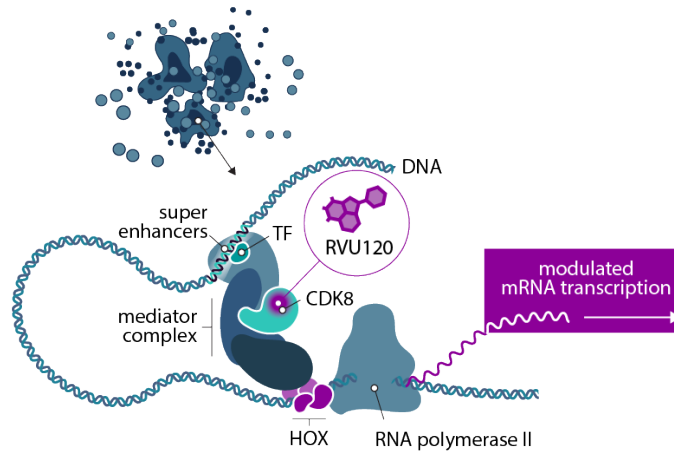
RVU120 is highly selective for CDK8/19

Viability of tumor cells

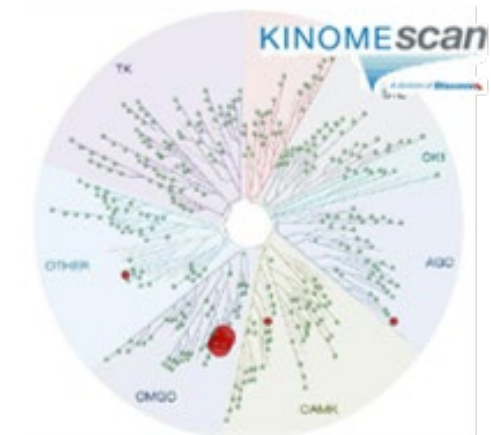


Maintenance of malignant stem cells  
Suppression of differentiation

Apoptosis of tumor cells



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

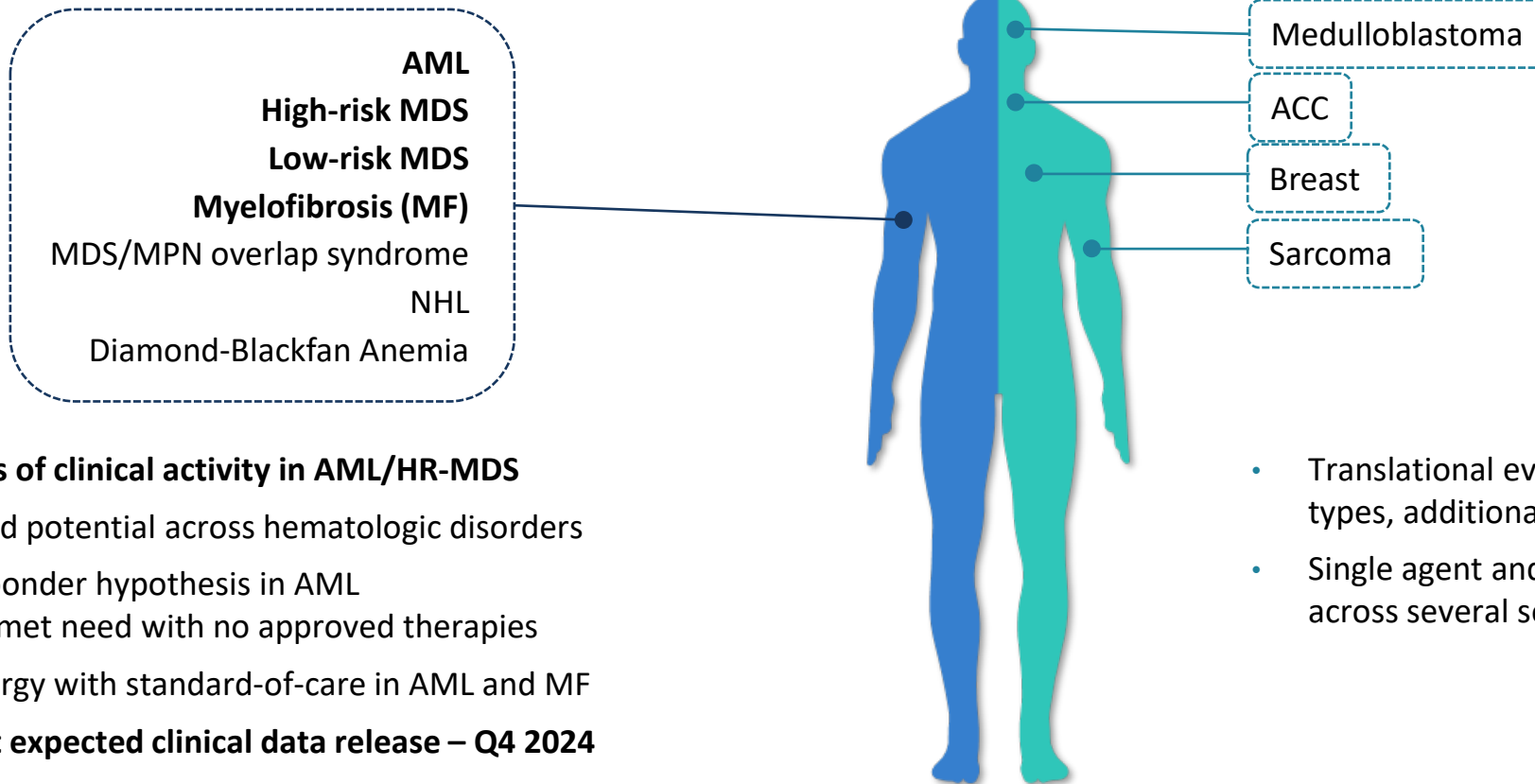


Current RVU120 development plan could lead to three accelerated approvals in 2026-2027

# RVU120: opportunities across a broad range of cancers

## Blood Cancers & Disorders

## Solid Tumors



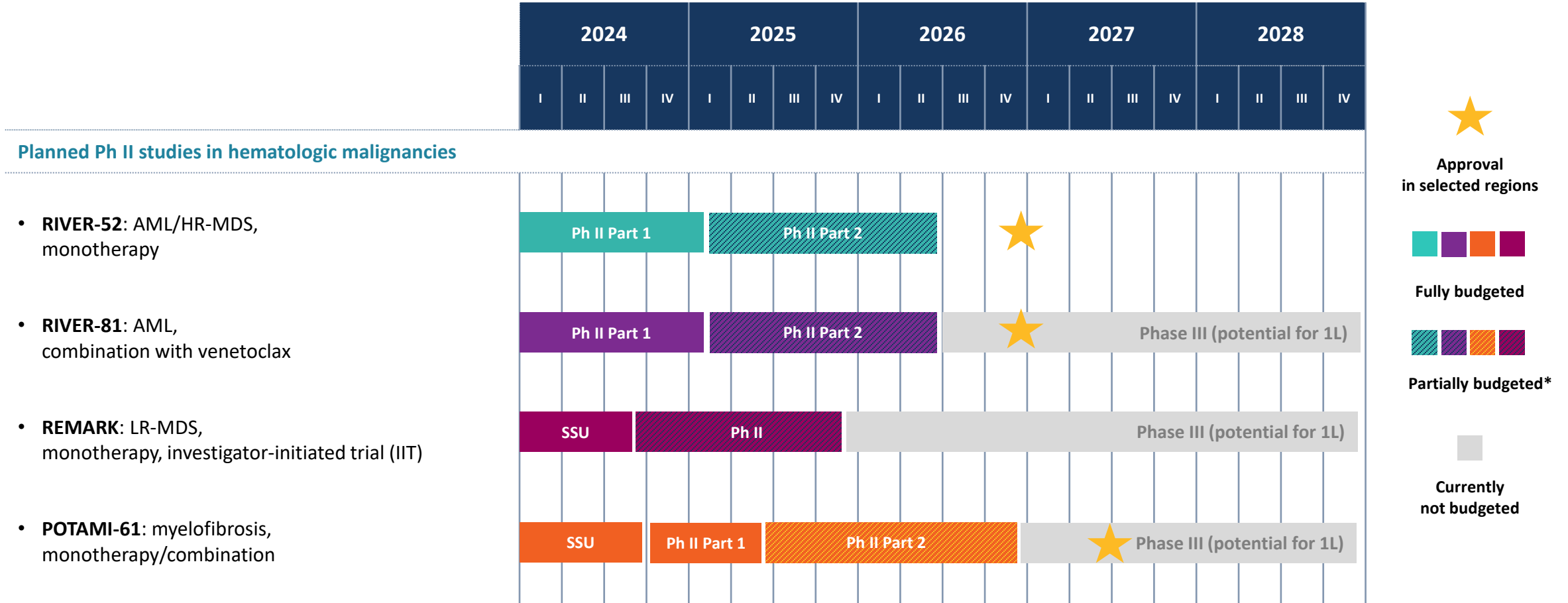
- **Signs of clinical activity in AML/HR-MDS**
- Broad potential across hematologic disorders
- Responder hypothesis in AML
  - unmet need with no approved therapies
- Synergy with standard-of-care in AML and MF
- **Next expected clinical data release – Q4 2024**

- 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

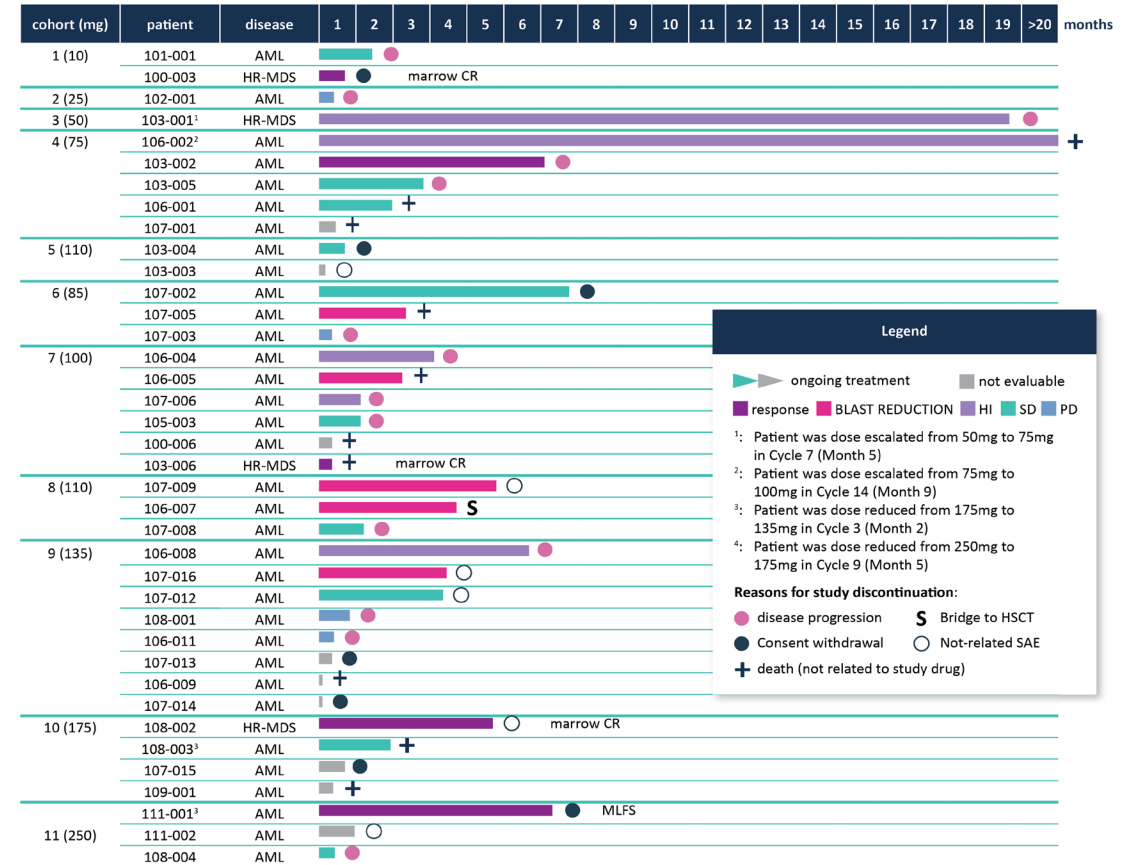
- 30 treated patients are evaluable for response (38 were treated in total)
- 9 patients achieved clinically significant BM blast reduction (including 1 CR, 1 MLFS, 3 marrow CRs)
- 5 patients achieved erythroid hematological improvement (HI-E), 4 of those became transfusion-independent, of which 2 normalized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

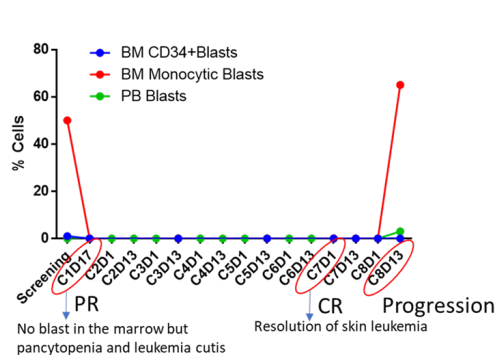
# Data generated in RIVER-51 study support further development of RVU120 in AML, HR-MDS, LR-MDS and MF

## 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



### SCREENING



### RVU120 C5D1

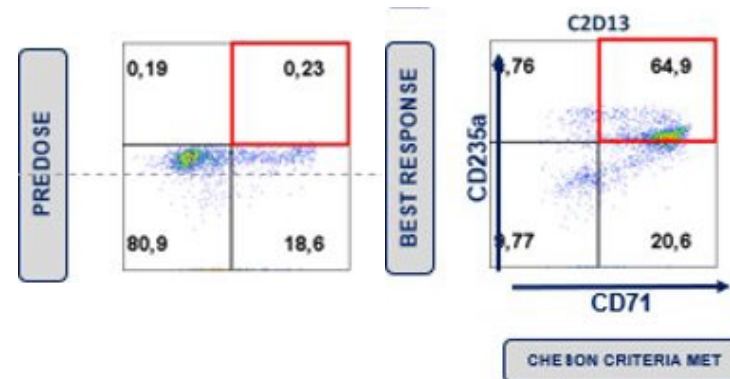


## Transfusion independence

- >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

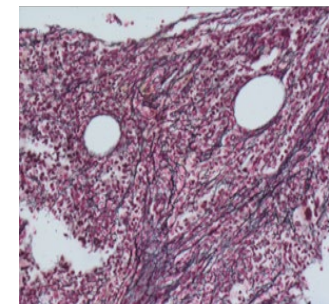
## Improvement of BM architecture

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

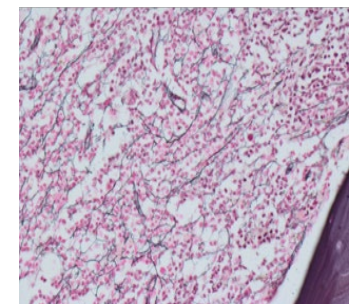
### P108-002 HR-MDS

- 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



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

## 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**



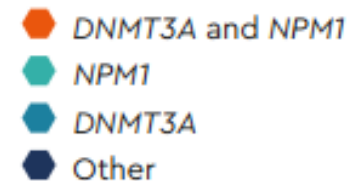
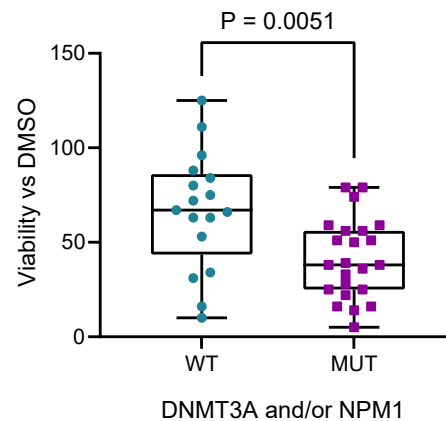
Ongoing assessment of Part 1 will drive selection of population for Part 2

# 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



OHSU, Nature 2018  
AML patients n=531



# 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)

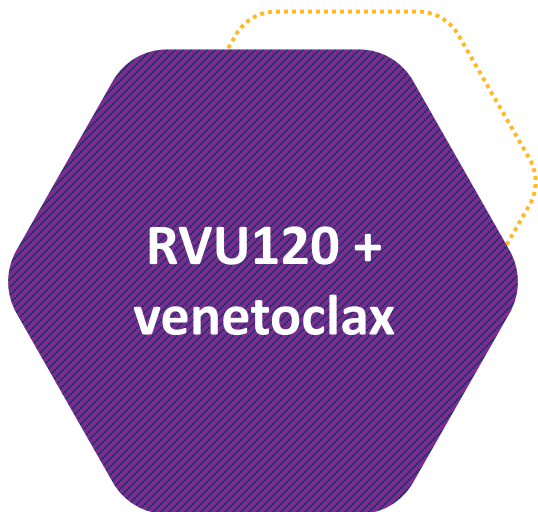
## Outcomes

- 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.

diagnosis	patient	disease	1	2	3	4	5	6	7	8	9
AML wt	523902-02	AML -7	█	█	▶						
	523902-03	AML complex	█	█	▶						
	524802-01	MF → AML	█	●							
	523901-02	AML	█	●							
	524807-01	AML FLT3+	█	+							
	524805-02	AML	█	●							
AML NPM mut	524809-01	AML NPM1+	█	▶							
AML DNMT3A mut	523902-04	AML DNMT3A+	█	█	▶						
	523902-01	AML DNMT3A+	█	█	▶						
HR-MDS	524807-02	HR-MDS	█	▶							

Higher sensitivity to RVU120 is expected in these genetically-defined cohorts

Enrollment and activation of additional sites are ongoing



## 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



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

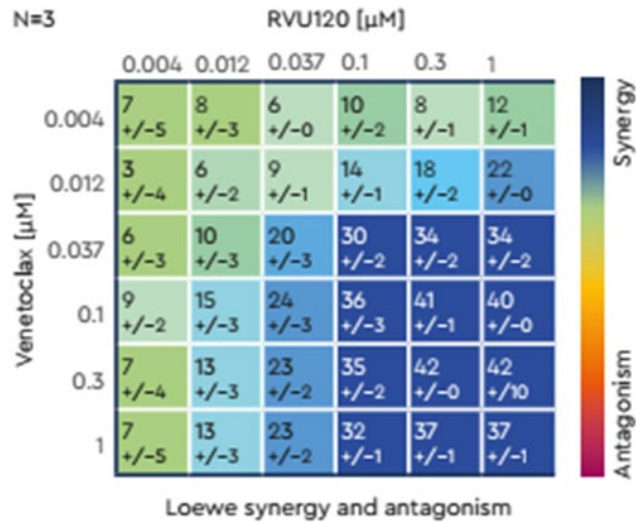
Expansion Cohort at selected dose of RVU120 and venetoclax  
Simon 2-stage design



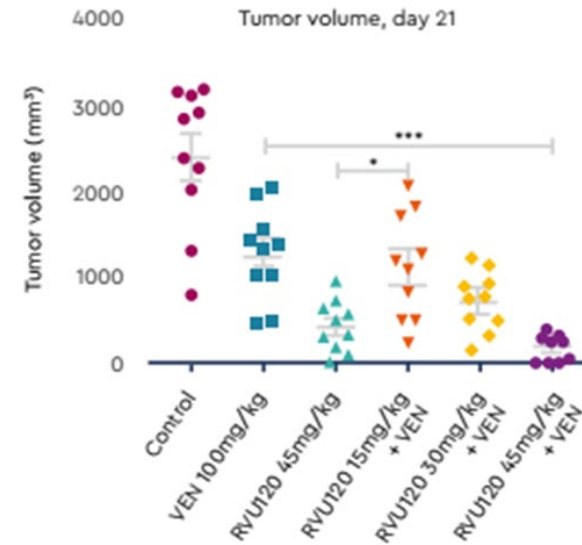
# CDK8 inhibition by RVU120 synergizes with venetoclax in nonclinical AML models

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

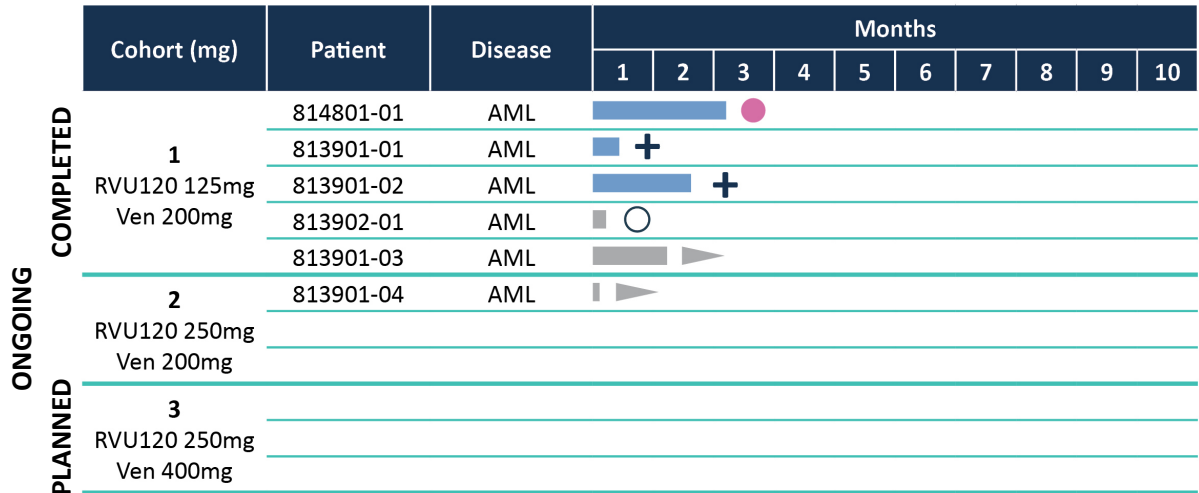


**RVU120 Opportunity**  
 Fast-to-market strategy as monotherapy in a potentially biomarker-selected population and broad opportunity in early lines of treatment in combination therapy

# 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	Grade 3-5
	n (%)	n (%)
Asthenia	3 (60)	1 (20)
Febrile neutropenia	2 (40)	2 (40)
Pneumonia	2 (40)	2 (40)

**Legend**

- ▶ ongoing treatment
- Disease assessment:**
  - not evaluable for disease assessment
  - CR
  - PD
- Reasons for study discontinuation:**
  - disease progression
  - Not-related SAE
  - ⊕ death (not related to study drug)

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



### 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

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

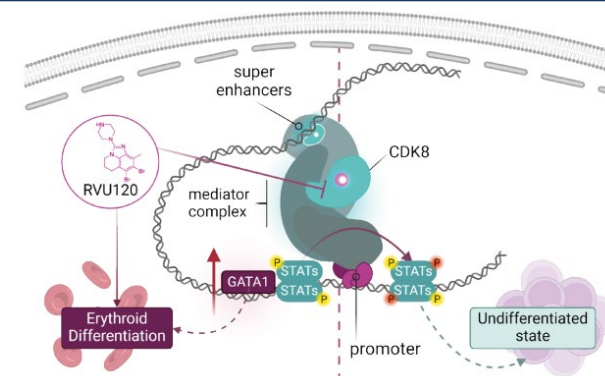
## Opportunity in LR-MDS

- 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

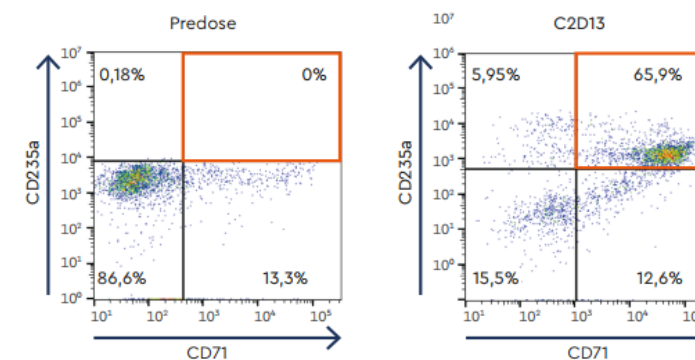
- MDS pathogenesis is influenced by gene expression alterations that hinder the maturation of hematopoietic cells.
- When aberrant stem cells from MDS patients are treated with RVU120, it triggers erythroid gene expression programs orchestrated by STAT5 and GATA1.
- Importantly, RVU120's activity does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



## 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

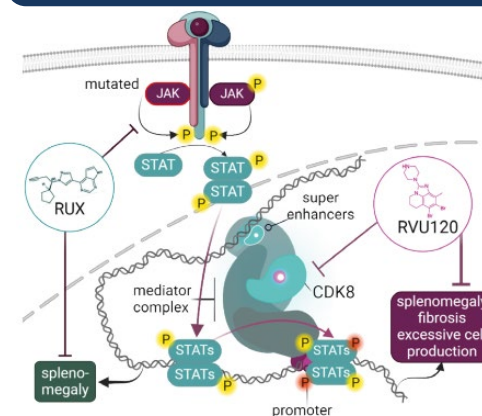
## Opportunity in myelofibrosis

- 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

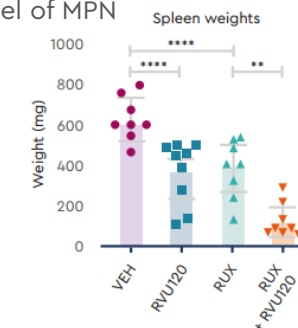
- CDK8 kinase is an important player in MPN pathogenesis, and RVU120 disrupts the downstream signaling events, mitigating MPN symptoms.
- In preclinical studies, RVU120 effectively reduced splenomegaly, bone marrow fibrosis, and abnormal blood cell production. RVU120 has also demonstrated synergy in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



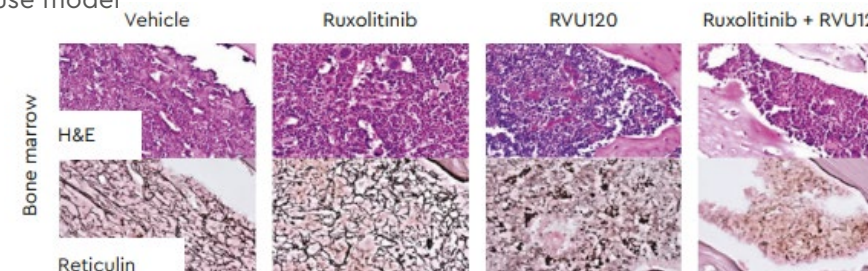
## RVU120 reduces splenomegaly

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

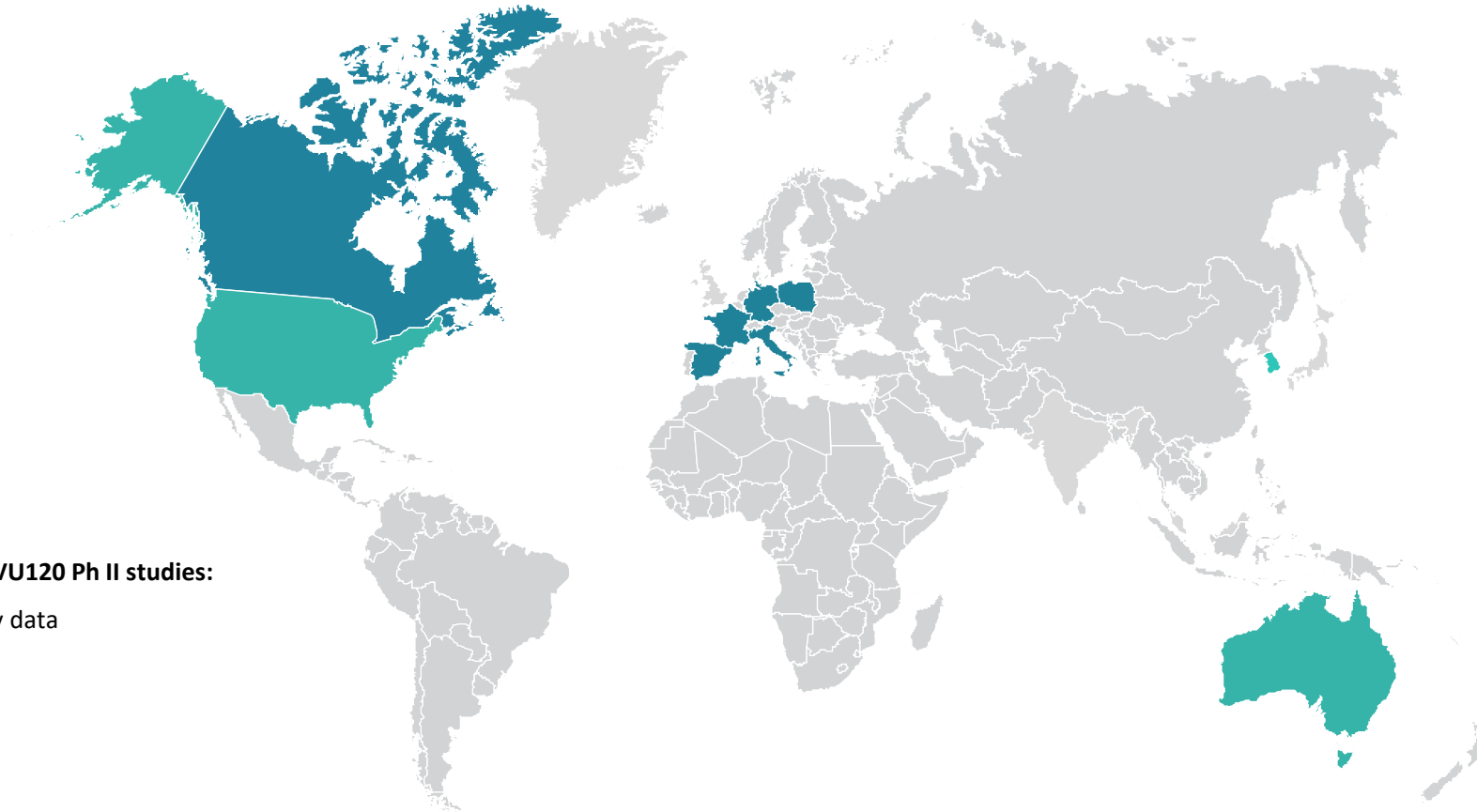


## RVU120 reduces bone marrow fibrosis

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



Global site locations and patient population

Global CROs and clinical vendors

Regulatory authorities worldwide

Number of Ph II clinical trials initiating in 2024

4

Number of countries across studies

10+

Number of clinical sites globally

170+

Number of patients to be enrolled

270+

Number of clinical vendors to be managed

30+

Number of internal Ryvu team members in Clinical Development and Translational teams

70+



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



Jun 2024

Dec 2024

Jun 2025

## 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 Zarogian et al (Dr Raajit Rampal's group at MSKCC, NY)*

## 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

## Anticipated RVU120 disclosures

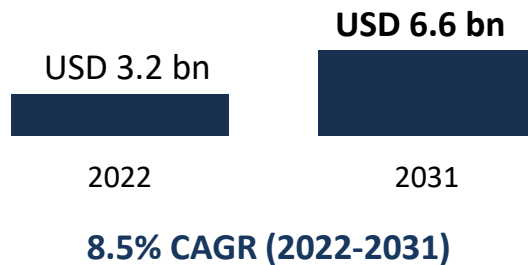
- **RIVER-52:** Part 1 data and interim data from Part 2
- **RIVER-81:** Part 2 data
- **POTAMI-61:** Part 1 data
- **REMARK:** interim data

# 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<sup>(1)</sup>
- Annual incidence in the US at ~20,800 with an estimated 11,220 deaths in the US in 2024<sup>(2)</sup>
- **Venclexta (venetoclax) sales estimated to exceed USD 3.5 bn in 2025<sup>(3)</sup>**

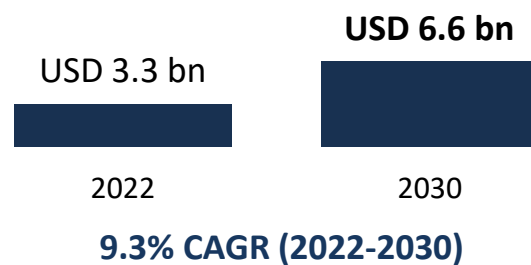
### Global AML Market <sup>(4)</sup>



## 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<sup>(4)</sup>
- **Reblozyl (luspatercept) projected peak sales of USD 3.2 bn by 2029<sup>(5)</sup>**
- **Rytelo (imetelstat) projected peak sales of USD 1.2 bn<sup>(6)</sup>**

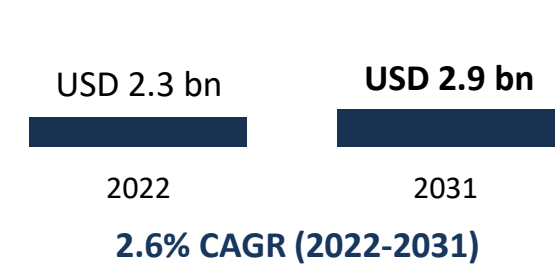
### Global MDS Market <sup>(4)</sup>



## 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<sup>(7)</sup>
- **Morphosys acquired by Novartis for EUR 2.7 bn in Feb 2024**  
– primary asset is Phase 3 MF drug pelabresib

### Global MF Market <sup>(7)</sup>



# 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



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

## RVU305/PRMT5i

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

### 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 demonstrates superior preclinical properties vs. competitors

Leading to a differentiated clinical strategy

- **Antiproliferative activity** demonstrated in MTAP-deleted cells *in vitro*; high potency and high efficacy in large cell line panel
- **Favorable PK profile** demonstrated in PK studies in various species
- **Antitumor efficacy** achieved *in vivo* in responder CDX models

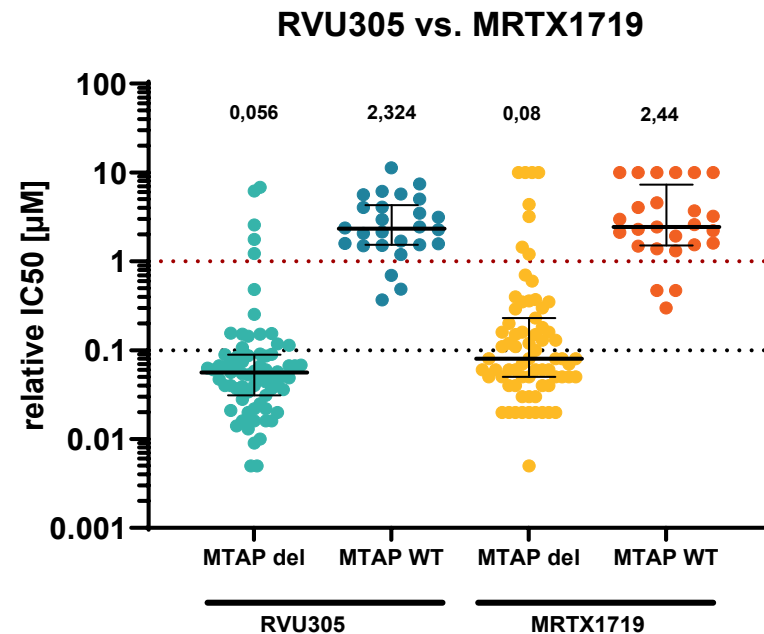
Ongoing translational work will support the selection of

- Indications/tumors
- Drug combination partners
- Patient sub-populations

# RVU305 shows superiority in multiple cell lines

Analysis of pancreatic, lung and bladder cancer origin cell lines shows RVU305 superiority over MRTX1719

- Panel of MTAP-deleted and MTAP-wt cells was profiled with RVU305 in a 5-day CellTiter-Glo assay
- A differential response to Ryvu PRMT5 MTA-cooperative inhibitor is seen between cells with different MTAP status
- RVU305 shows higher potency than MRTX1719 (comparing to results published by Engstrom et al., 2023)

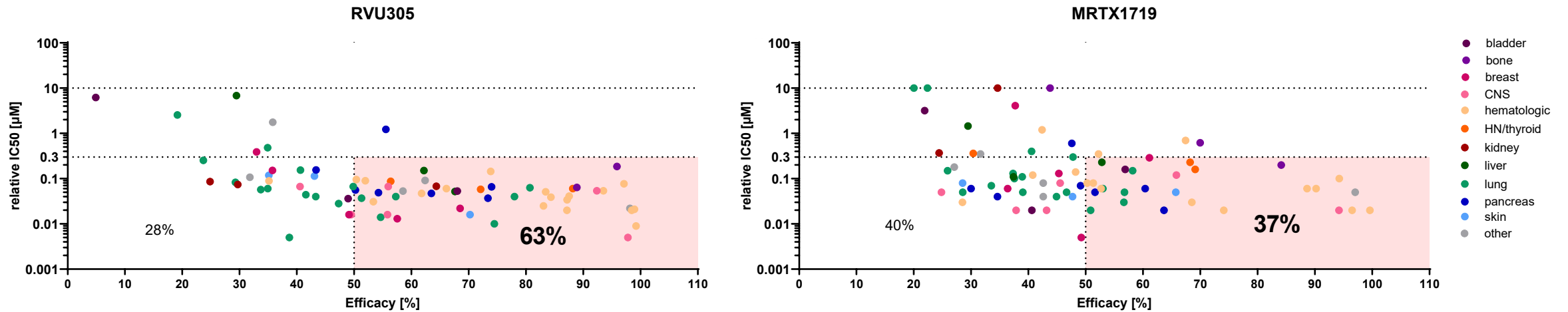




# RVU305 shows strong antiproliferative activity in cell lines

RVU305 shows superior potency and efficacy in cell line panel vs. MRTX1719

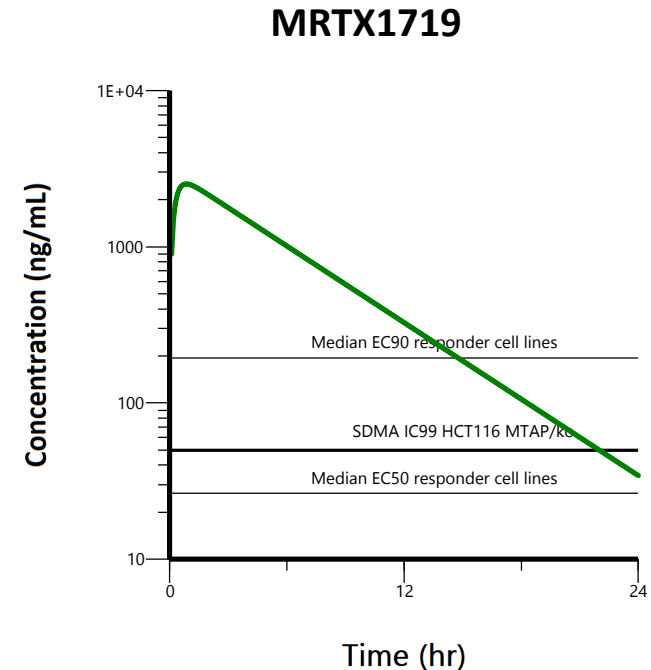
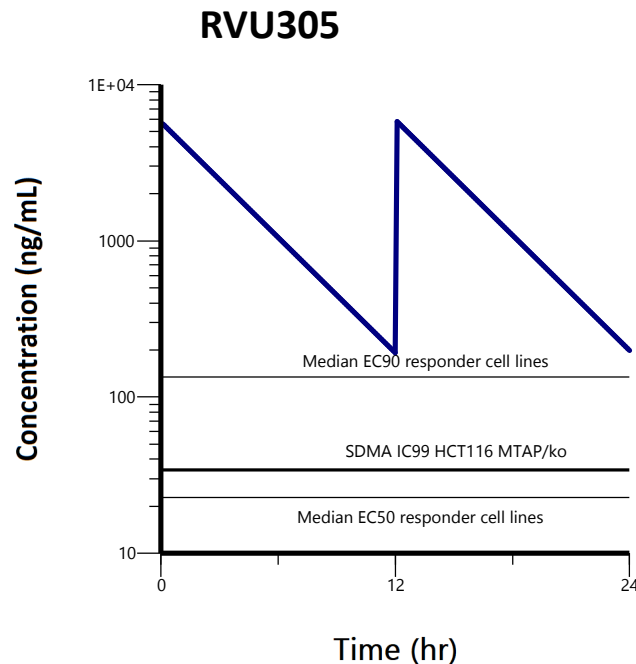
RVU305 shows a better profile of potency and efficacy in the cell line panel with 63% of the cell lines below a threshold of 300nM IC50 (at which most sensitive MTAP WT cell line responded) and efficacy above 50% comparing to 37% for MRTX1719



# Favorable PK profile for RVU305 is promising for clinical development

**RVU305 shows improved exposure and target coverage compared to MRTX1719.**

The murine pharmacokinetic profile and exposure at pharmacologically relevant doses—75 mg/kg BID for RVU305 and 100 mg/kg QD for MRTX1719 – indicates that RVU305 achieves higher exposure, target engagement, and target coverage

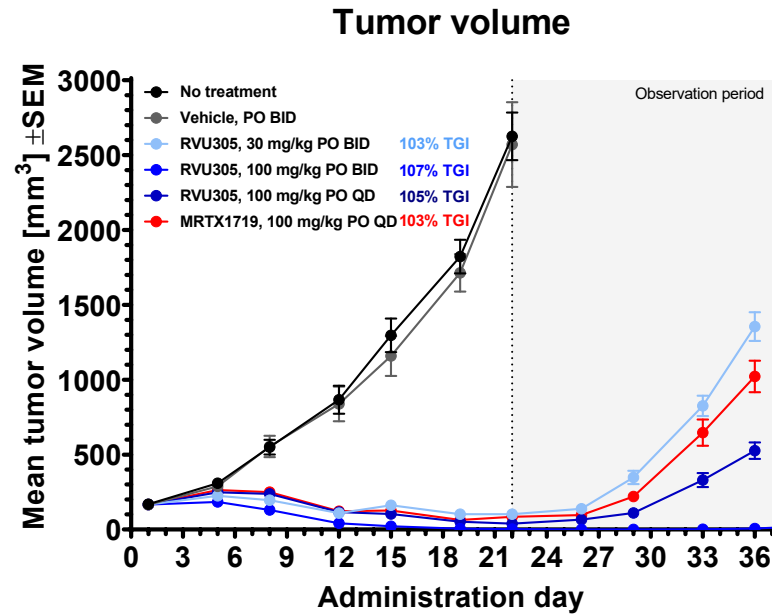


SDMA EC99 (measured via ELISA assay in HCT116 MTAP knockout cells) was used as a target engagement marker. The 2D viability assay median EC50/90 values were derived from panel of multiple MTAP/del cell lines (BXPC3, Lu99, HUPT4, MiaPaca2, A549, DoHH2, HCT116-MTAP-DEL).

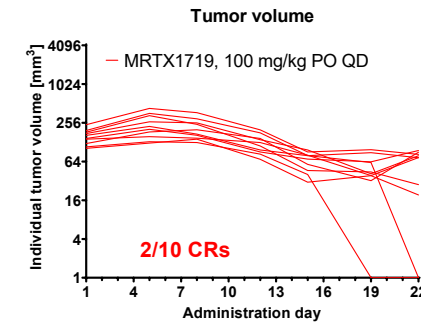
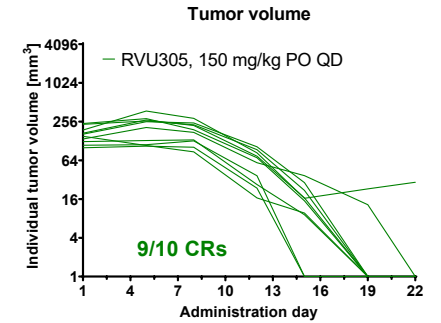
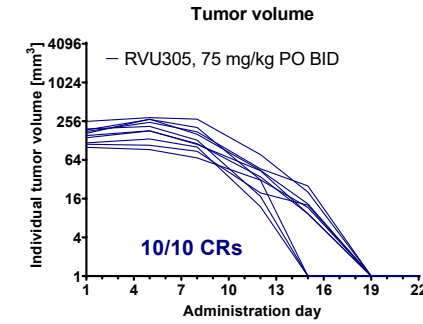
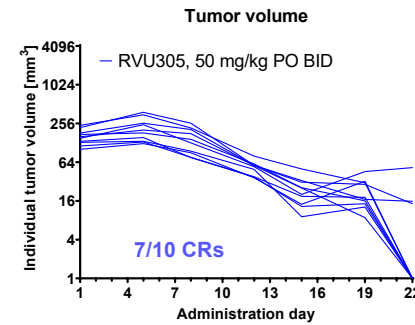
# RVU305 shows significant antitumor efficacy *in vivo*

## Strong antitumor efficacy

DoHH2 MTAP-deleted model (DLBCL)



## Complete responses demonstrated *in vivo*: favorable vs. MRTX1719



DoHH2 MTAP-deleted model. Individual tumor volumes in a log<sub>2</sub> scale from efficacy study in which RVU305 was administered orally (PO) once (QD) or twice (BID) daily, and MRTX1719 was administered PO QD to SCID mice bearing DoHH2 (DLBCL carcinoma) tumors (n=10 animals/group). Either no tumor growth (10 mg/kg BID) or tumor volume regression (other BID dose levels and QD administration) were present after RVU305 treatment.

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



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

# 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

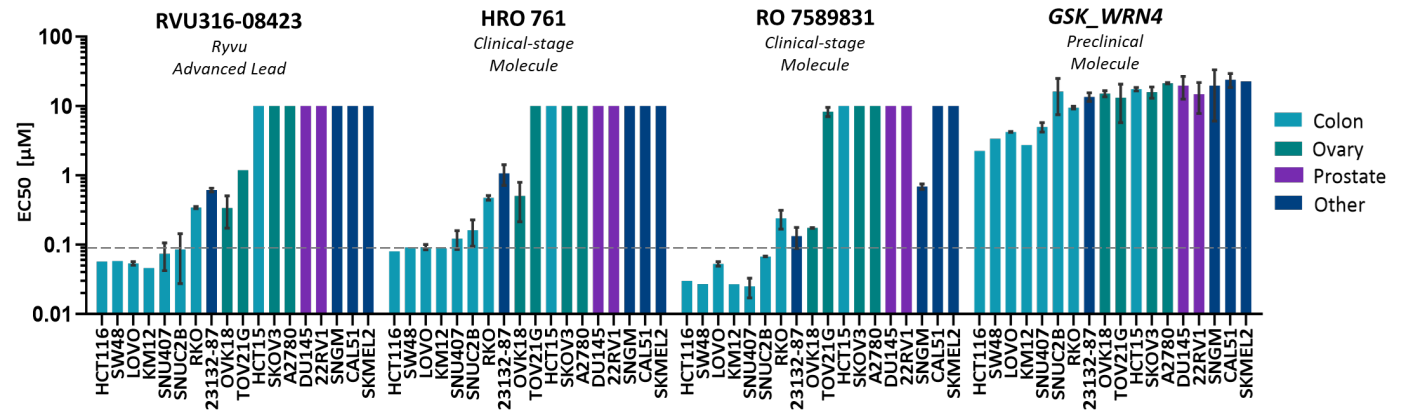
Tumor agnostic with MSI-high vulnerability (~10-30% of colorectal, endometrial, gastric, ovarian cancers)

### STATUS

Lead Optimization

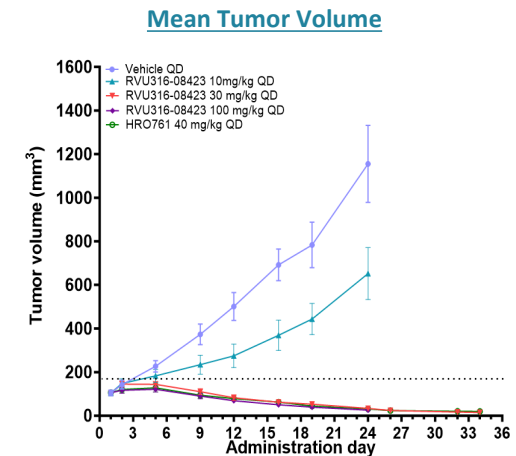
01

Third generation of Ryvu WRN inhibitors shows strong in vitro potency in MSI-H cell lines, comparing favorably to competitor benchmarks



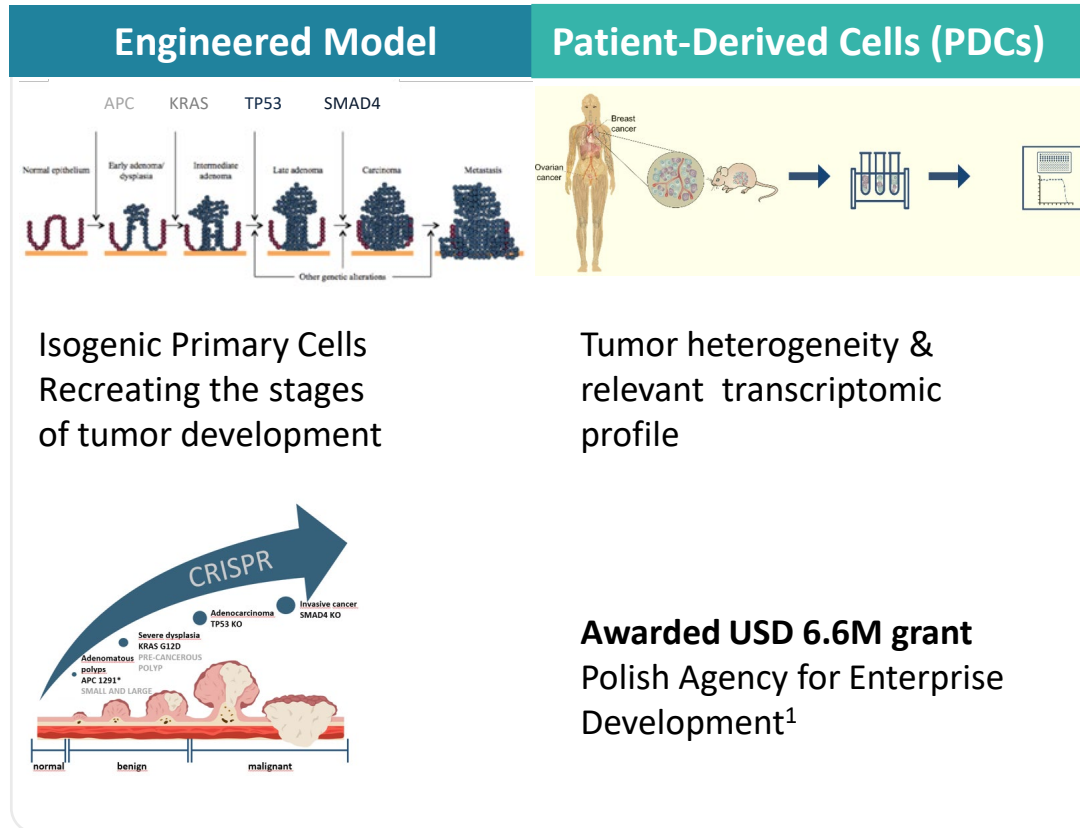
02

Potent and dose-dependent inhibition of tumor growth in SW48 CDX CRC model compares favorably to competitor benchmark

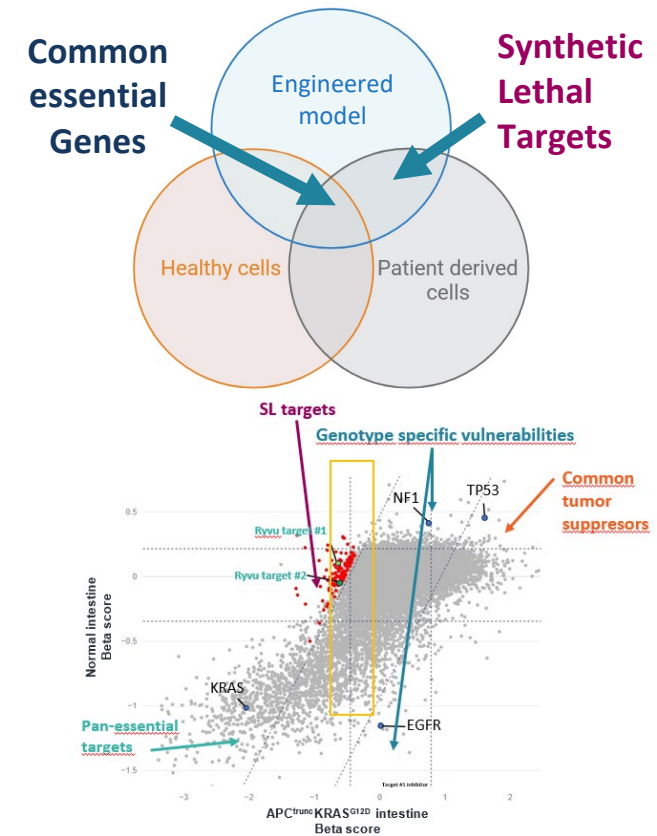


# Driving novel synthetic lethal target discovery with Ryvu's ONCO Prime platform

## Ryvu's CRISPR-based target Discovery Platform



## 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.

# Initial ONCO Prime data presented in CRC; broad applicability across oncology

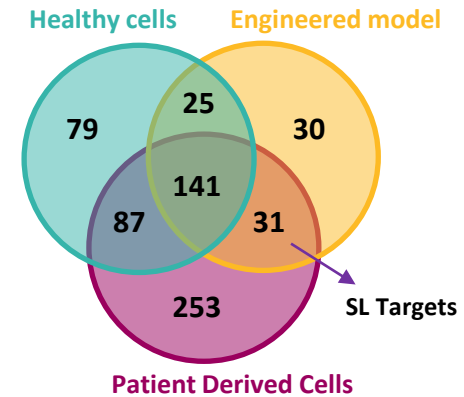
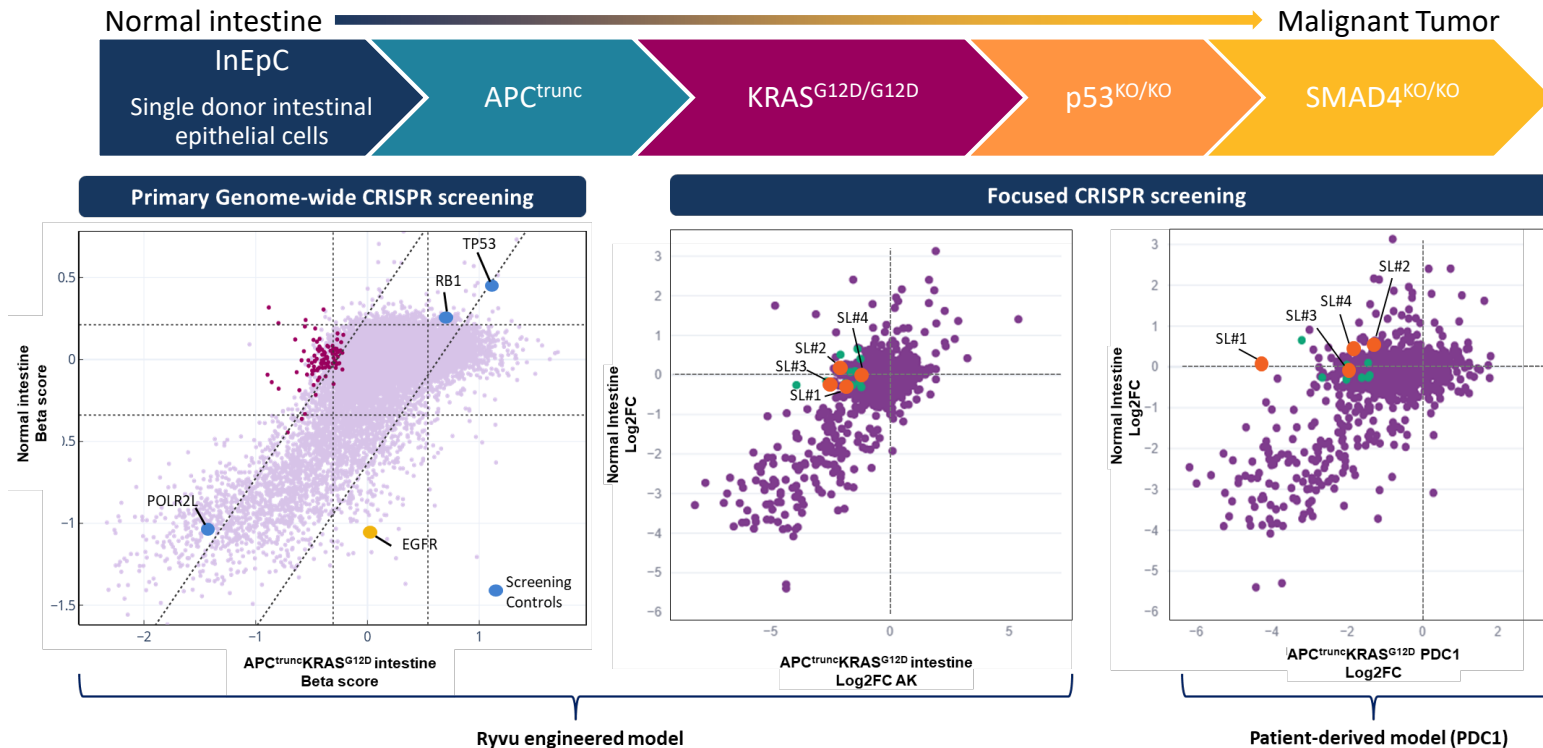


- The third most prevalent cancer worldwide
- Estimated number of colorectal cancers in the US for 2024 are 153,000 new cases<sup>1</sup>
- Diagnosed usually at an advanced stage. Mortality still remains high. Five-year survival shown by SEER database is **around 65%**, the survival drops to **13%** at stage 4.
- **Lack of targeted therapies** (except KRAS G12C which showed moderate PFS)

Conventional adenomas progress through the sequential accumulation of genetic mutations and chromosomal instability



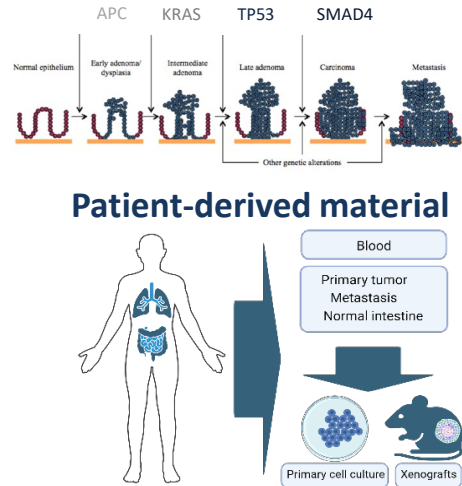
Based on East et al. 2017



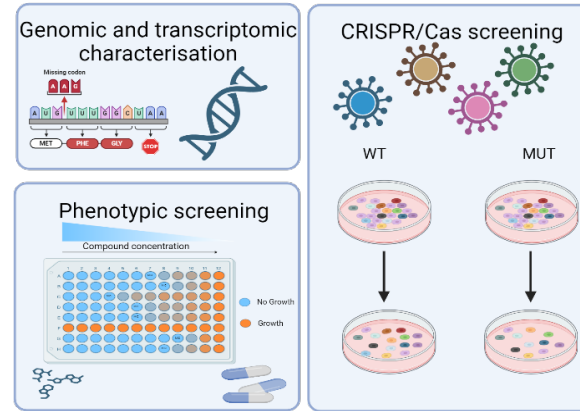
1) American Cancer Society

# ONCO Prime is accelerating the development of 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



# 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



## Key Financial Terms

- **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.
- 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



## Key Financial Terms

- 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)
- \$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, a double-digit milestone at first development candidate selection, and additional milestones
- 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: Q3 2024

\$ million	2023*	Q3 YTD 2023*	Q3 YTD 2024*
<b>Revenues</b>	<b>16.3</b>	<b>11.9</b>	<b>18.6</b>
<i>Partnering</i>	11.2	8.4	13.2
<i>Grants</i>	4.9	3.3	5.3
<b>Total Costs**</b>	<b>37.6</b>	<b>27.4</b>	<b>38.2</b>
<i>Clinical Pipeline</i>	13.0	6.4	17.4
<i>Early Pipeline</i>	15.8	13.9	14.2
<i>G&amp;A</i>	8.8	7.1	6.6
<b>EBIT**</b>	<b>-21.3</b>	<b>-15.5</b>	<b>-19.6</b>
<b>EBITDA**</b>	<b>-18.7</b>	<b>-13.6</b>	<b>-17.6</b>
<b>Net Results***</b>	<b>-20.0</b>	<b>-13.5</b>	<b>-18.5</b>

Cash position  
November 4, 2024

**\$58.1M**

Ryvu  
Employees

**>300**

Employees  
with PhD

**~100**

## Partnering revenues in Q3 YTD 2024:

Exelixis (\$1.2 million), BioNTech (\$7.8 million recognized)

\* Recalculated from PLN using 4.1823 PLN/USD, 4.2337 PLN/USD and 3.9600 PLN/USD – for 2023, Q3 YTD 2023 and Q3 YTD 2024, respectively

\*\* Excluding the impact of the non-dilutive, cash-neutral Employee Incentive Scheme (of \$2.0m, \$1.7m and \$0.7m in 2023, Q3 YTD 2023 and Q3 YTD 2024 respectively) and valuation of NodThera (+\$0.9m (increase of costs) in 2023, +\$0.2m in Q3 YTD 2023, and +0.2m in Q3 YTD 2024, respectively)

\*\*\* Excluding the impact of the non-dilutive, cash-neutral Employee Incentive Scheme (of \$2.0m, \$1.7m and \$0.7m, in 2023, Q3 YTD 2023 and Q3 YTD 2024 respectively)

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

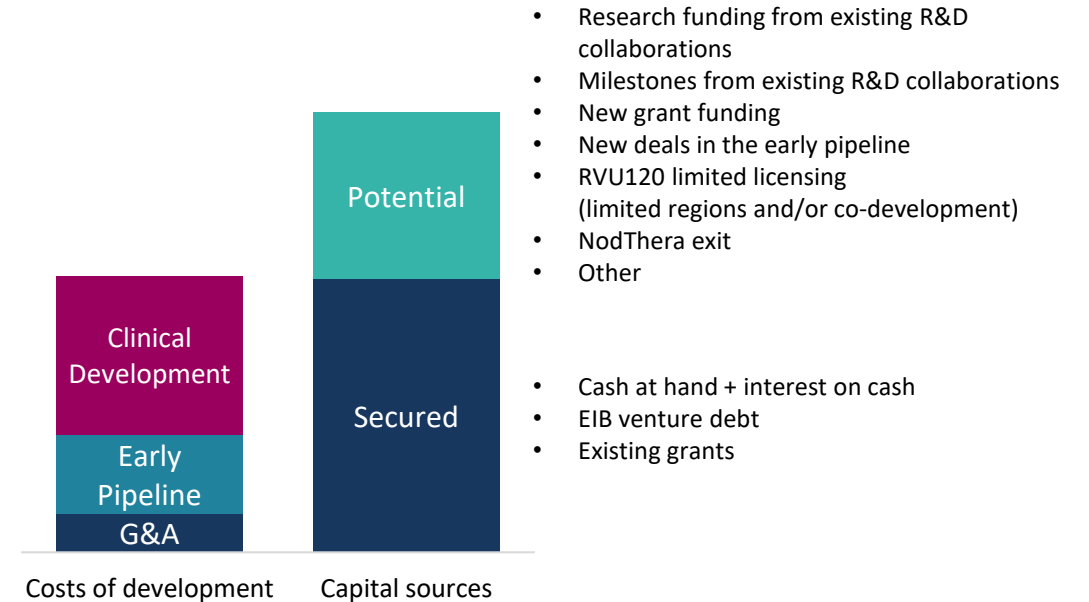
## 2024 KEY GOALS AND FINANCING

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**



## 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

<b>IPO on WSE</b>	Nov 2014
<b>Corporate Split: Selvita and Ryvu</b>	Oct 2019
<b>Ticker: WSE</b>	RVU
<b>52-Week Range<sup>1</sup></b>	PLN 39.50 – 67.10
<b>Average Daily Volume (YTD)<sup>1</sup></b>	5,877
<b>Market cap<sup>1</sup></b>	PLN 960 M (USD 240M)
<b>Shares outstanding</b>	23.1 M
<b>Cash<sup>2</sup></b>	USD 58.1M

Top Holders <sup>3</sup>		
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	Bogusław 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



Vladimira  
Urbankova



Beata Szparaga-  
Waśniewska



Krzysztof  
Radojewski



Katarzyna  
Kosiorek



Łukasz  
Kosiarski



Marcin  
Górnik



Tomasz  
Krukowski

1. As of 07 November 2024 2. As of 04 November 2024 3. As of 29 Dec 2023

# Thank you

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