RYVU THERAPEUTICS

CORPORATE PRESENTATION

Targeted therapeutics
at the forefront of oncology

January 2024

Note on the presentation and forward-looking statements

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Ryvu at a glance

First-in-class clinical pipeline

RVU120

- First-in-class, selective, oral CDK8/19 inhibitor
- Fully-owned
- Broad development strategy in heme-oncology
- Phase II initiation in four different paths planned for 2024

MEN1703 (SEL24)

- First-in-class dual PIM/FLT3 kinase inhibitor in Phase II
- Potential across hematology
- Partnered with the MENARINI group

Small Molecule Discovery Platform
Novel Synthetic Lethality Targets & IO partnerships

Developing small molecule therapies
which address high-value emerging targets and pathways in oncology

Synthetic Lethality

- PRMT5
- WRN
- Novel SL targets

Immuno-Oncology

- STING BIONTECH
- Multi-target research collaboration with EXELIXIS BIONTECH
- HPK1

Fully Integrated Research & Development

Listing	WSE:RVU (mWIG40 index); cash runway to Q1 2026
Team	>260 employees, incl. ~150 scientists (with ~90 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, Ph.D., MBA
CSO

HENDRIK NOGAI, M.D.
CMO

KAMIL SITARZ, Ph.D., MBA
COO

VATNAK VAT-HO, MBA
CBO

MIIKA AHDESMÄKI, Ph.D., MBA
CIO

JAKUB JANOWSKI, MSc
General Counsel

BARTLOMIEJ KONICKI, MSc
Financial Director

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Director of Translational Medicine

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Director of HR

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TADEUSZ WESOŁOWSKI, Ph.D	**PETER SMITH**, Ph.D
THOMAS TURALSKI	

Broad pipeline addressing emerging targets in oncology

CLINICAL PROJECTS

PROGRAM / TARGET NAME	INDICATION	DISCOVERY	PRECLINICAL	PHASE I	PHASE II	PARTNER	NEXT ANTICIPATED MILESTONE
RVU120 CDK8/19	Hematologic Malignancies (AML/HR-MDS, MF, LR-MDS)					LEUKEMIA & LYMPHOMA SOCIETY	Initiate Phase II in Q1 2024
	SOLID TUMORS						Complete Phase I & translational studies in 2024
SEL24 (MEN1703) PIM/FLT3	DLBCL					MENARINI	

DISCOVERY & PRECLINICAL PROJECTS

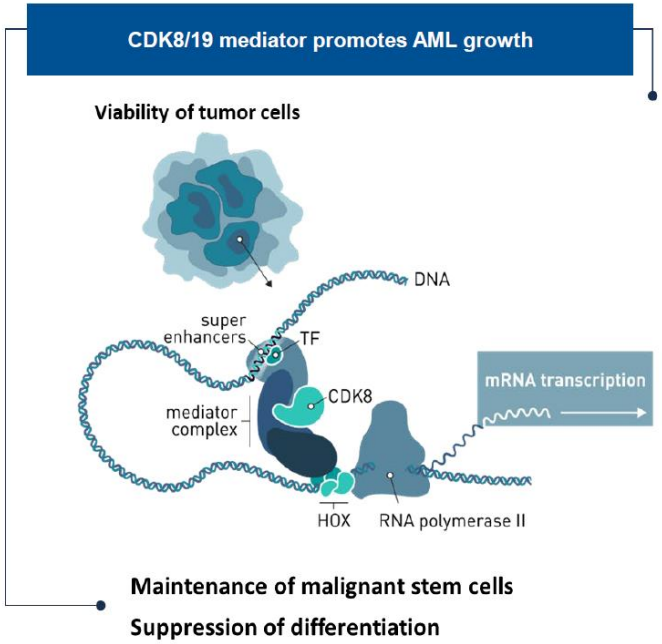
PROGRAM / TARGET NAME	INDICATION	DISCOVERY	PRECLINICAL	PHASE I	PHASE II	PARTNER	NEXT ANTICIPATED MILESTONE
SYNTHETIC LETHALITY							
PRMT5	SOLID TUMORS						IND-enabling studies in 2024
WRN	SOLID TUMORS						Development Candidate in 2024
Novel Targets	ONCOLOGY						
IMMUNO-ONCOLOGY							
STING Standalone	ONCOLOGY					BIONTECH	
STING ADC	ONCOLOGY					EXELIXIS	
HPK1	SOLID TUMORS						
IMMUNE MODULATION RESEARCH COLLABORATION (MULTI-TARGET)						BIONTECH	
DISCOVERY COLLABORATION						MERCK	

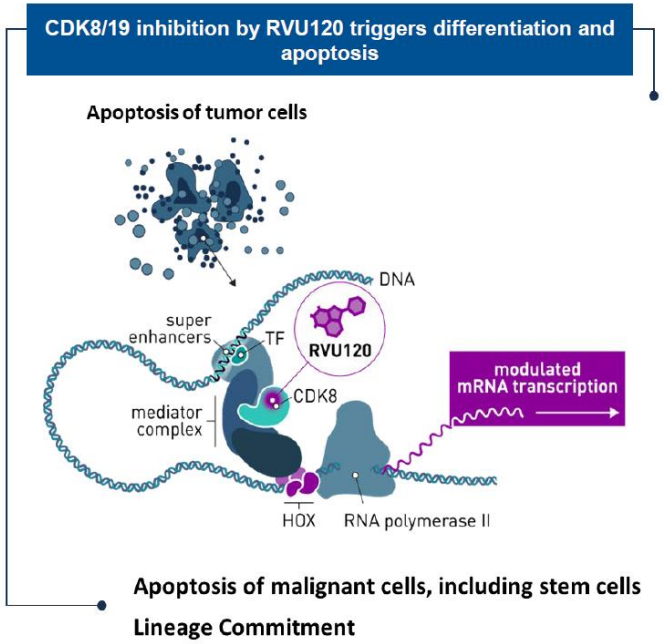
RYVU THERAPEUTICS

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

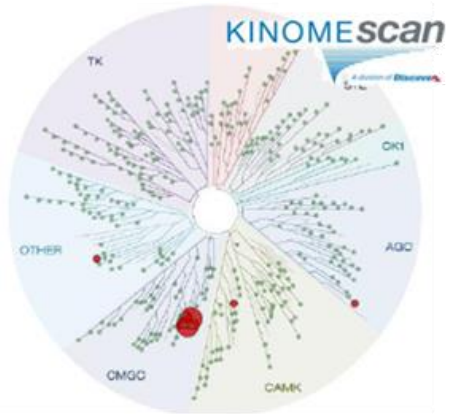
RVU120 is a fully-owned CDK8/19 inhibitor currently in clinical development to address unmet medical needs

- First-in-class
- High potency
- High selectivity
- Low risk of DDI
- Easy to formulate
- Orally available





RVU120 is highly selective for CDK8/19



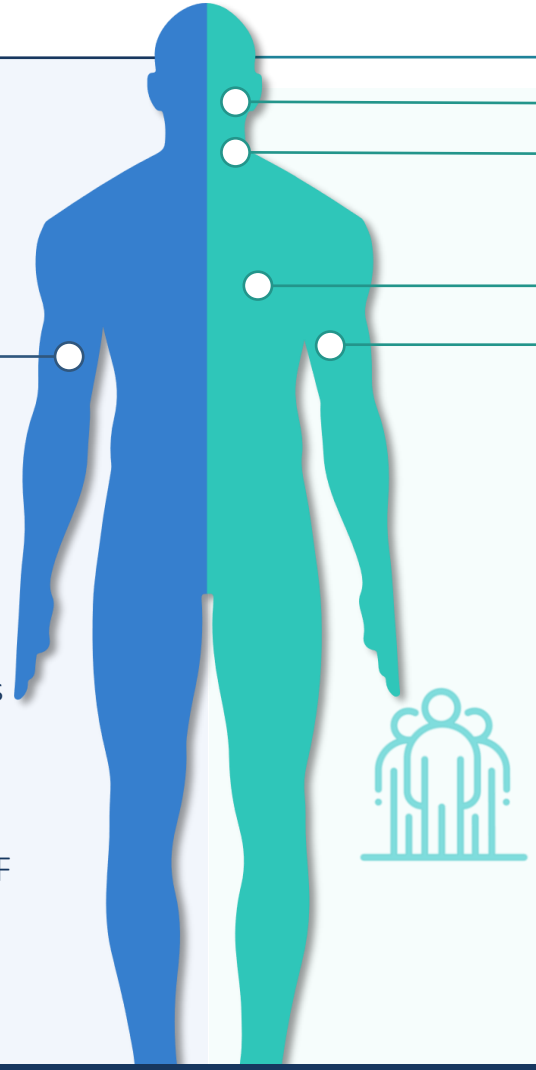
Current RVU120 development plan may lead to **three accelerated approvals in 2026-2027**

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

- **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 2024**



Solid tumors

Medulloblastoma
ACC
Breast
Sarcoma

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

RVU120 development plan focused on hematological malignancies
Expected Phase II initiation in Q1 2024

RVU120 for Potential Treatment of Acute Myeloid Leukemia (AML)

AML

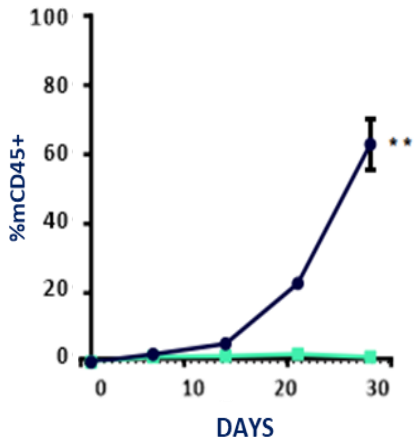
- Most common, highly aggressive type of acute leukemia in adults
- Poor outcomes in most patients[1]
- Annual US incidence ~20,500[2]; 11,300 deaths in the US in 2023[2]

1. Mayo Clinic
2. Cancer.net

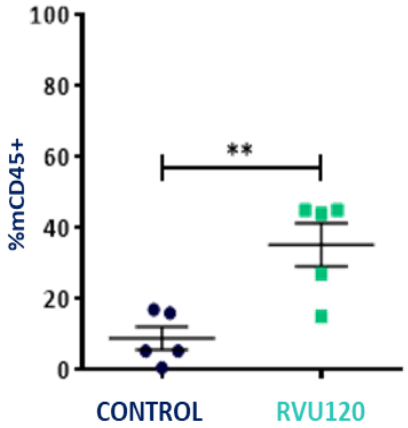
Preclinical Evidence: AML

CD34+ AML patient-derived xenografts:

Complete regression (peripheral blood)



Hematologic recovery (bone marrow)

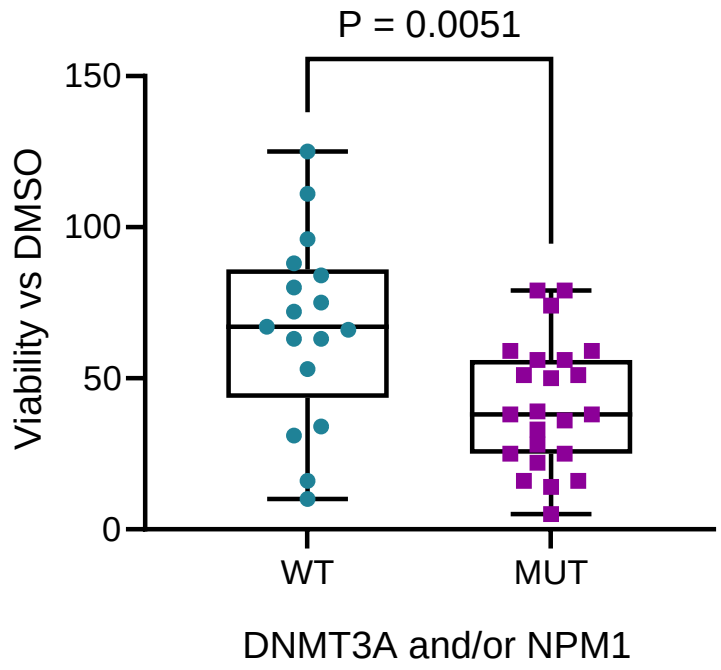


DNMT3A and NPM1 are candidates for patient selection markers in AML

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

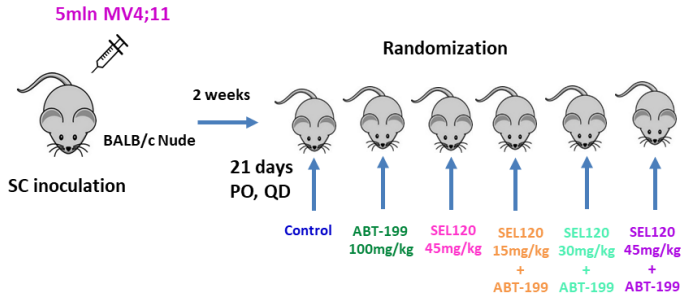
- **Low nM activity on CDK8/19**: RVU120 reduces the viability of AML PDCs, in particular those bearing recurrent DNMT3A and NPM1 mutations
- Open chromatin status of DNMT3A and NPM1 mutants makes cells more sensitive to transcriptional changes induced by RVU120
- DNMT3A and NPM1 mutants are dependent on high expression of MEIS1 and homeobox (HOX) genes that can be regulated by RVU120
- Currently no approved therapies targeting DNMT3A or NPM1 mutations in AML

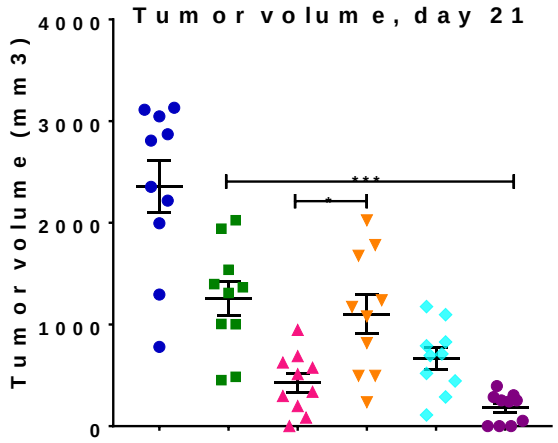
Loss of viability with RVU120 treatment



Combination potential with venetoclax was shown in preclinical models

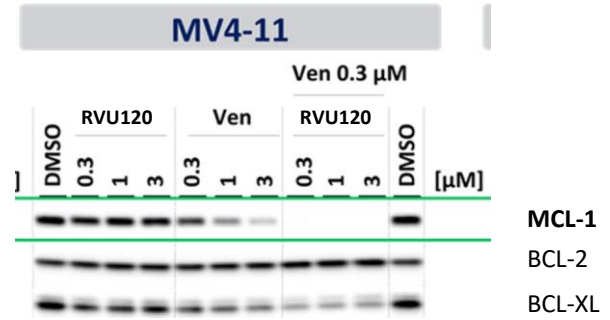
Synergistic activity was demonstrated in venetoclax sensitive and venetoclax resistant models:



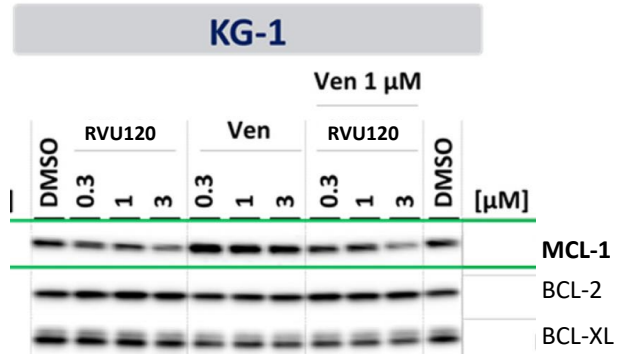


Synergy is driven by regulation of MCL-1:

Venetoclax sensitive cell line



Venetoclax resistant cell line



RVU120 OPPORTUNITY

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

RVU120 validated preclinically as a drug candidate in myelofibrosis (MF)

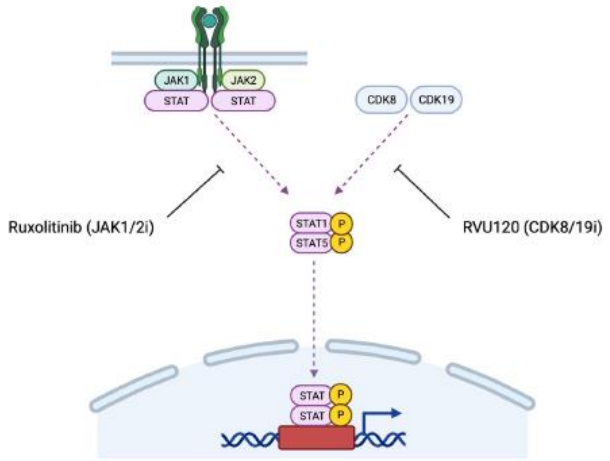
Opportunity in myelofibrosis

- 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

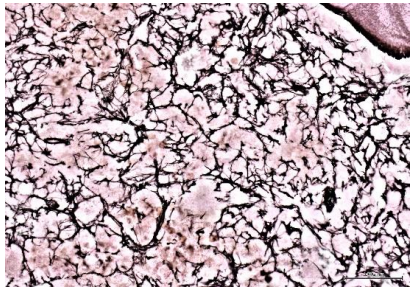
- **RVU120 alone and in combination can reduce symptoms and has disease-modifying potential in MF**
- Favorable RVU120 toxicity profile may enable targeting of patients who are not eligible for ruxolitinib treatment
- Preclinical results confirm RVU120's potential in ruxolitinib r/r MF patients
- Synergy with ruxolitinib indicates potential for combination therapy in the frontline setting and in patients with suboptimal response to JAKi

Mechanism of RVU120 activity in MF

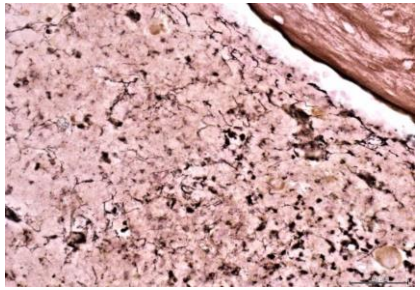


Reduction of bone marrow fibrosis

RUX



RUX + RVU120



Memorial Sloan Kettering Cancer Center

Clinical results demonstrating erythroid improvement support further studies in HR-MDS and LR-MDS

Growing number of patients treated with RVU120 show hematological improvement

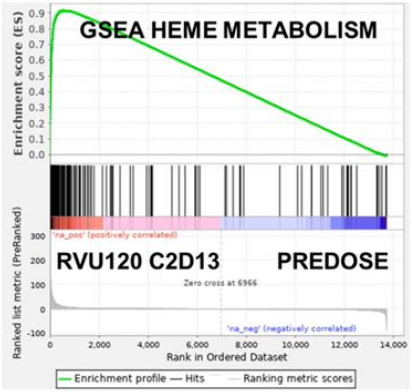
Several patients with AML and HR-MDS showed signs of improved erythropoiesis in RIVER-51:

- Increasing hemoglobin and platelets counts
- Transfusion independency
- Molecular changes indicating on-target activity

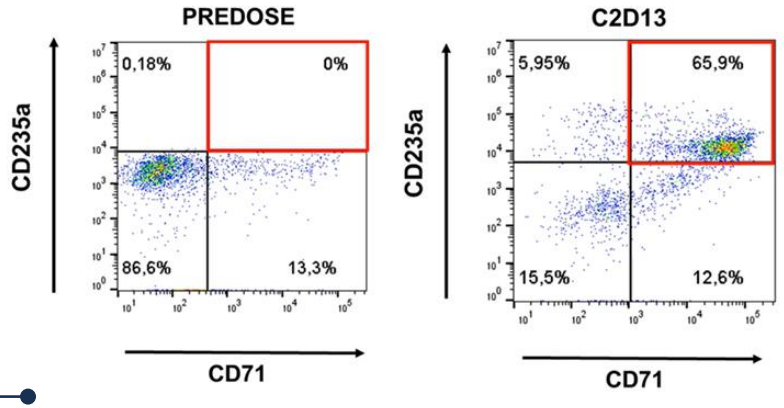
Overall non-clinical and clinical findings provide a strong rationale for RVU120 as a novel drug candidate in MDS – both high- and low-risk

AML patient	→	**RVU120 treatment** (100mg)
▪ High-risk group		▪ Disease Stabilization (SD)
▪ Transfusion dependent	→	▪ Erythroid Response (HI-E)
▪ 3 prior lines of treatment		▪ Platelet Response (HI-P)

Induction of erythroid gene expression programs confirmed by RNAseq



Induction of erythropoiesis confirmed by flow cytometry

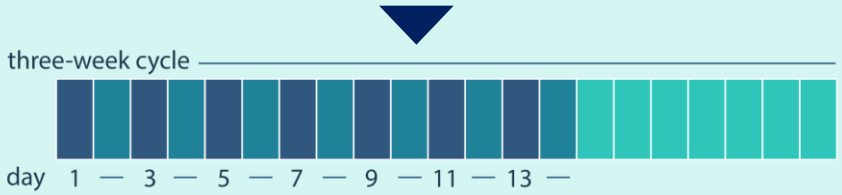


RVU120: Phase I AML/MDS Study – RIVER-51

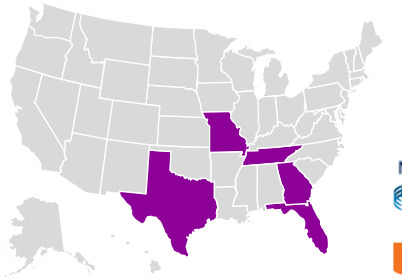
STUDY POPULATION:

- Patients with relapsed/refractory AML or high risk MDS
- No upfront patient stratification

TREATMENT: Three-week cycle: Single oral dose of RVU120 every other day for a total of 7 doses/cycle followed by one week off



5 SITES IN US



The University of Texas MD Anderson Cancer Center
Washington University in St. Louis School of Medicine
Northside Hospital
Sarah Cannon Fighting Cancer Together
Sylvester Comprehensive Cancer Center, University of Miami Health System

5 SITES IN POLAND

Medical University of Gdańsk
DCO Dolnośląskie Centrum Onkologii we Wrocławiu
Medicover Integrated Clinical Services
IHiT Instytut Hematologii i Transfuzjologii
Świętokrzyskie Centrum Onkologii

PHASE I: ESTABLISHING RECOMMENDED PHASE II DOSE (RP2D)

3+3 design

RP2D

SAFETY, EFFICACY, PK, PD

PHASE II in patients with R/R AML and HR-MDS

Data from the initial dose-escalation cohorts updated at ASH Conference in December 2023
Phase II enrollment to initiate in Q1 2024

RVU120 has a favorable safety profile at doses tested to date

Antiemetic prophylaxis introduced recently improves compliance and tolerability at higher doses

Most common* Treatment Emergent Adverse Events (TEAE)	RVU120 (10-250 mg)	
	Any grade n of pts (%)	Grade 3-5 n of pts (%)
Nausea	24 (60%)	0
Vomiting	16 (40%)	1 (2%)
Thrombocytopenia	11 (28%)	8 (20%)
Febrile neutropenia	9 (22%)	8 (20%)
Decreased appetite	7 (18%)	1 (2%)
Pneumonia	7 (18%)	7 (18%)
Cough	6 (15%)	0
Hypokalemia	6 (15%)	0

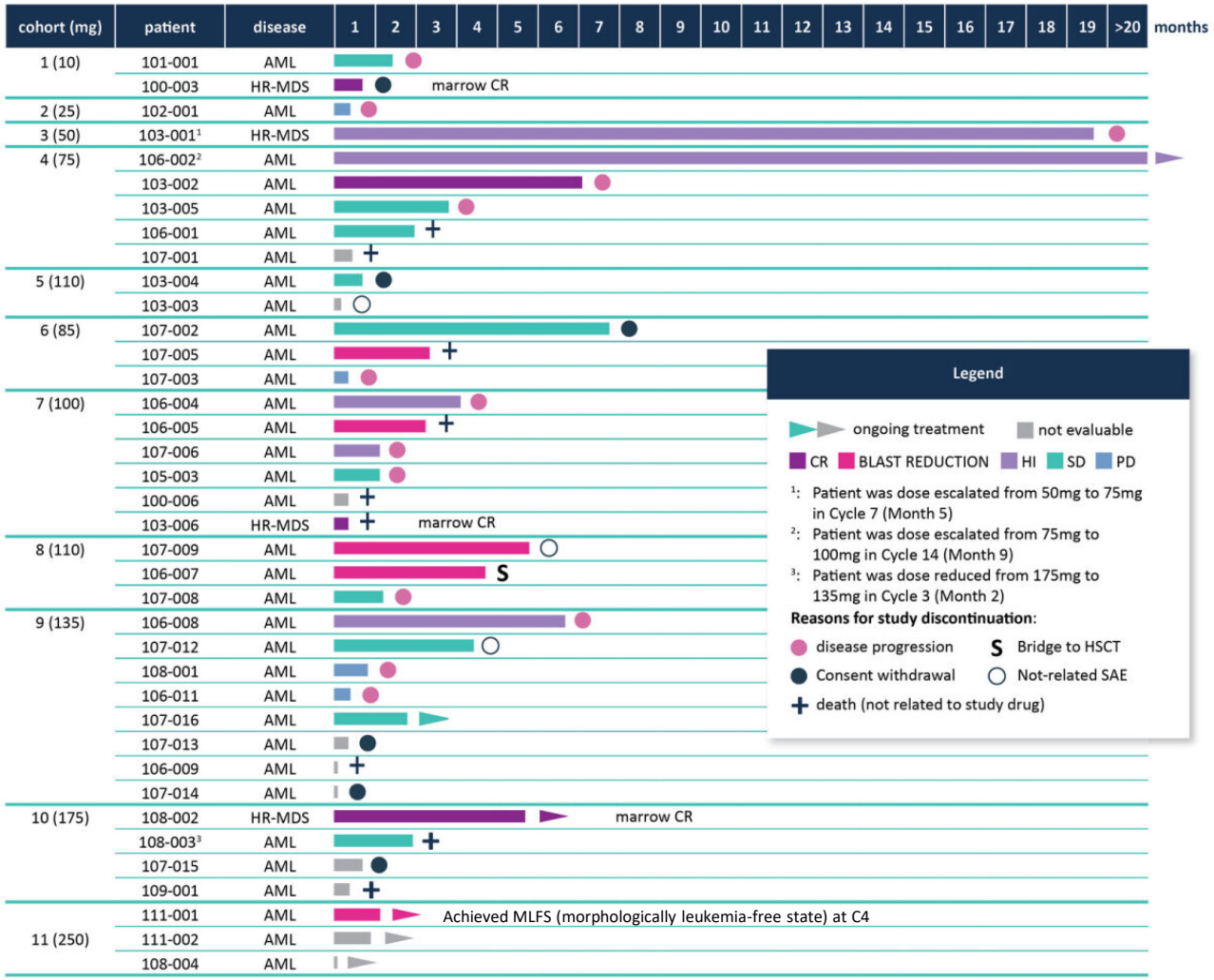
* Most common TEAEs occurring in at least 15% of enrolled patients

RVU120 was well tolerated at doses between 10 and 250 mg

- No DLTs and no study drug interruptions due to adverse drug reactions were observed
- No trend for increased toxicity at higher doses was observed during the dose escalation phase
- The most frequent TEAEs were nausea/vomiting, manageable with common antiemetics
- Among three patients treated at 250 mg and receiving recommended antiemetic prophylaxis, none experienced nausea or vomiting in the entire first cycle of treatment

Data cut-off: November 10, 2023

RIVER-51 Clinical Update at ASH 2023: 14 of 28 (50%) evaluable patients showed clinical benefit



Data cut-off: Nov 10, 2023

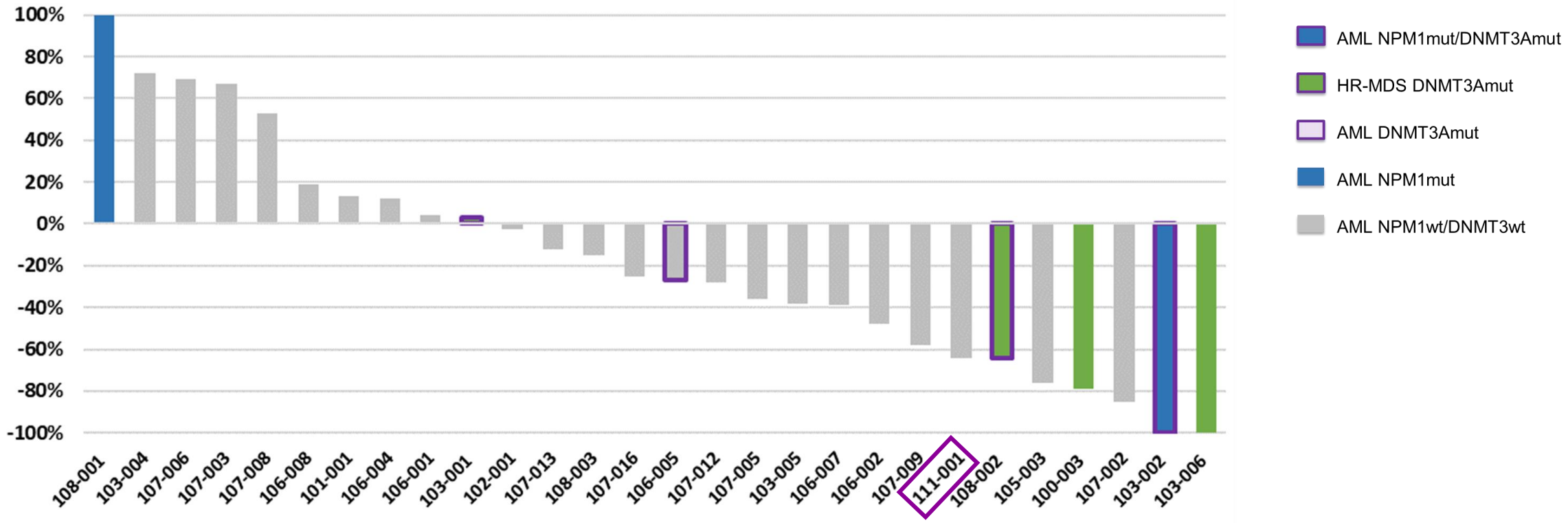
- A total of 38 patients have been treated (28 evaluable)
  - Median age 72 years
  - 34 patients had AML and 4 had HR-MDS
  - Patients relapsed or were refractory to a median of 3 prior lines of therapy

Clinical benefits

- 9 clinically significant BM blast reduction
  (1 CR, 1 MLFS, 3 marrow CRs,
  and 4 other clinically relevant BM blast reductions)
  - 1 patient with double leukemic clones and BM blast reduction received transplant after nearly 4 months of treatment
- 5 patients with erythroid hematological improvement (HI-E),
  4 of those became transfusion-independent,
  of which 2 normalized also their Grade 3 thrombocytopenia
- The dose of 250 mg was well tolerated in all three patients, without gastrointestinal events and selected for Phase II development

Patients with NPM1- and DNMT3A-mutated AML and HR-MDS achieved significant blast reductions

Best BM blast % reduction



After the disclosure of the chart at the ASH Annual Meeting & Exposition a further decrease of blasts from 24% to 3% (88% reduction) was reported **in patient 111-001** consistent with an outcome of MLFS.

Clinical activity for RVU120 was observed in multiple populations

NPM1 and DNMT3A mutations

An NPM1 mutation was identified in 2 pts who received RVU120

- pt 103-002: achieved a **CR** with skin leukemia resolution, this patient had a co-occurring DNMT3A mutation
- pt 108-001: **disease control** at the beginning of C2, but progressed after missing 4 doses in cycle 2 due to SAE (cholecystitis) not related to study drug

Three additional patients had a DNMT3A mutation without NPM1 mutation

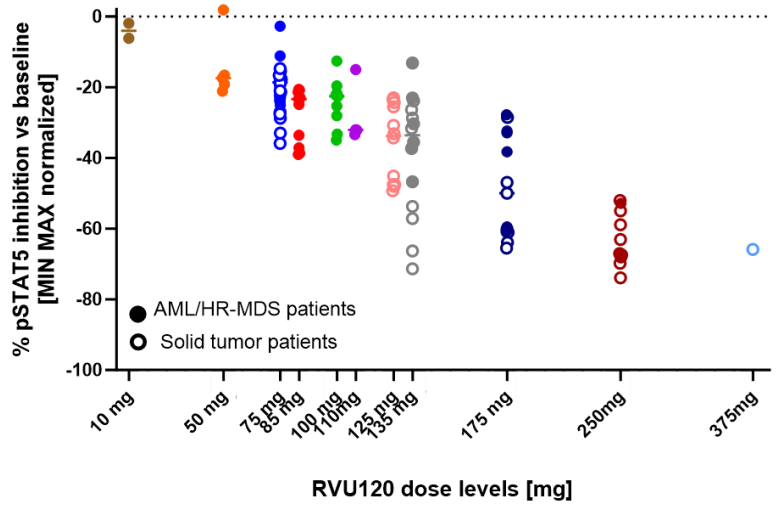
- pt 103-001: HR-MDS; maintained 0-4% Blasts in the BM up to C25 (**≥ 18 months of treatment**) in addition to erythroid hematological improvement
- pt 106-005: 37% BM **blast reduction** in C2
- pt 108-002: **marrow CR** in C2 and is ongoing in C7 with BM fibrosis reduction and RBC transfusion reduction

HR-MDS

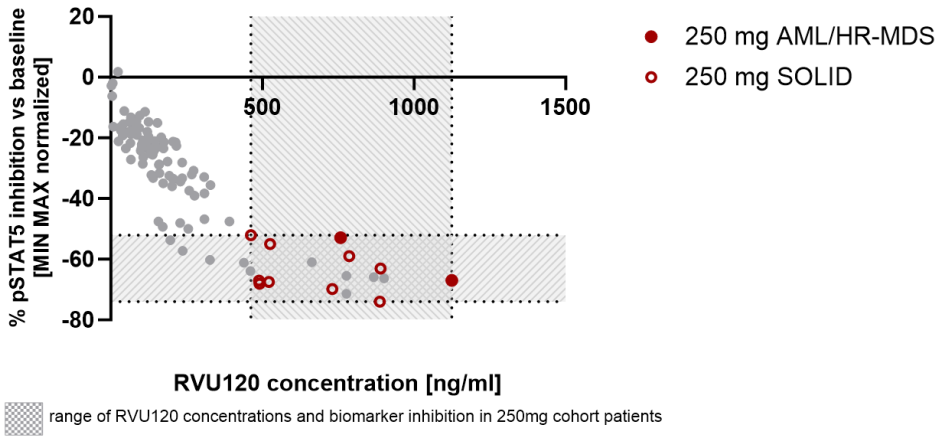
- 4 pts with HR-MDS treated were failing 1-5 prior lines of treatment, including hypomethylating agents, and were heavily transfused prior to study entry
- **3 of these pts had >10 % blasts at baseline, all of them met the Cheson criterion of marrow CR during treatment with RVU120**

RVU120 achieved target engagement levels between 50-70% at a dose of 250mg
These levels are expected to result in robust antileukemic efficacy

RVU120 dose - pSTAT5 inhibition



RVU120 concentration – pSTAT5 inhibition



- Pharmacodynamic (PD) activity of RVU120 was assessed by measuring changes to baseline in the CDK8-specific phosphorylation site of STAT5 (S725) from patient-derived leukemic cells *ex vivo*
- pSTAT5 percentage change at steady state (CxD13) represents the target engagement of RVU120

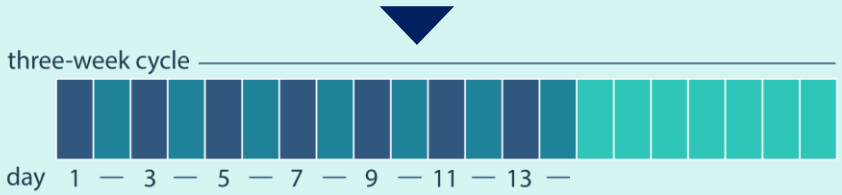
- Results of RVU120-induced pSTAT5 changes from patients enrolled in CLI120-001 and from the concomitant phase 1 study in patients with solid tumors show a tight correlation between pSTAT5 inhibition and drug exposure at doses up to 375mg

RVU120: Phase I Solid Tumor Study – AMNYS-51

STUDY POPULATION:

- Patients with r/r solid tumors progressing after at least one previous line of systemic therapy

TREATMENT: Three week cycle: Single oral dose of RVU120 every other day for a total of 7 doses/cycle followed by one week off



PHASE I: ESTABLISHING RECOMMENDED PHASE II DOSE (RP2D)

3+3 design

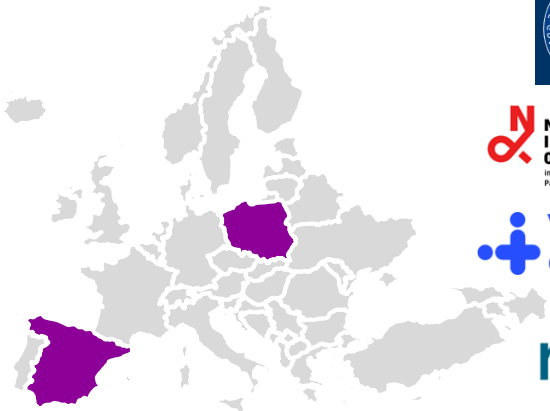
RP2D

SAFETY, EFFICACY, PK, PD

PHASE II: Efficacy and Safety Expansion

TNBC and other solid tumors

2 SITES IN POLAND + 3 SITES IN SPAIN



Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie Państwowy Instytut Badawczy

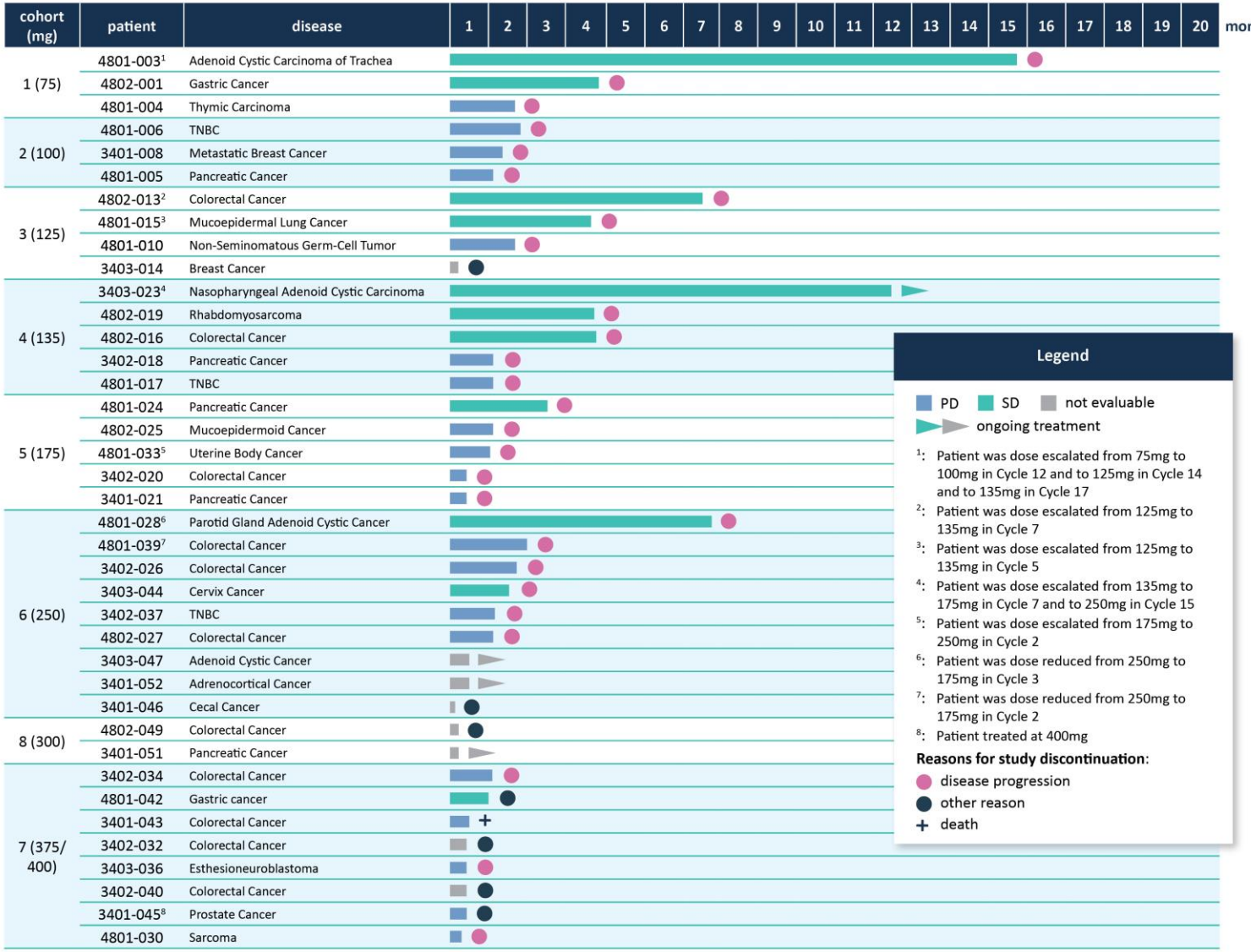
Vall d'Hebron

next ONCOLOGY

MADRID
BARCELONA

Preliminary data from the initial dose-escalation cohorts were released at the ESMO Conference in October 2023

AMNYS-51 - ESMO 2023 data release - 39 patients were treated at doses up to 400 mg



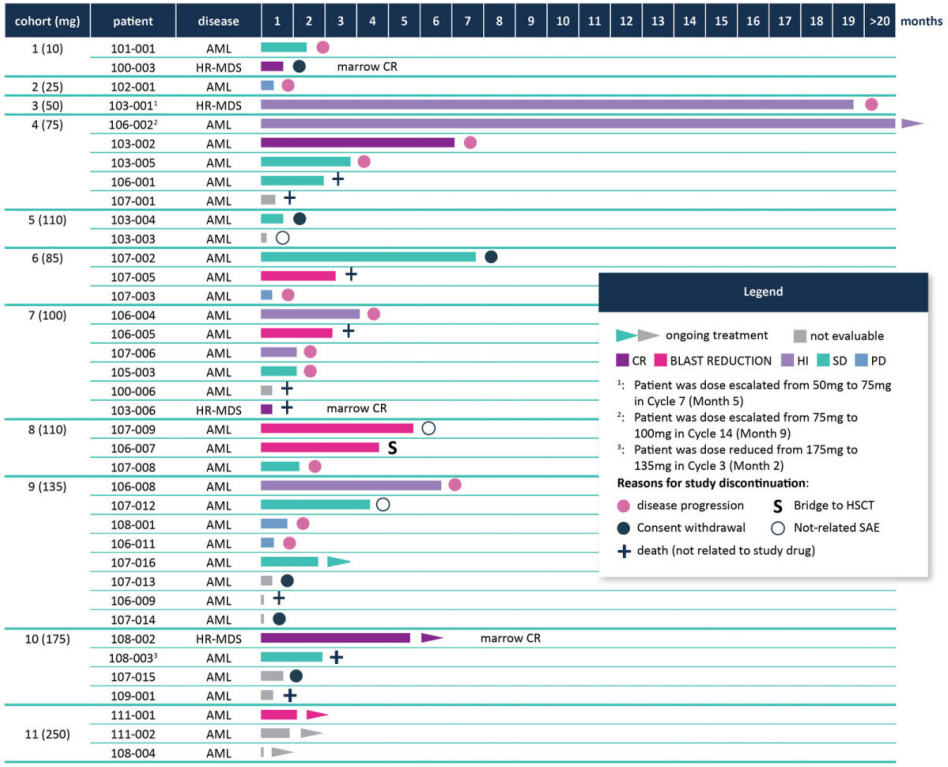
Data cut-off: Sep 26, 2023

- A total of 39 patients have been treated in 8 cohorts
- Patients were unselected and heavily pretreated
- RVU120 demonstrates a favorable safety profile. No dose limiting toxicities (DLTs) or other safety signals were observed, confirming CDK8/19 inhibition as a viable approach for cancer therapies.
- Low grade nausea and vomiting were the most frequent AEs, contributing to suboptimal tolerability in Cohort 7
- Out of 12 patients who achieved a stable disease on RVU120, treatment in 8 patients lasted longer than on previous therapy line
- The trend to longer treatment duration was specifically observed in patients with adenoid cystic carcinoma
- Dose schedule optimization will continue

SD=Stable Disease
PD=Progressive Disease

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

RIVER-51 (Phase I)



Data as of ASH 2023.

Blast reductions

Induction of erythropoiesis

Transfusion independence

Improvement of bone marrow architecture

Evidence in medulloblastoma, sarcoma, TNBC, and other (undisclosed) indications

AML and HR-MDS
RIVER-52
RIVER-81

LR-MDS
REMARK

MF
POTAMI-61

Translational Studies
Solid tumors

Clinical data + translational (preclinical) data

RVU120 Development Plan

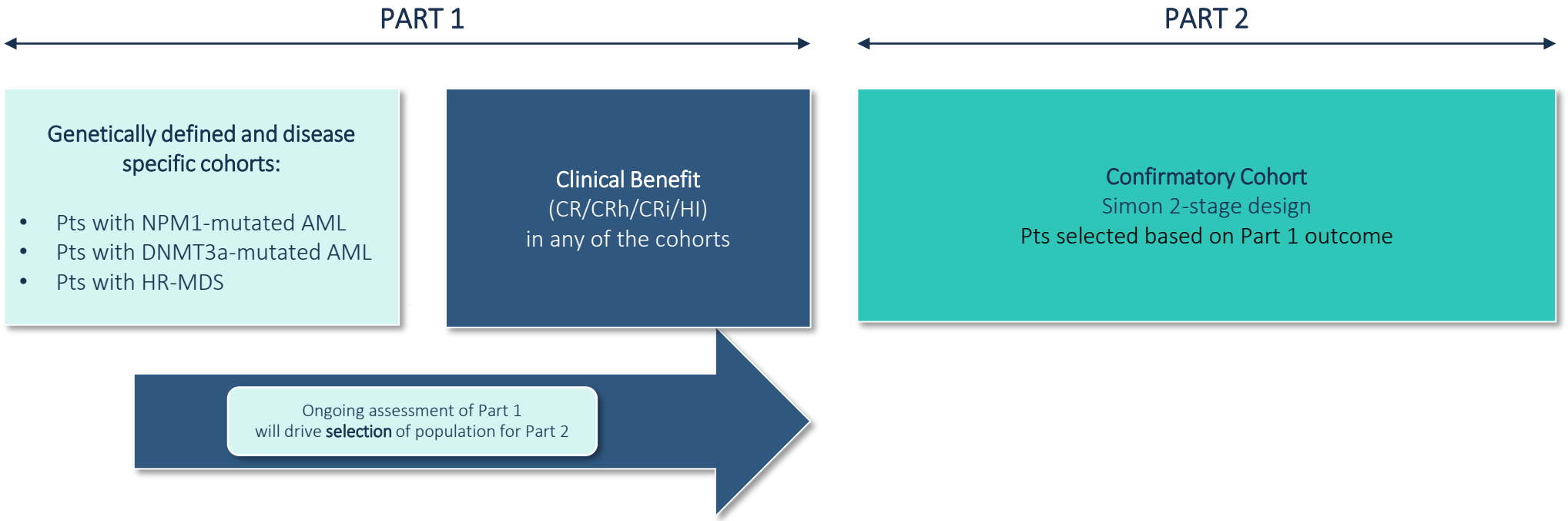
CR=Complete Remission, HI=Hematologic Improvement
SD=Stable Disease PD=Progressive Disease

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: 134 patients in total



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

RVU120 + **venetoclax**

STUDY DESIGN

- Primary endpoints:
  - Rate of CR, CRh, CRi, with and without MRD, and DoR
- Secondary endpoints: Transfusion independence, PFS, RFS, OS
- For Stage 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

PART 1

START

Run-in, 3+3

PART 2

SIMON 2-STAGE DESIGN

Stage 1 | Stage 2 | Confirmatory

RIVER-81 study is supported with €13.3M grant from the Polish Medical Research Agency (ABM)

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 approx. 40 patients planned

Ongoing assessment of Phase II will drive further development

IIT

Study will be conducted as an Investigator Initiated Trial with **Prof. Uwe Platzbecker within EMSCO**
- European Myelodysplastic Neoplasms Cooperative Group

UNIVERSITÄT LEIPZIG

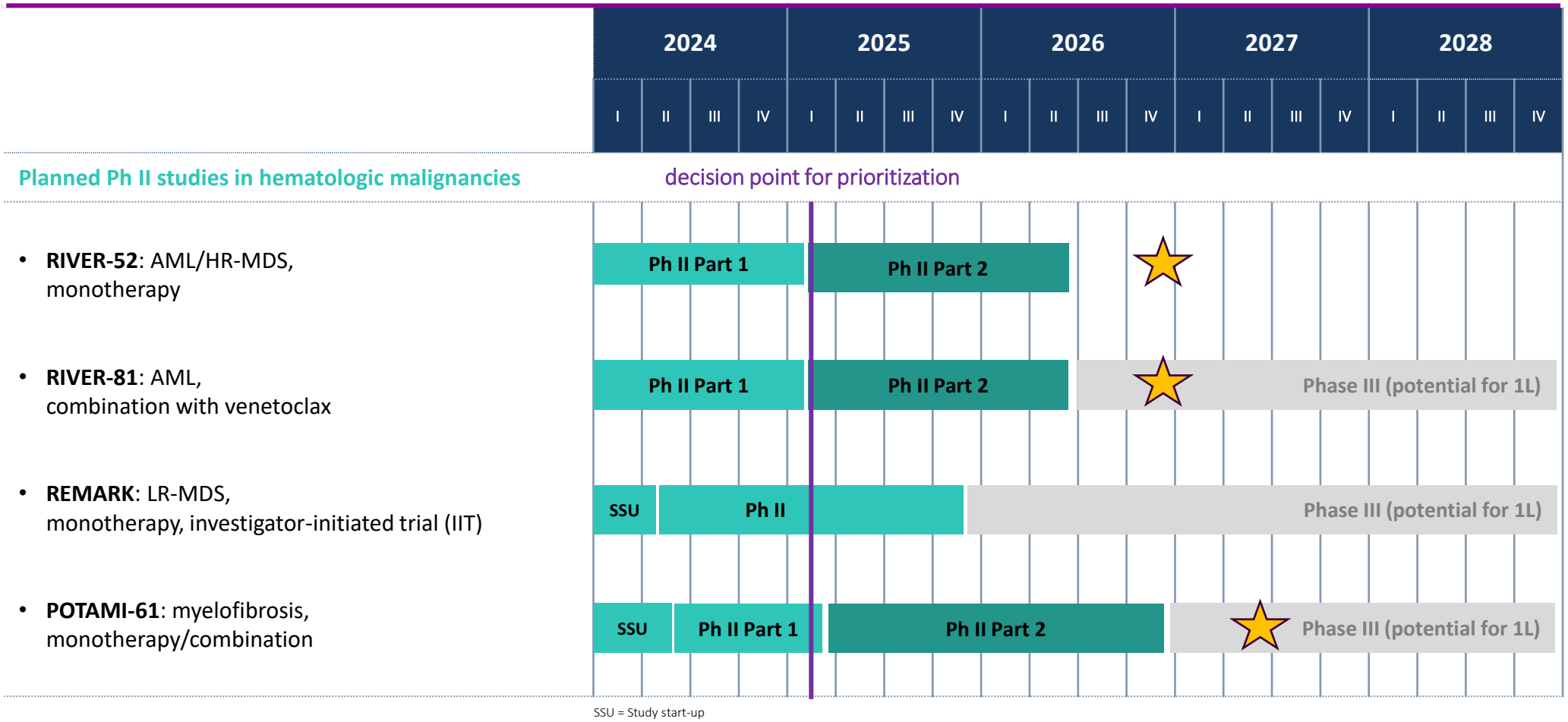
EMSCO MYELODYSPLASTIC SYNDROMES

- 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

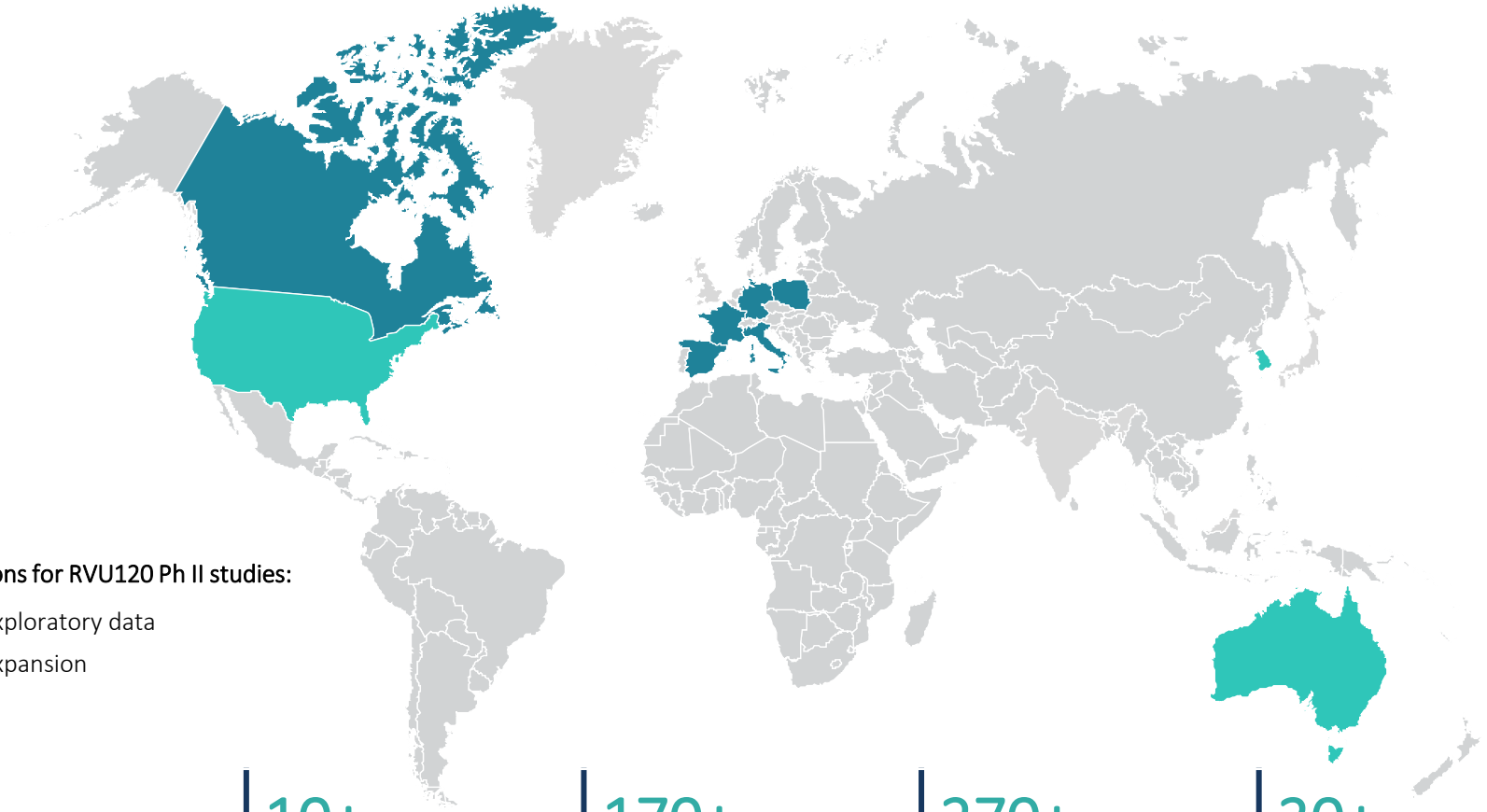
Clinical Development of RVU120 focuses on hematologic malignancies, while translational research explores additional opportunities



Continuing translational research actively supporting ongoing clinical trials and exploring additional indications, incl.: medulloblastoma, sarcoma, TNBC, and other (undisclosed) indications

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

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

4
Number of Ph II clinical trials initiated in H1 2024

10+
Number of countries across studies

170+
Number of clinical sites globally

270+
Number of patients to be enrolled

30+
Number of clinical vendors to be managed

50+
Number of internal Ryvu team members in Clinical Development and Translational teams

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 ~20,500 with an estimated 11,300 deaths in the US in 2023[2]
- **Venclexta (venetoclax) sales estimated to exceed USD 3.5 bn in 2025**[3]

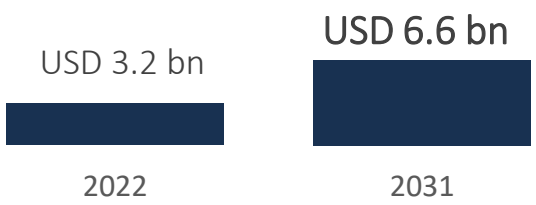
MDS (MYELODYSPLASTIC SYNDROME)

- 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 2 bn**

MF (MYELOFIBROSIS)

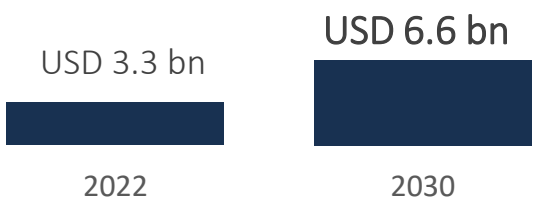
- MF is a bone marrow disease characterized by JAK mutations; often leads to severe anemia
- Chronic disease with long duration of therapy; US prevalence is estimated to be ~13,000 patients[4]
- **CTI BioPharma was acquired for USD 1.7 bn** in May 2023 – the lead asset is Vonjo (pacritinib) - a JAK inhibitor with accelerated approval in subset of MF

Global AML Market[4]



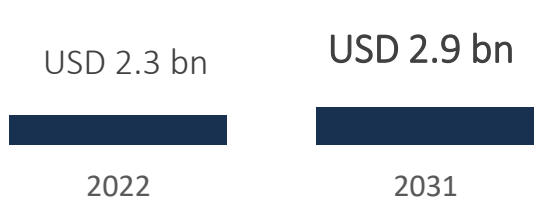
8.5% CAGR (2022-2031)

Global MDS Market[5]



9.3% CAGR (2022-2030)

Global MF Market[4]



2.6% CAGR (2022-2031)

1. Mayo Clinic
2. Cancer.net, June 2023
3. Biomedtracker 5 March 2023
4. GlobalData forecast
5. Coherent Insights

RYVU THERAPEUTICS

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

MEN1703 (SEL24) – Summary

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 – 2023+

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

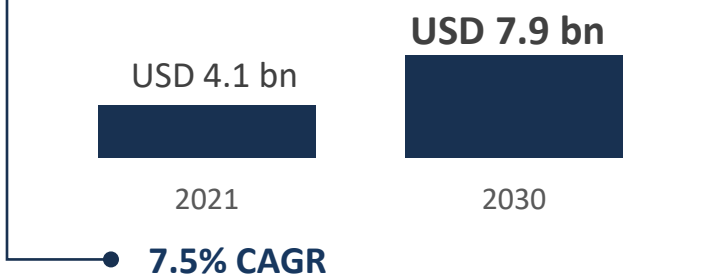
- As of September 2023, Ryvu will increase involvement in the program as Menarini's operational partner for Phase II
- The licensing partnership with Menarini remains unchanged, with Menarini funding all R&D. The total milestones and royalties due to Ryvu upon achievement of certain events remains unchanged

Unmet medical need and high commercial potential for MEN1703 in DLBCL

DLBCL (Diffuse Large B-Cell Lymphoma)

- Non Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders with DLBCL the being the most common type
- 30% to 40% of DLBCL patients will relapse during the first 2 years
- These patients often have significant comorbid conditions, which complicate the choices of often toxic treatment options and lead to decreased treatment rates in 3L+

Global DLBCL Market (1)



COMMERCIAL POTENTIAL AND UNMET NEED

- Strong unmet medical need: estimated 23k incident DLBCL cases in North America in 2027 and 37k in the EU
- Targeted therapies have emerged as the dominant treatment options; choice of therapy is informed by type and response to prior therapies; timing of relapse; patient age, fitness, and comorbidities; disease kinetics; and product availability

RELAPSED/REFRACTORY PATIENTS INELIGIBLE FOR TRANSPLANT:

- Currently there is no optimal SOC defined for patients not candidates for transplant. Tafasitamab + lenalidomide reflect a preferred option for these patients. CAR-T cells and bispecific antibodies will move to the second line space
- The post CAR-T cell setting will require novel effective options in hard-to-treat patients that are often not eligible for clinical trial enrolment due to prolonged cytopenias

1. Data Intelligence, Aug 2023.

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 H1 2024; protocol currently in development with Menarini

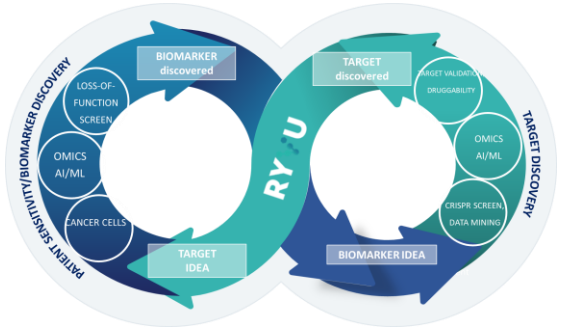
RYUU THERAPEUTICS

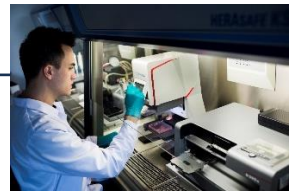
Small Molecule Platform with Focus on Synthetic Lethality

Integrated Discovery Engine at Ryvu

TARGET IDENTIFICATION AND VALIDATION

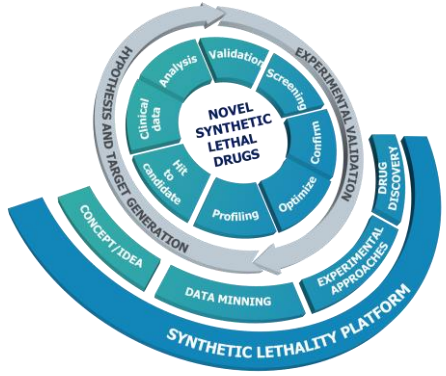
- ✓ Discovery of novel synthetic lethal target pairs and actionable oncogenic drivers
- ✓ Combination of the experimental engine and bioinformatic analysis using proprietary approaches





DRUG DISCOVERY

- ✓ Integrated, multidisciplinary processes: rapid lead identification/optimization with deep translational biology support
- ✓ Platform has delivered two projects in clinical development; multiple projects in discovery/research
- ✓ Team of ~150 scientists (with ~90 PhDs) with international expertise in drug discovery and track record in delivering new clinical candidates



RESEARCH PIPELINE

- ✓ Broad portfolio of synthetic lethal and immuno-oncology targets at various stages of the cycle – clinical candidate selection to target validation and hit finding

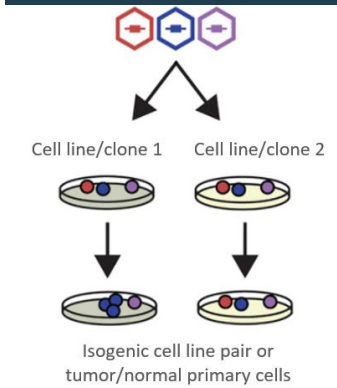
Synthetic Lethality → **PRMT5, WRN, Novel SL targets**

Immuno-Oncology → **Partnerships with BioNTech (STING and multi-target IO collaboration) and Exelixis (STING ADCs)**

Ryvu's Target Discovery Platform is focused on identification of novel synthetic lethal pairs and oncogenic drivers

INPUT DATA

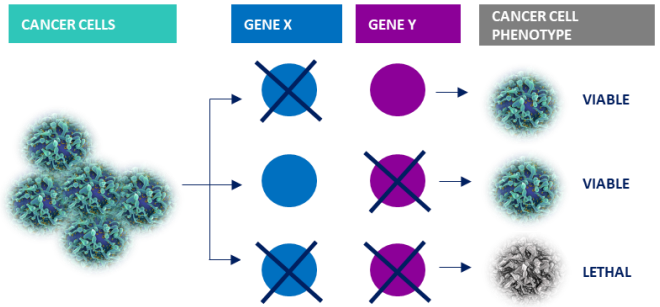
CRISPR / shRNA Screens



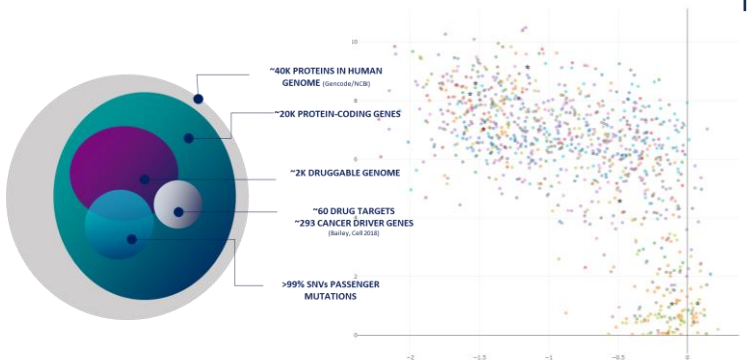
Published Data Sets

TARGET DISCOVERY PLATFORM

Novel Synthetic Lethalities

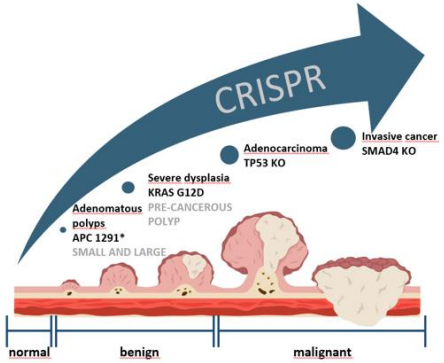


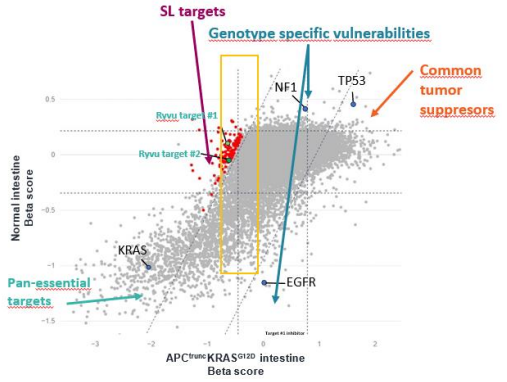
Novel oncogenic drivers



PLATFORM OUTPUT

Novel and Proprietary SL Targets



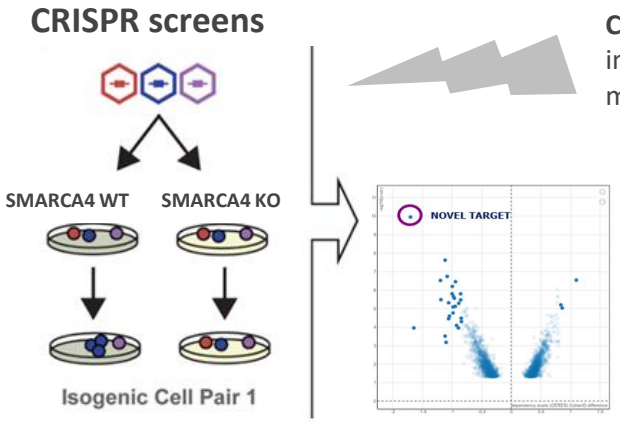


Ryvu experimental target discovery platform – three approaches

Experimental CRISPR-based target discovery platforms with the use of:

Isogenic cell line pair

Normal conditions | **Stress conditions**

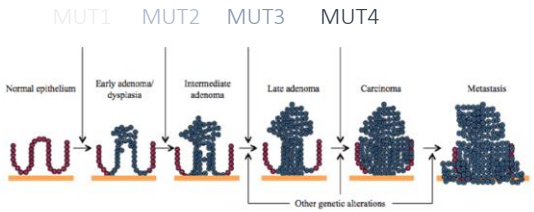


Cellular stress in tumor microenvironment

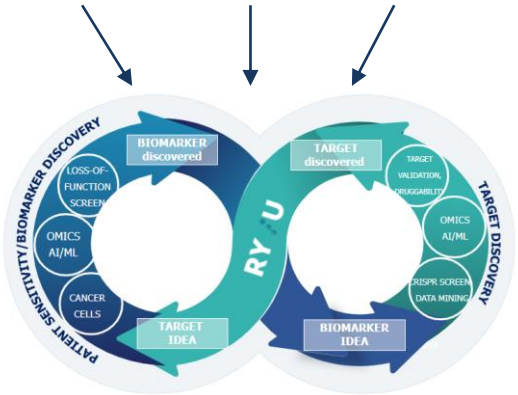
- Oxidative
- Genotoxic
- Hypoxic
- Nutrition
- Irradiation

- "Classical" approach, genome-wide screens in isogenic pairs
- Focus on unexplored genomic alterations
- **2D / 3D / *in vivo* formats**

Isogenic primary cells

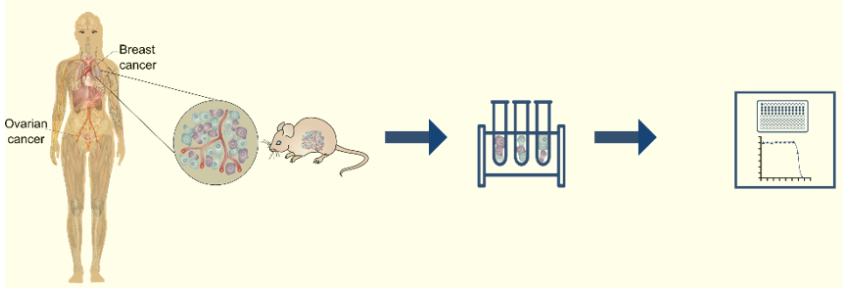


- Gradual transformation of healthy primary cells with mutations typical for tumor evolution of specific tissue type
- CRISPR screens on stages modeling bigger populations



TARGET GENERATION

Patient-derived material



- Clones derived from actual primary tumor tissue
- Tumor heterogeneity retained in the procedure
- Collaboration with Polish academic institutions
- Unparalleled translational value

PRMT5 MTA-cooperative inhibitors

PRMT5 SL INHIBITOR PROGRAM IN RYVU

KEY RATIONALE	PRMT5 MTA-cooperative inhibitors exert synthetic lethal phenotype in MTAP deleted cells
MECHANISM OF ACTION	MTA-cooperative inhibitors
NOVELTY	Best-in-class potential (vs Mirati, Tango, Amgen)
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)
BIOMARKERS	MTAP deletion status SAM (plasma), SDMA (tissue) levels
STATUS	Lead optimization to candidate nomination is ongoing
TIMELINES	2024 IND-enabling studies

RYVU HAS SL PRMT5 INHIBITORS WITH THE BEST-IN-CLASS POTENTIAL

Ryvu PRMT5 inhibitors demonstrate high potency and MTA-cooperativity *in vitro* coupled with favorable ADME profile.

	MRTX 1719	TNG908	AMG193	RVU-01	RVU-02	RVU-03	RVU-04
SDMA IC50 HCT116 MTAP del nM	0.4	2	ND	3	5	0.8	0.6
SDMA IC50 ratio to HCT116 MTAP WT	144	31	ND	136	200	65	34
3DSA IC50 HCT116 MTAP del nM	3	55	15	19	32	5	6
3DSA IC50 ratio to HCT116 MTAP WT	186	35	143	195	305	120	70
Papp MDCKII-WT/efflux ratio	2.9/36	38/0.8	28/0.9	28/2	20/4	1/508	24/4
Cl_{int} Mouse/Rat uL/min/mln cells	13/17	14/24	6/17	20/9	5/8	8/5	9/17
LogD	1.8	2.4	2.8	2.7	2.7	2.7	3.7

ND – Not determined

MULTIPARAMETER OPTIMIZATION OF RYVU PRMT5 INHIBITORS HAS RESULTED IN:

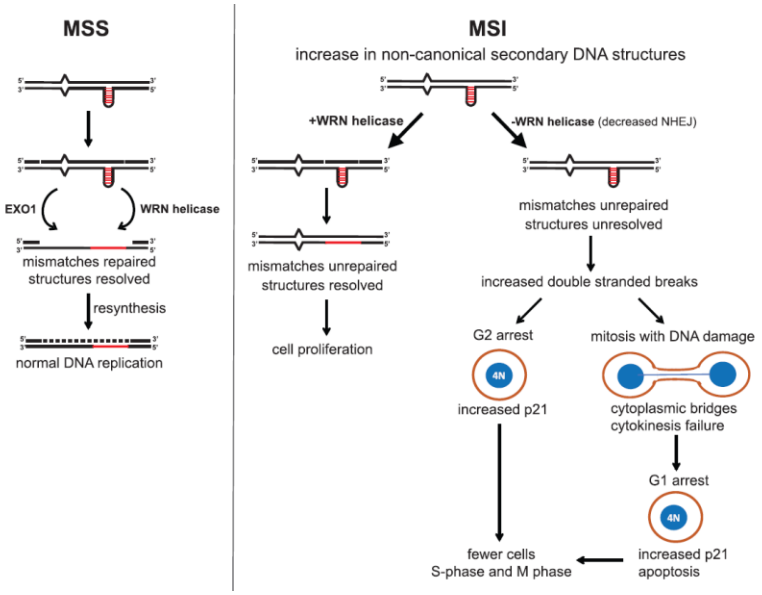
- **Antiproliferative activity for MTAP-deleted cells *in vitro:*** high proportion of efficacy in Ryvu cell line panel
- **Improved PK profile of Ryvu PRMT5 inhibitors vs. competitors**: demonstrated in mouse PK studies
- **Antitumor efficacy and target engagement achieve *in vivo* in responder DoHH-2 CDX model**

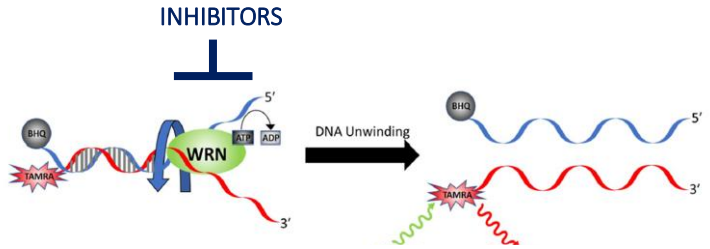
Small molecule inhibitors of WRN

WRN INHIBITOR PROGRAM AT RYVU

KEY RATIONALE	Synthetic lethality of WRN with microsatellite instability (MSI-high)
MECHANISM OF ACTION	WRN inhibitors of ATPase activity selectively targeting tumors with microsatellite instability (MSI)
NOVELTY	First- or best-in-class potential Focus on selectivity (RecQ family)
TOP TUMOR INDICATIONS	Tumor agnostic with MSI-high vulnerability (~10-30% of colorectal, endometrial, gastric, ovarian cancers)
STATUS	Hit-to-lead generation ongoing
TIMELINES	2024 Development Candidate

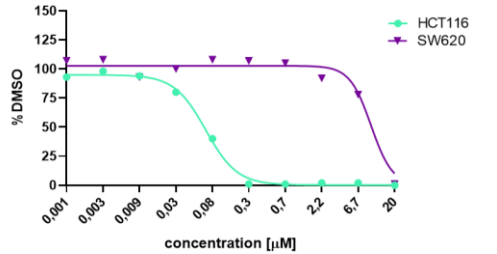
WRN INHIBITORS OF ATPase ACTIVITY SELECTIVELY TARGETING TUMORS WITH MICROSATELLITE INSTABILITY

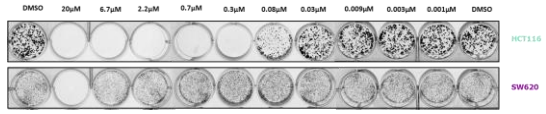




WRN confirmed as specific vulnerability of MSI-H cell lines in several genome-wide screens

1. Helicase function validated *in vitro* as critical requirement for synthetic lethal phenotype
2. Full in-house cascade developed
3. Ryvu identified small molecule inhibitors of WRN with strong and selective activity on MSI-H cells





BioNTech and Ryvu: Global Collaboration to Develop and Commercialize Immune Modulation Small Molecule Candidates

Largest-ever Ryvu deal

November 2022

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

Partnership

- **Multi-target research collaboration**: Ryvu will conduct 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

- Building STING-based antibody drug conjugates (ADCs)
- 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
- 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

RYUU THERAPEUTICS

Corporate Progress

Full-Year Financial Results: Q3YTD 2023

$ million	2022*	Q3YTD 2022*	Q3YTD 2023*
Revenues, *incl.:*	**15.8**	**8.0**	**11.9**
Partnering	*8.7*	*3.2*	*8.4*
Grants	*6.6*	*4.4*	*3.3*
Total Costs**, *incl.:*	**26.4**	**19.2**	**27.4**
Clinical Pipeline	*6.4*	*5.0*	*9.7*
Early Pipeline	*12.8*	*9.3*	*11.7*
G&A	*7.2*	*4.9*	*6.0*
EBIT**	**-10.6**	**-11.3**	**-15.5**
EBITDA**	**-7.7**	**-9.0**	**-13.6**
Net Results***	**-13.8**	**-12.5**	**-13.5**

** recalculated from PLN using 4.4679 PLN/USD, 4.4413 PLN/USD and 4.2337 PLN/USD – for 2022, Q3YTD 2022 and Q3YTD 2023, respectively*
*** excluding the impact of the non-dilutive, cash-neutral Employee Incentive Scheme (of $5.0m, $4.5m, $1.7m in 2022, Q3YTD 2022 and Q3YTD 2023 respectively) and valuation of NodThera (+$2.0m (increase of costs), +$1.8m, +$0.2m, in 2022, Q3YTD 2022 and Q3YTD 2023, respectively)*
**** excluding the impact of the non-dilutive, cash-neutral Employee Incentive Scheme (of $5.0m, $4.5m, $1.7m, in 2022 and Q3YTD 2022, Q3YTD 2023, respectively)*

Cash position November 24, 2023

$64.5M

Available EIB Venture Debt

€22M

RYVU

# of employees

> 260 employees

~90 PhDs

- Partnering revenues in Q3 YTD 2023: Exelixis ($1.1 million), BioNTech ($7.3 million recognized)

EUR 22m venture debt obtained from the European Investment Bank

Long-term financing for innovative growth companies:

Instrument structure adapted to the business model

Long-term financing repaid through *bullet repayment*, and remuneration independent of interest rates, partially secured by the Company's capital

Non-dilutive funding

Additional financial leverage to motivate the management board and existing shareholders, as well as significantly increasing the potential ROI for equity investors

Proof of confidence from one of the largest funding institutions in the EU

EIB financing is seen as an instrument that strongly validates the business model and attracts additional capital investors

Amount of credit:	Pay-off date:	Debt cost:
Up to **EUR 22m (~100 mPLN)** in 3 tranches	Up to **5 years** for each tranche	**Fixed annual interest,** warrants subscription

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

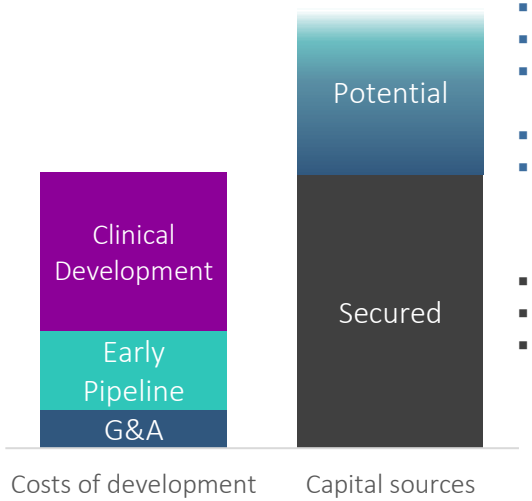
2024 KEY GOALS AND FINANCING

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 Q2 and Q4**
- New preclinical candidate in the early pipeline

Ryvu Equity Summary

IPO on WSE **Corporate Split: Selvita and Ryvu**	Nov 2014 Oct 2019
Ticker: WSE	RVU
52-Week Range[1]	PLN 51.70 – 72.40
Average Daily Volume (YTD) [1]	15,099
Market cap[1]	PLN 1,460 M ($345 M)
Shares outstanding	23.1 M
Cash[2]	$64.5 M (€58 M)

Top Holders[3]		
1	Paweł Przewięźlikowski	18%
2	Allianz OFE	9.2%
3	BioNTech SE	8.3%
4	Allianz TFI	8.3%
5	Nationale-Nederlanden OFE	8.2%
6	Tadeusz Wesolowski (incl. Augebit)	5.9%
7	PZU OFE	4.5%
8	Boguslaw Sieczkowski	3.6%
9	Goldman Sachs TFI	1.9%
10	Uniqa OFE	1.8%
11	Aegon OFE	1.6%
12	NN Life 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 02 Jan 2024
2. As of 24 Nov 2023
3. As of 12 June 2023

RYVU THERAPEUTICS

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