RYVU THERAPEUTICS

RVU120

First-in-class CDK8/19 inhibitor in hematologic and solid malignancies

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RYVU at a glance

Company overview

RYVU is a clinical-stage drug discovery and development company focused on novel small-molecule therapies that address emerging targets in oncology

- One of the largest biotech companies in the CEE region, established and based in Krakow, Poland

>320 Employees, including ~185 scientists (with ~100 PhDs)

>70 Clinical Development Team members

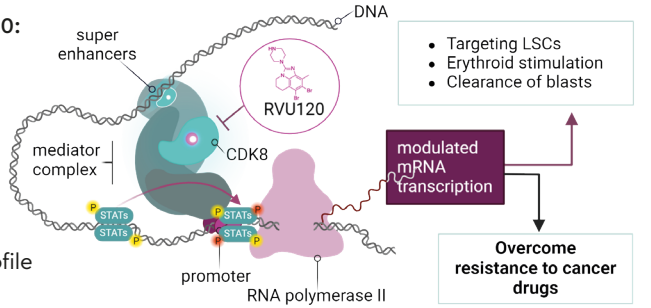
- State-of-the-art 10,000m² R&D Center for Innovative Drugs
- Validated by global partnerships with BioNTech, Merck KGaA, Exelixis, Menarini Group and Leukemia & Lymphoma Society

Program / target name	Indication	Discovery	Preclinical	Phase I	Phase II	Partner	Expected milestones
CLINICAL PROJECTS							
RVU120 (CDK8/19)	R/R AML/HR-MDS (monotheraphy)					LEUKEMIA & LYMPHOMA SOCIETY®	Complete Ph I data in 2Q24; Initial Ph II data in 4Q24
	R/R AML (combination therapy)					MEDICAL RESEARCH AGENCY	Initial Ph II data in 4Q24
	Other hematology LR-MDS, MF					EMSCO MYELODYSPLASTIC SYNDROMES	Initiation of Ph II in mid-2024
	Solid Tumors					NCBR	Translational studies and complete Ph I data in 2024

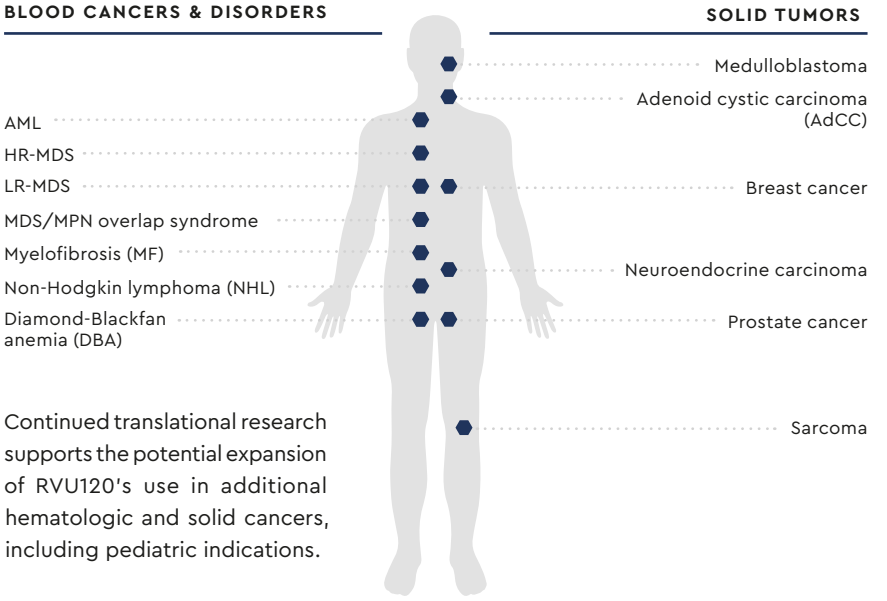
RVU120 is a clinical-stage, first-in-class, small molecule CDK8/19 kinase inhibitor developed by Ryvu Therapeutics

Key facts about RVU120:

- high selectivity
- low risk of DDI
- easy to formulate
- orally bioavailable
- favorable safety profile



RVU120 is an innovative dual CDK8/19 inhibitor designed to target the expression of genes crucial for cancer cell survival and differentiation.[1]



Continued translational research supports the potential expansion of RVU120's use in additional hematologic and solid cancers, including pediatric indications.

Phase II studies in 2024 exploring its efficacy across various hematological indications:

- **RIVER-52:** AML and HR-MDS in monotherapy (*NCT06268574*) – ongoing
- **RIVER-81:** AML in combination with venetoclax (*NCT06191263*) – ongoing
- **REMARK:** LR-MDS in monotherapy (*NCT06243458*) – to be initiated
- **POTAMI-61:** Myelofibrosis in monotherapy and combination with JAK inhibitors (add-on) (*NCT06397313*) – to be initiated

RVU120 clinical trials

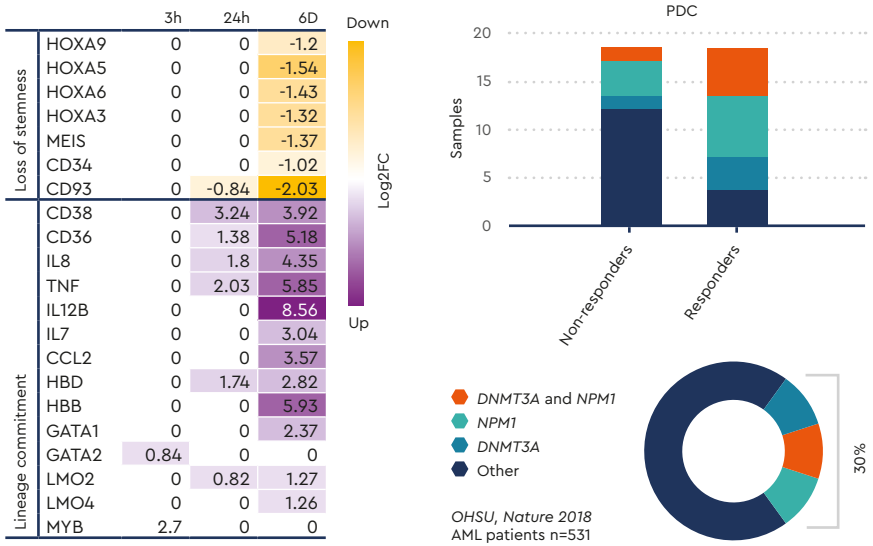
References

[1] *Rzymski et al., Oncotarget, 2017; 8(20):33779–33795.* doi: 10.18632/oncotarget.16810.

RVU120 shows promise as a targeted therapy for specific subgroups of AML patients.

Its combined mechanisms of action involve the inhibition of aberrant transcription in AML cells. Key effects of RVU120 include loss of stemness, induction of differentiation, reduced viability, and increased cell death in cancer cells.[1,2]

Notably, RVU120 exhibits strong differential anticancer efficacy in AML cases driven by *NPM1* and *DNMT3A* mutations, as well as in leukemic stem cells. These promising results have paved the way for clinical development in molecularly defined populations of AML patients carrying mutations in the *NPM1* and/or *DNMT3A* genes.[3,4]



Transcriptomic profiling of LSC-like cells after treatment with RVU120 (TLS-ERG transformed CD34+ cells, TEX; *DOI=10.1038/sj.leu.2403917*)

Patient-derived cells (PDC) sensitive to RVU120 treatment are enriched in *NPM1* and/or *DNMT3A* mutations (n=33); these type of patients represent in total 31% of all AML patients in OSHU dataset (Tyner et al. 2018, Nature).

Additionally, an encouraging aspect of RVU120's activity is blast control and erythroid stimulation, which may broaden its potential application to HR-MDS and other transfusion dependent patients.[5]

Study design

PART 1	PART 2
Genetically defined and disease specific cohorts: ▶ Pts with *NPM1*-mutated AML ▶ Pts with *DNMT3A*-mutated AML ▶ Pts with HR-MDS	**Confirmatory cohort** Simon 2-stage design Pts selected based on Part 1 outcome

Endpoints

Primary: rate of CR, CRh, CRi, with and without MRD, and DoR

Secondary: PFS, RFS, OS, transfusion independence, bridging to transplant

For Part 2: PROand HRQoL change from baseline

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

Study population

Patients with r/r AML or HR-MDS with >10% blasts in BM and no alternative treatment options

- ~140 patients
- Up to 70 sites

Treatment

Three-week cycle: single oral dose of 250 mg of RVU120 every other day for a total of 7 doses/cycle followed by one week off in a 21-day cycle of treatment

RVU120 DRUG ADMINISTRATION DAYS

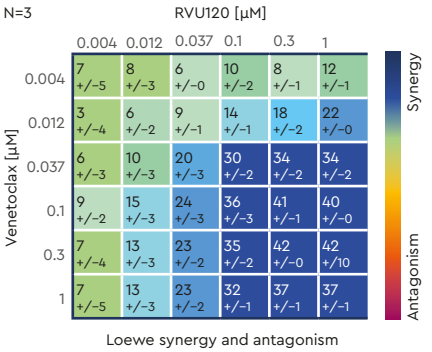
1	–	3	–	5	–	7	–	9	–	11	–	13	–	15		17		19		21

In addition, study will assess safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD)

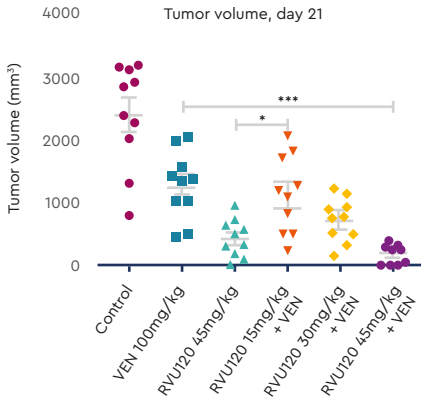
RVU120 exhibits strong synergistic activity when paired with the BCL2 inhibitor venetoclax.

Mechanism of action involves increased expression of proapoptotic proteins like BAD and reduced expression of antiapoptotic proteins like MCL1 and BCL-XL, which counteract cell death signals.

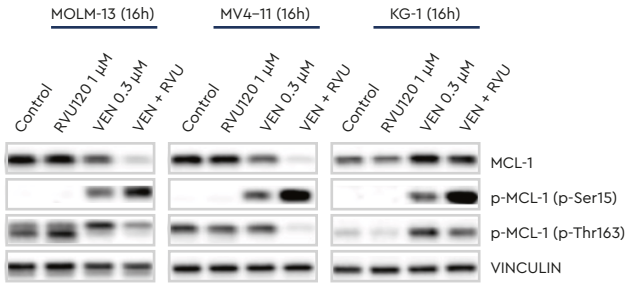
RVU120 and venetoclax work together synergistically across various AML subgroups, even in chemoresistant stem cells, which often trigger relapse in patients. These findings provide a strong rationale for clinical development of the RVU120-venetoclax combination, including patients who have not responded to previous venetoclax treatment.[6]



Concomitant treatment with RVU120 and venetoclax resulted in synergistic effects in tested AML cell lines (KG-1; Loewe synergy and antagonism matrix).



RVU120 treatment in combination with venetoclax led to regressions in AML subcutaneous xenografts (Ordinary one-way ANOVA multiple comparisons analysis; * p<0.05, **p<0.01, ***p<0.001).



RVU120 and venetoclax results in degradation of MCL-1 (Western Blot analysis from 3 different AML cell lines). Upregulation of MCL-1 is proposed as one of the major mechanisms of resistance to venetoclax treatment.

Study design

PART 1	PART 2
Dose finding in patients with relapsed/refractory AML after failing a venetoclax-based regimen	Expansion cohort at selected dose of RVU120 and venetoclax Simon 2-stage design

Endpoints

Primary: rate of CR, CRh, CRi, with and without MRD, and DoR

Secondary: transfusion independence, PFS, RFS, OS

Part 1 will follow a 3+3 study design to establish a recommended combination dose for expansion in Part 2

Study population

r/r VEN-failed AML patients with no alternative treatments

▶ ~57–98 patients ▶ Up to 60 sites

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

MEDICAL RESEARCH AGENCY

Treatment

Three-week cycle: single oral dose of RVU120 starting at 125 mg, and escalating, administered every other day on days 1–13, and oral dose of venetoclax starting at 200 mg, and escalating, administered daily on days 1–14 of each 21-day cycle of treatment

RVU120 DRUG ADMINISTRATION DAYS

1	–	3	–	5	–	7	–	9	–	11	–	13	–	15		17		19		21

VENETOCLAX DRUG ADMINISTRATION DAYS

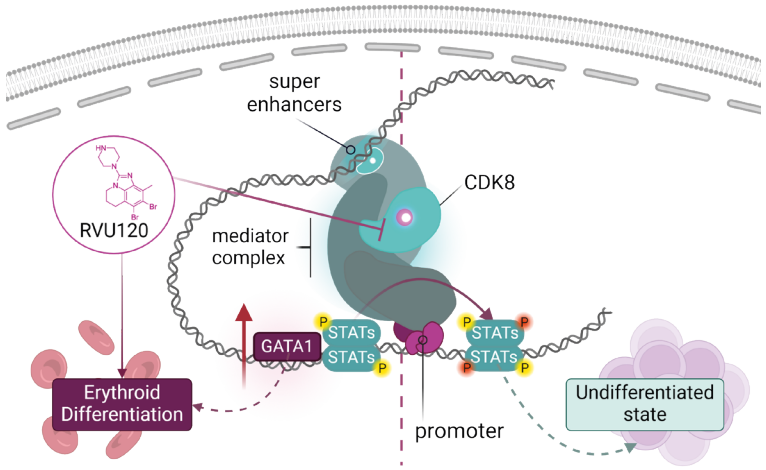
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		17		19		21

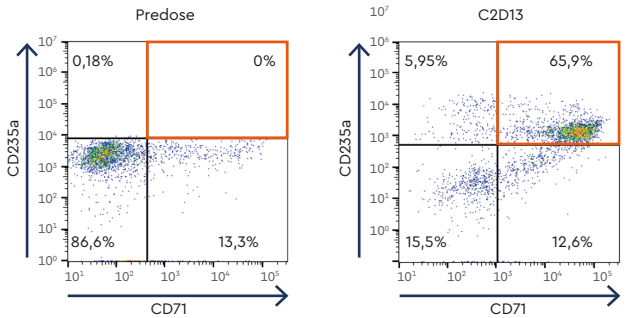
In addition, study will assess safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD)

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.[7]





Several patients with AML and HR-MDS showed signs of hematological improvement including erythroid response in the RIVER-51 study. Induction of erythropoiesis was confirmed by flow cytometry.[8]

Study design

PHASE II

Exploratory: RVU120 as a single agent in patients with LR-MDS failing available options

Endpoints

Primary: erythroid response (HI-E)

Secondary: RBC transfusion independence, Hb improvement, QoL, disease progression, mutational pattern and burden of selected genes

Ongoing assessment of phase II will drive further development

Study population

r/r LR-MDS for the treatment of anemia in patients failing available options; opportunity for the first line (1L) setting

▶ ~40 patients ▶ Up to 25 sites

Treatment

Three-week cycle: single oral dose of RVU120 every other day for a total of 7 doses /cycle followed by one week off in a 21-day cycle of treatment

RVU120 DRUG ADMINISTRATION DAYS

1	–	3	–	5	–	7	–	9	–	11	–	13	–	15		17		19		21

All patients will be treated at a starting dose of 150 mg for at least 8 full cycles. Dose escalation to 250mg after Cycle 8 – at the investigator's decision.

IIT

Study will be conducted as an Investigator Initiated Trial led by Prof. Uwe Platzbecker within EMSCO (European Myelodysplastic Neoplasms Cooperative Group)

EMSCO MYELODYSPLASTIC SYNDROMES

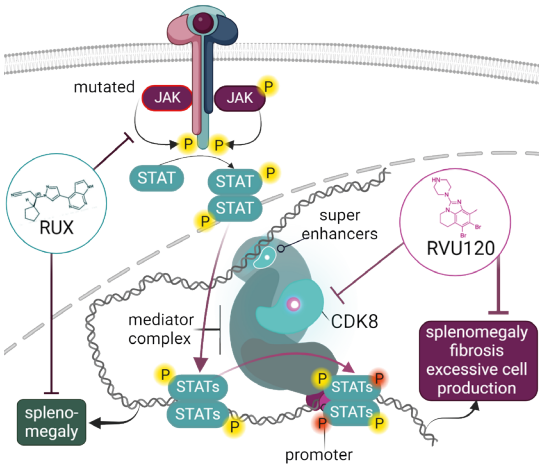
Prof. Uwe Platzbecker Co-founder and chairman of EMSCO and co-chairman of the European Hematology Association Scientific Working Group on MDS. Primary focus on myelodysplastic neoplasms (MDS) and its treatment. Worked on trials assessing luspatercept (Reblozyl) and imetelstat in patients with LR-MDS.

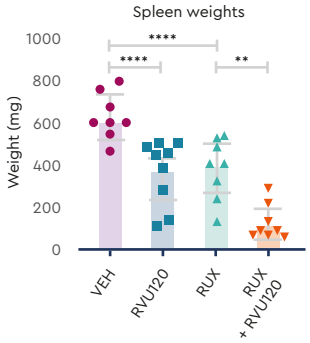
Targeting CDK8/19 by RVU120 is a promising therapeutic strategy in myeloproliferative neoplasms.

CDK8 kinase is an important player in MPN pathogenesis, as it regulates the activity of STAT proteins. By inhibiting CDK8, RVU120 disrupts the downstream signaling events mitigating MPN symptoms.

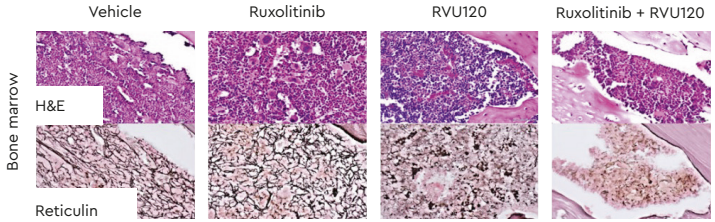
In preclinical studies, RVU120 effectively reduced splenomegaly, bone marrow fibrosis, and abnormal blood cell production. When used in combination with JAK inhibitors, RVU120 may offer enhanced therapeutic benefits through a synergistic effect.

RVU120 has also erythroid stimulating activity and demonstrated a favorable safety profile on normal hematopoiesis, making it a potential candidate for a broad clinical use in treating MPNs.[9]





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



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

Study design

PART 1	PART 2
Cohort 1 RVU120 as single agent **Cohort 2** (add-on strategy) RVU120 in combination with RUX	**Expansion of Cohort 1 and/or 2** **Cohort 3** RVU120 in combination with RUX treatment naïve

Endpoints

Primary: SVR35 after 24 weeks

Secondary: BM fibrosis reduction, DoR, leukemic transformation, HI, PFS and OS

Ongoing assessment of Phase II will drive further development

Study population

Patients with intermediate or High-Risk, primary or secondary myelofibrosis who have been:
(1) previously treated, (2) are ineligible for or
(3) had a suboptimal response to JAK inhibitor

- **~20 patients in Part 1**
- **Up to 20 sites in Part 1**

Treatment

RVU120 is administered at 250 mg as a single oral dose every other day (QOD) between Day 1 and Day 13 of each cycle for a total of 7 doses per 21-day treatment cycle. Doses of RUX should be individualized based on safety and efficacy.

RVU120 DRUG ADMINISTRATION DAYS

1	–	3	–	5	–	7	–	9	–	11	–	13	–	15		17		19		21

Additional cohorts may be enrolled in order to further characterize the safety, PK, PD, and preliminary efficacy of RVU120 given as monotherapy or in combination with Jakafi and to ensure the optimal dose and schedule is chosen as the RP2D in a myelofibrosis population.

Collaboration opportunities

References

[1] *Rzymski et al., Oncotarget, 2017; 8(20):33779–33795.* doi: 10.18632/oncotarget.16810.
[2] *Mazan et al., Blood, 2019; 134 (Supplement_1): 3774.* doi: 10.1182/blood-2019–128073.
[3] *Mazan et al., Blood, 2023; 142 (Supplement_1): 4175.* doi: 10.1182/blood-2023–188866.
[4] *Pakulska et al., HemaSphere, 2022; 6 (): 350–351.* doi: 10.1097/01.HS9.0000844688.25652.68.
[5] *Pakulska et al., Blood, 2021; 138 (Supplement_1): 1518.* doi: 10.1182/blood-2021–150662.
[6] *Rzymski et al., Cancer Research, 2020; 80 (16_Supplement):6217–6217.* doi: 10.1158/1538–7445.AM2020–6217.
[7] *Rzymski et al., EHA Library. 06/09/21; 324572; S164.* Oral presentation.
[8] *Lech-Marańda et al., HemaSphere, 2023; 7 (Suppl): e27994b8.* doi:10.1097/01.HS9.0000969012.27994.b8.
[9] *Zaroogian et al., HemaSphere, 2023; 7 (Suppl): e133428d.* doi:10.1097/01.HS9.0000970848.13342.8d.

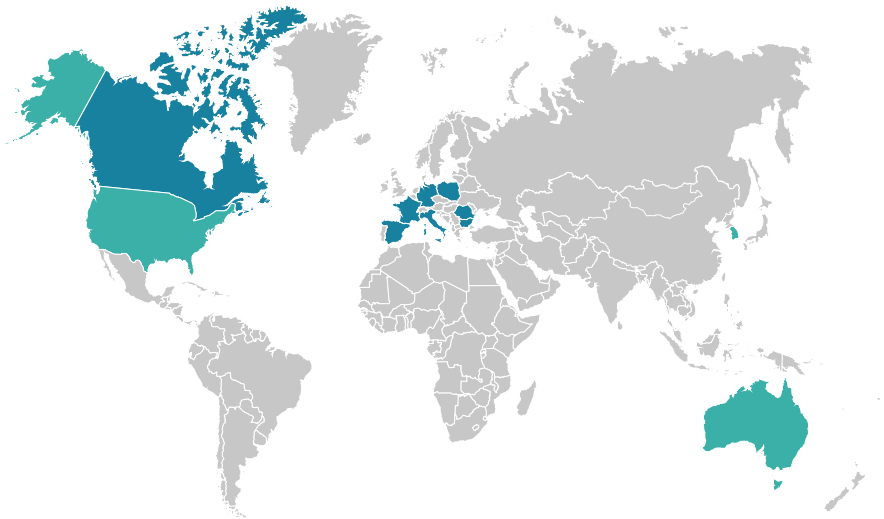
Ready to advance hemato-oncology care?

Partner with RYVU and contribute to groundbreaking studies!

At RYVU, we are driven by the desire to redefine patient care in hemato-oncology. Our well-established expertise, dedicated teams, and cutting-edge pipeline reflect our commitment to pushing the boundaries of medical possibility.

Global site locations and patient population + Global CROs and clinical vendors + Regulatory authorities worldwide

Phase II clinical development of RVU120 with a global footprint



Planned locations for RVU120 Ph II studies:

- Part 1: exploratory data
- Part 2: expansion

4 Number of Ph II clinical trials initiated in 2024

10+ Number of countries across studies

290+ Number of patients to be enrolled

170+ Number of clinical sites globally

>70 Number of RYVU team members in Clinical Development and Translational Medicine teams

30+ Number of supporting clinical vendors

RYVU Therapeutics is a clinical-stage drug discovery and development company focused on novel **small molecule therapies** that address emerging targets in oncology.

RYVU THERAPEUTICS

Join us in our mission to transform lives through innovative therapies!

If you want to learn more about our clinical studies:

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