RYVU THERAPEUTICS

EHA 2023

RVU120 in AML and HR-MDS

RVU120 Opportunity in MPNs

09 June 2023

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AGENDA

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Chief Medical Officer

NOEMI ANGELOSANTO
Medical Director,
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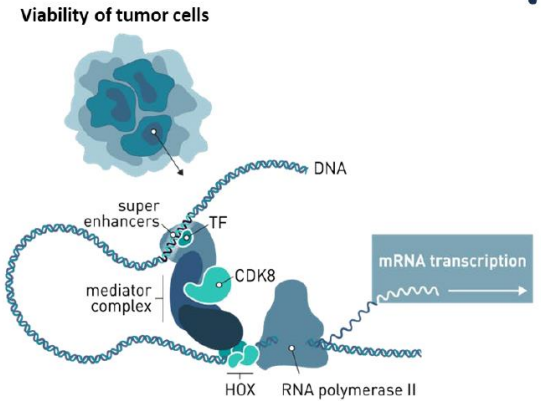
- Introduction to RVU120
- Safety and Efficacy of RVU120 in AML/HR-MDS
- RVU120 potential in Myeloproliferative Neoplasms
- Summary / Q&A

TOMASZ RZYMSKI
Director of Translational Medicine

RVU120 is a CDK8/19 inhibitor currently in clinical development to address unmet medical need in hematologic and solid tumors

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

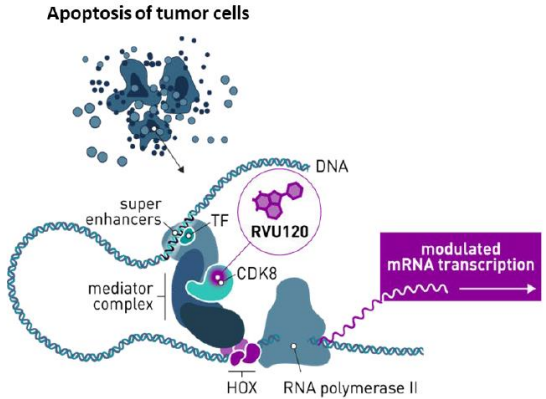
CDK8/19 mediator promotes AML growth



Maintenance of malignant stem cells

Suppression of differentiation

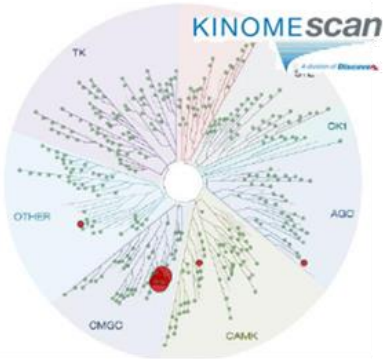
CDK8/19 inhibition by RVU120 triggers differentiation and apoptosis



Apoptosis of malignant cells, including stem cells

Lineage Commitment

RVU120 is highly selective for CDK8/19



RVU120 is currently in development in two clinical trials

CLINICAL PROJECTS

PROGRAM / TARGET NAME	INDICATION	DISCOVERY	PRECLINICAL	PHASE I	PHASE II	PARTNER	NEXT ANTICIPATED MILESTONE
RVU120 CDK8/19	AML/MDS					LEUKEMIA & LYMPHOMA SOCIETY	Complete Phase I & Initiate Phase II in H2 2023
	SOLID TUMORS						Complete Phase I & Initiate Phase II in H2 2023
SEL24 (MEN1703) PIM/FLT3	AML					MENARINI	

DISCOVERY & PRECLINICAL PROJECTS

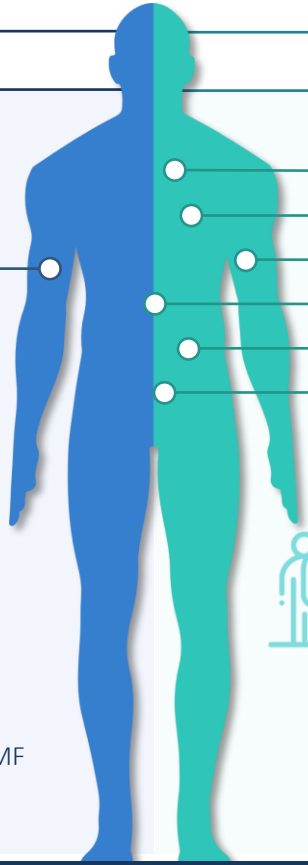
PROGRAM / TARGET NAME	INDICATION	DISCOVERY	PRECLINICAL	PHASE I	PHASE II	PARTNER	NEXT ANTICIPATED MILESTONE
SYNTHETIC LETHALITY							
PRMT5	SOLID TUMORS						Development candidate in 2023
WRN	SOLID TUMORS						*In vivo* POC in 2023
Novel Targets	ONCOLOGY						
IMMUNO-ONCOLOGY							
STING Standalone	ONCOLOGY					BIONTECH	
STING ADC	ONCOLOGY					EXELIXIS	
HPK1	SOLID TUMORS						
IMMUNE MODULATION RESEARCH COLLABORATION (MULTI-TARGET)						BIONTECH	
DISCOVERY COLLABORATION						MERCK	

RVU120: Potential across a broad range of cancers

Blood Cancers & Disorders

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

- **Signs of clinical activity in AML/HR-MDS**
- Broad potential across AML/HR-MDS (biomarker agnostic)
- Responder hypothesis in AML – unmet need with no approved therapies
- Synergy with standard-of-care in AML and MF
- **Next data release - Q4 2023**



Solid tumors

- Neuroendocrine
- **Breast**
- Sarcoma
- HCC
- Colorectal
- Prostate

- Preclinical evidence in TNBC
- Phase I ongoing
- Single agent and combination potential across several solid tumors
- **Next data release - Q4 2023**

Phase II launch planned for H2 2023

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]
- **Venetoclax sales estimated to exceed USD 3.5 bn in 2025**[3]

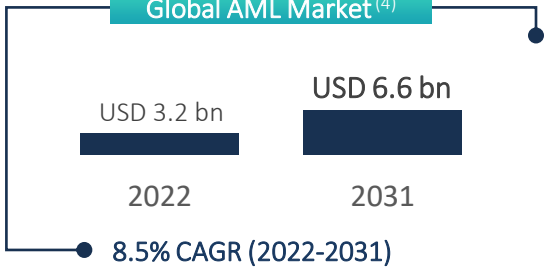
MDS (MYELODYSPLASTIC SYNDROME)

- 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 projected peak sales of USD 2 bn**

MF (MYELOFIBROSIS)

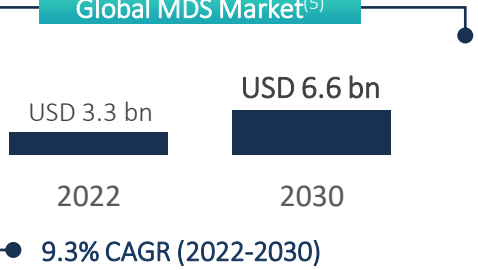
- MF is a bone marrow disease characterized by JAK mutations; often leads to severe anemia
- Chronic disease with long duration of therapy; US prevalence is estimated to be ~12,800 in 2023[4]
- **CTI BioPharma was acquired for USD 1.7 bn** in May 2023 – lead asset is a JAK inhibitor with accelerated approval in subset of MF

Global AML Market[4]



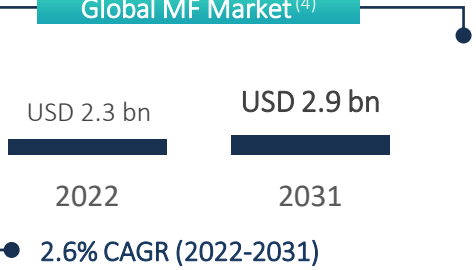
8.5% CAGR (2022-2031)

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

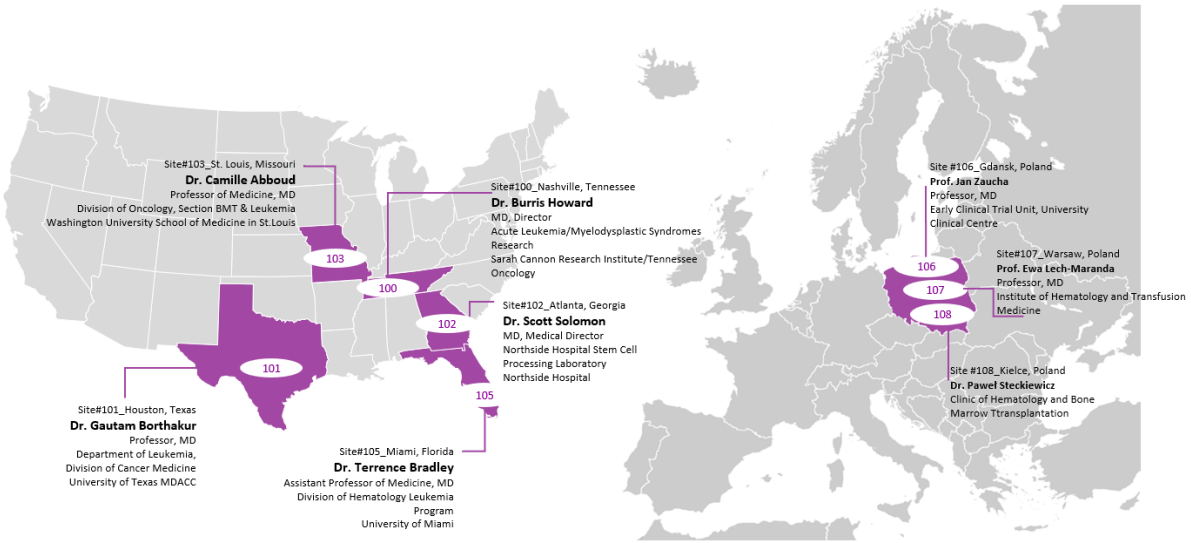
AGENDA

Safety and Efficacy of RVU120 in AML/HR-MDS

NOEMI ANGELOSANTO

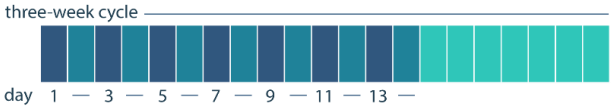
Medical Director, Hematology

The ongoing Phase 1b dose escalation trial in AML/HR-MDS is currently open at 5 Sites in the US and 3 Sites in Poland

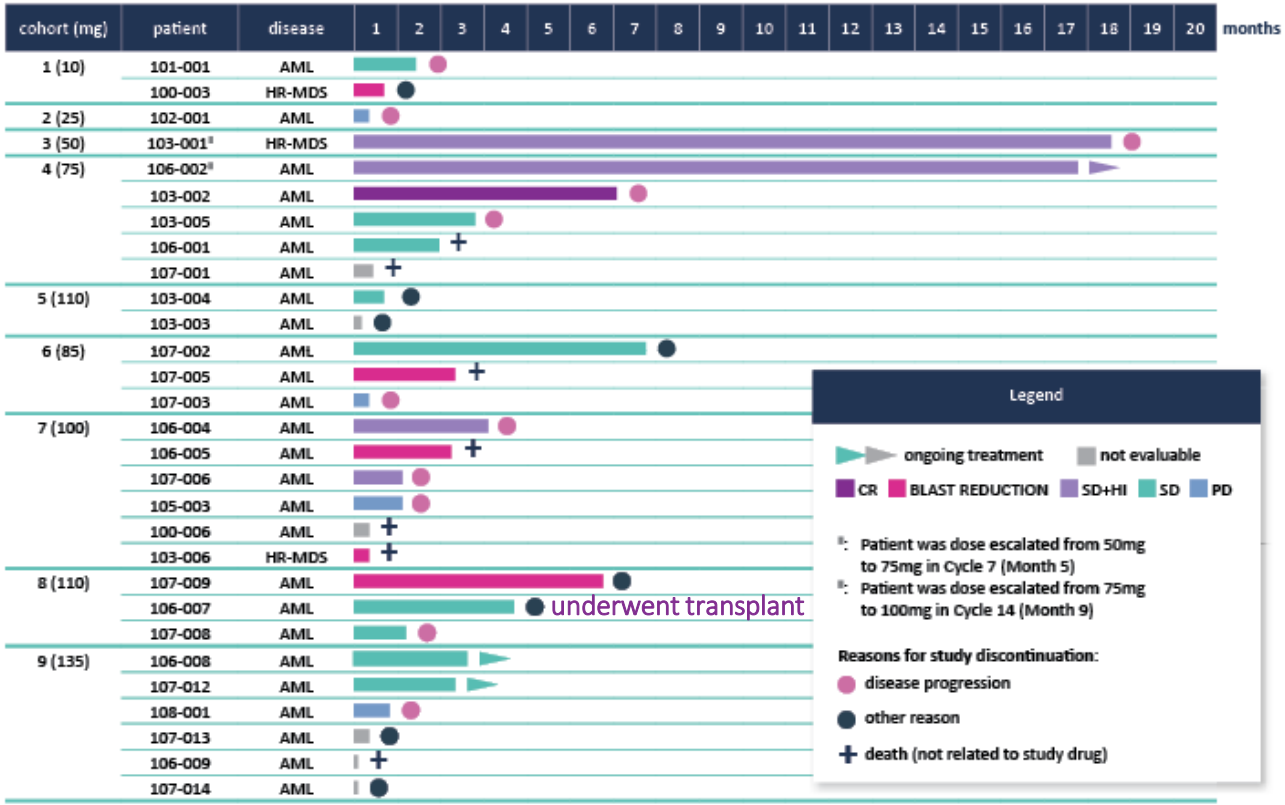


RVU120 is given:

- orally EOD between D1 and D13
- in a 21-day cycle
- until disease progression or unacceptable toxicity



Clinical Update: 11 of 24 evaluable patients showed clinical benefit



Data cut-off: May 25, 2023

- A total of 29 patients have been treated
  - Median age 71 years
  - 26 patients had AML and 3 had HR-MDS
  - Patients relapsed or were refractory to a median of 3 prior lines of therapy

Patients with poor prognostic characteristics demonstrated clinical benefit with RVU120 treatment

Dose(mg)	Pt (Diagnosis)	Mutational profile NGS/PCR	Karyotype/FISH	Prior regimen	Best Response
10	100-003 (HR-MDS)	NA	45, XY, add(5)(q22), der(6)+	2	Marrow CR
	101-001 (AML)	**TP53**+	Complex+	3	SD
25	102-001 (AML)	NA	Inv(3)(q21.3;q26.2),+14+	3*	PD
50	103-001(HR-MDS)	**STAG2, BCOR, U2AF1,** DNMT3A, **RUNX1,**+ **NRAS**@	NA	2*	SD+HI-E
75	103-002 (AML)	**FLT3-ITD, NRAS, DNMT3A, IDH2, NPM1**+	NA	3*	CR
	106-001 (AML-MRC)	**BCOR, NRAS, U2AF1,** ETV6	t(9;11)(p21.3; q23.3) /MLLT3-KMT2A+	3*	SD
	103-005 (secondary AML)	**SF3B1, NRAS, RUNX1, ASXL2,** CSF3R	Normal	4	SD
	107-001 (AML-MRC)	**TP53, NF1,** KDM6A	Complex	4*	PD
	106-002 (AML sec to MF)	**JAK2, RUNX1,** KMT2D, ATM	Normal	2*	SD+ HI-E and HI-P
85	107-002 (AML-MRC)	**SF3B1,** SMC1A, **WT1**	Inv(3)(q21q26),del(20)(q11q13), t(2;12)(q22;p13)/GATA2-MECOM	3	SD
	107-003 (AML-MRC)	**CEBPA (biallelic), TET2, SRSF2, ASXL1, RUNX1, KRAS,** CTCF, EP300, SH2B3	Normal	2*	PD
	107-005 (AML)	**TP53**	Complex	2	37% BM Blast reduction
100	106-004 (AML-MRC)	**GATA2, RUNX1, SF3B1, TET2, WT1**	47, XY,+21	4	SD + HI-E and HI-P
	100-006 (AML-MRC)	**DDX41,** EZH2, **CTCF,**CUX1, **ASXL1**	NA	5	NE
	103-006 (HR-MDS)	**TET2, ASXL1, NRAS, RUNX1,** SMC1A, RB1, ETV6	46,XY,+1, der(1;16)(q10;p10)	5*	100% BM blast reduction(FC)
	107-006 (AML-MRC)	**CBL, FLT3-TKD, NRAS,** SF3B1, **TET2, WT1**	Normal	3	SD+HI
	106-005 (AML)	**DNMT3A, ETNK1, KRAS, NRAS, SETBP1, TET2, U2AF1**	45,XX,-7	2	28% BM Blast reduction
	105-003 (AML-therapy related)	**ASXL1, ZRSR2, RUNX1**+	+20	5*	PD
110	103-003 (AML)	**TP53 biallelic** mutation	Complex	3*	NE
	103-004 (AML-MRC)	**PPM1D, NF1**+	Complex	3*	SD
	107-008 (AML-MRC)	**TET2, SRSF2, ASXL1, CEBPA (single mutated) JAK2, RUNX1**	46,XY, t(3;9;21)(p12;q22;q22), t(18;21)(q21;q22)/RUNX1	1	PD
	106-007 (AML-MRC)	**RUNX1, BCOR, BCORL1, NRAS**	46 XY, t(1;13) (q41;q11)/MECOM rearrangement	4*	SD, bridge to HSCT
	107-009 (AML-MRC)	**TP53 mutated + del(17p) ,DDX41c1564G>A, DDX41c 645G>T, SRSF2, ASXL1**	Complex Karyotype	2*	74% BM Blast reduction
135	106-008 (AML-MRC)	**BCOR, STAG2c3364dup,STAG2c3133C>T,SRSF2,RUNX1, CEBPA (single mutated), IDH1, KRAS,** TET2	47,XY,+8	2	SD
	107-012 (AML)	**STAG2, TET2c1888A>T, TET2c697dup, ASXL1, SRSF2, CEBPA (single mutated)**	Normal	3*	SD
	107-013 (AML sec to CMML)	**CEBPA(double mutated$), EZH2c98C>T, CBL,** SMC3, **EZH2, TET2 c1486 del,TET2c 5734C>G, RUNX1, EZH2c378 385del, TET2 c3340_3341InsGA**	47,XX,+21/RUNX1	3*	NE
	107-014 (AML)	**TP53 mutated + del(17p)**	+del17p, +21q,+11q,+17p,+17q,+5p,+5q	1	NE
	108-001 (AML)@	**NPM1,** SMC1A	Normal Karyotype	2	PD
	106-009 (AML)	**TP53, PHF6,EZH2**	TP53+/Complex hypotetraployd karyotype	4*	NE

CR=Complete Remission, HI-E=Erythroid Response, HI-P=Platelet Response.

MPN=Chronic Myeloproliferative Disorders, *received prior venetoclax

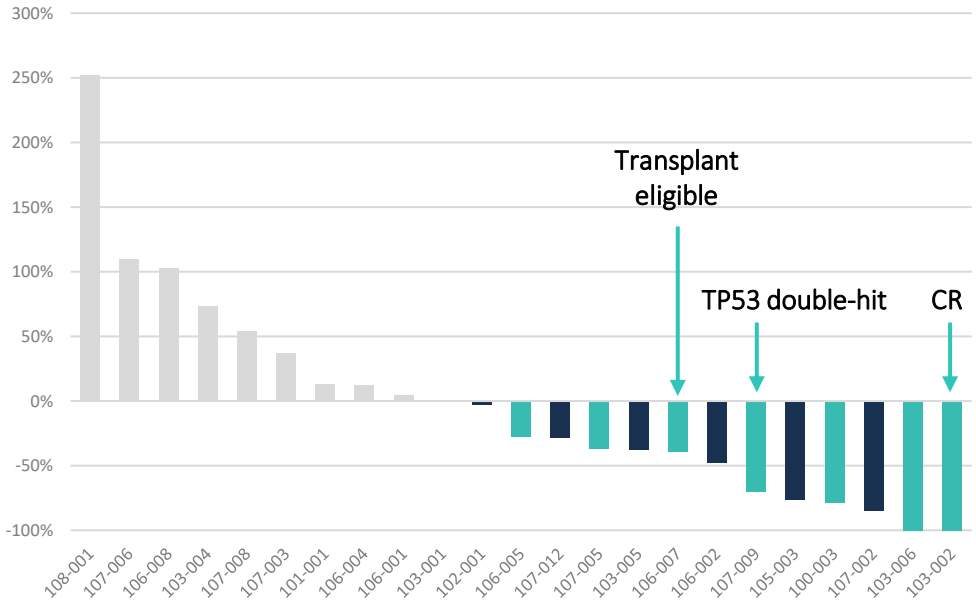
Blast reduction/Hematological Improvement

Signs of clinical benefit were observed in 11 patients

- In total, seven patients experienced meaningful BM blast reductions
  - One patient with AML achieved a **Complete Remission**
  - One patient with AML refractory to four prior lines of therapy became **eligible for allogeneic stem cell transplantation**
- Four patients achieved a hematological improvement (hemoglobin and/or platelet increase)
  - A patient with a secondary leukemia is ongoing at 100 mg with clinical benefit after more than 16 months
- Additional patients with blast reductions were observed

BM blast reduction observed in 12 patients with evidence of clinical benefit confirmed in 7 patients

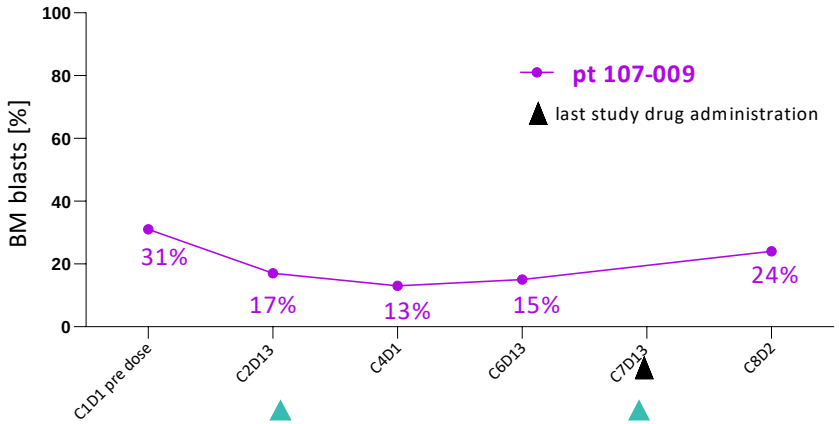
Best BM blast % reduction



- A total of 12 patients showed BM blast reduction while on RVU120 treatment
- Seven of them experienced meaningful clinical benefit:
  - 1 Pt achieved a CR (103-002)
  - 5 pts (2 HR-MDS and 3 AML) with conclusive reduction
  - 1 Pt with AML refractory to 4 lines of therapy received transplant (106-007)

Patient 107-009 with AML and TP53 double-hit achieved a durable >70% blast reduction

PT 107-009 BM blast reduction while on RVU120



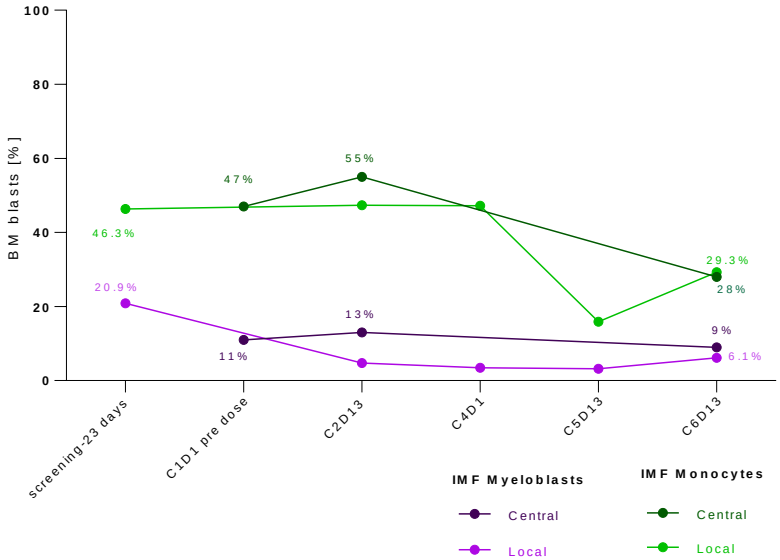
- AML with TP53 mutation is associated with poor prognosis[1]
- When TP53 gene mutation and/or deletion involves both copies of this gene, it is called ***"double hit"*** and is associated with even worse prognosis than single TP53 mutation, with median OS of 2 months in first line treatment[2]
- Pt 107-009 was failing 2 prior lines of therapy when he started RVU120 and is still alive after 7 cycles of treatment with RVU120
- Treatment was discontinued due to febrile neutropenia, unrelated to RVU120

1. H. Dohner Blood (2022) 140 (12): 1345–1377
2. A. Stengel Luekemia (2017), 31, 705-711

Response was maintained up to study drug discontinuation

Reduction of blasts in patient 106-007 allowed an allogeneic stem cell transplant with potential for long term benefit

PT 106-007 BM blast reduction while on RVU120

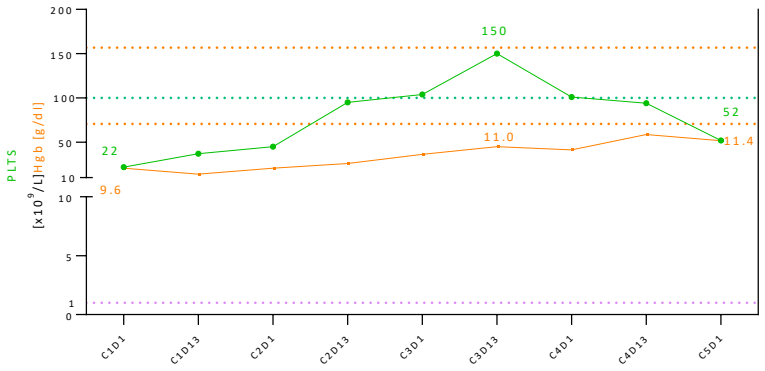


- AML with myelodysplasia
- Patient was refractory to all four prior lines of therapy, including venetoclax
- After six cycles of treatment with RVU120 and a reduction of bone marrow blasts, the patient became eligible for an allogeneic transplant

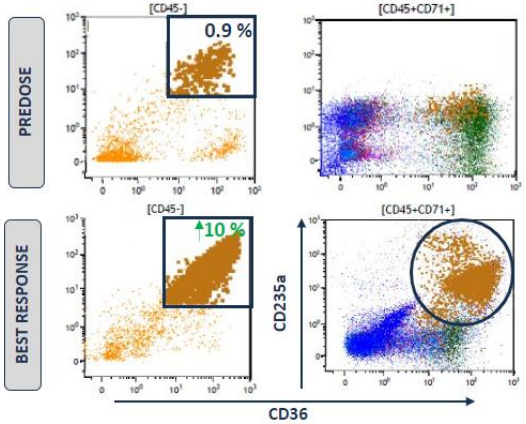
Patient was successfully transplanted

RVU120 differentiation on hematopoietic cells: 6 patients with evidence of increased erythroid differentiation

Pt 106-004 Erythroid and Platelet response



Pt 106-004 Enhanced Erythroid differentiation



- In total, **6 patients** experienced an increase in CD71 and CD235 markers on erythroid progenitors in the BM (Enhanced erythroid differentiation)
  - 4 of those patients met objective criteria for erythroid response
  - 2 of them also with platelet improvement
- Findings are consistent with the non-clinical evidence for erythroid and myeloid differentiation effects on bone marrow progenitors

RVU120 has a favorable safety profile at doses tested to date

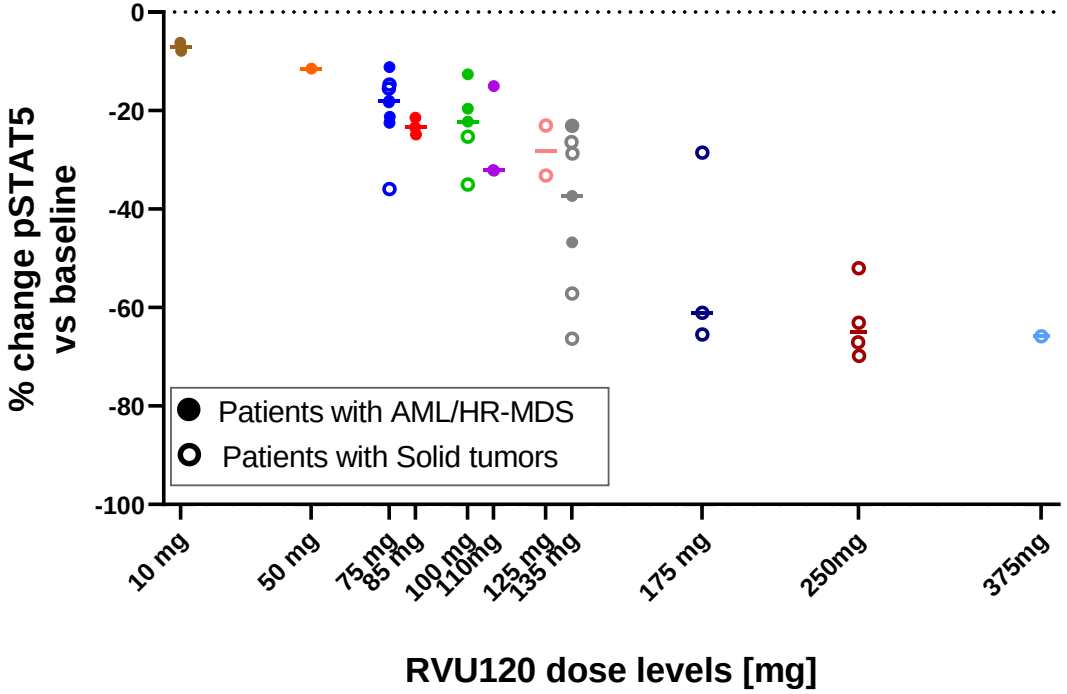
Most common* Treatment Emergent Adverse Events (TEAE)	RVU120 (10-135 mg)	
	Any grade n of pts (%)	Grade 3-5 n of pts (%)
Nausea	19 (61%)	0
Vomiting	10 (32%)	1 (3%)
Febrile neutropenia	9 (29%)	9 (29%)
Thrombocytopenia	9 (29%)	7 (22.5%)
Pneumonia	7 (22.5%)	7 (22.5%)
Hypokalemia	6 (19%)	0
Anemia	5 (16%)	5 (16%)
Urinary tract infection	5 (16%)	3 (9%)
Cough	5 (16%)	0
Decreased appetite	5 (16%)	1 (3%)

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

RVU120 was well tolerated at doses between 10 and 135 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, in most cases Grade 1 and 2
- Hematologic events are expected in the study population and the majority of them were considered unrelated to RVU120

In patients treated in both ongoing RVU120 studies, pSTAT5 inhibition correlates with drug exposure



Relevant pharmacodynamic effects were observed in both trials

- STAT5 is a direct target of CDK8
- A decreasing level of pSTAT5 indicates increasing target engagement by RVU120
- A consistent decrease of >70% can be achieved at doses of 250 mg and 375 mg and is expected to be efficacious in certain settings
- No DLTs were observed up to a dose of 375 mg

RVU120 is well tolerated and has demonstrated signs of efficacy

- Treatment with RVU120 has resulted in clinical benefit in 11 out of 24 patients
- RVU120 induces erythropoiesis at a clinically relevant level, which supports further testing of RVU120 in patients with anemia
- Available pharmacodynamic data indicate that higher doses result in higher level of target inhibition and may be associated with more pronounced anti-leukemic activity of RVU120
- Clinical efficacy and safety data warrant further development of RVU120 in AML/HR-MDS

Enrollment is currently ongoing at 175 mg

AGENDA

RVU120 potential
in Myeloproliferative Neoplasms
(MPNs)

TOMASZ RZYMSKI

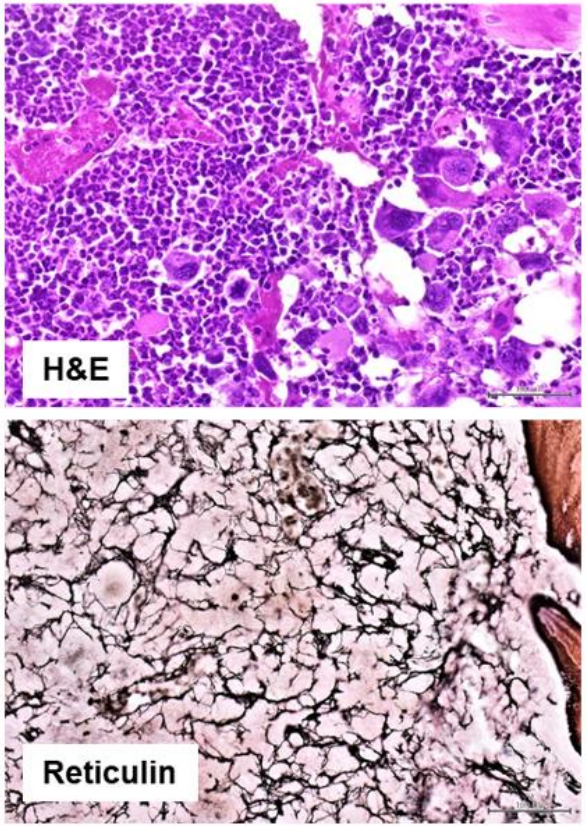
Director
of Translational Medicine

Introduction to Myeloproliferative Neoplasms (MPNs)

MPNs (MYELOPROLIFERATIVE NEOPLASMS)

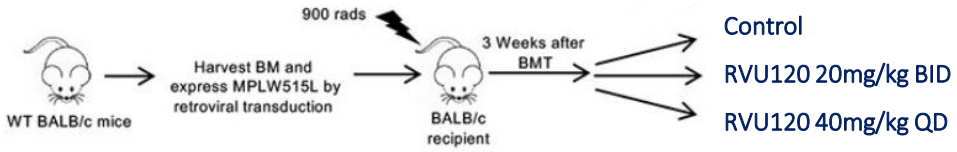
- MPNs comprise a class of chronic leukemias
  characterized by abnormal cell growth and fibrotic scars in BM
- Three main types:
  - myelofibrosis (MF)
  - polycythemia vera (PV)
  - essential thrombocythemia (ET)
- Current SoC targets JAK -STAT pathway
- Risk of progression to AML
- High unmet medical need

Pathologic picture of BM myelofibrosis



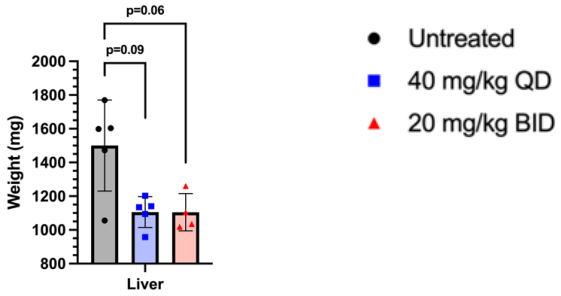
Confirmed efficacy of RVU120 in myelofibrosis models *in vivo*

Confirmed high efficacy of RVU120 in MF model *in vivo*



1. Reduction of spleen and liver volume
2. Reduction of WBC and PLT overproduction
3. Change from increased to appropriate number of megakaryocytes
4. Reduction of BM and spleen fibrosis grade from 3+ to 0
5. Change from left-shifted to trilineage hematopoiesis in BM
6. Reduction of disease reporter percentages

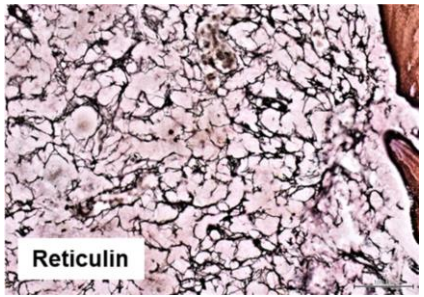
Reduction of spleen size



*p-values based on Mann-Whitney tests

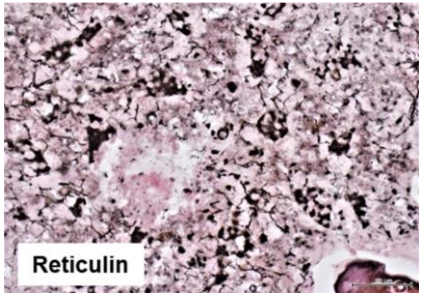
Reduction of bone marrow fibrosis

untreated



3+ reticulin fibrosis

RVU120



0-1+ reticulin fibrosis

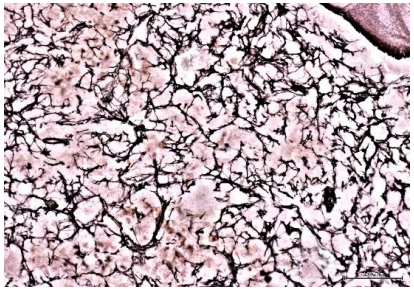
Memorial Sloan Kettering Cancer Center

RVU120 improves over SoC in myelofibrosis ruxolitinib *in vivo*

- Ruxolitinib (Jakafi) is a SoC drug that reduces symptoms in MF patients
- RVU120 is efficacious in JAK mutant cells resistant to ruxolitinib
- Confirmed synergy between RVU120 and ruxolitinib *in vitro*
- RVU120 improves MF symptoms over ruxolitinib in combinations *in vivo*

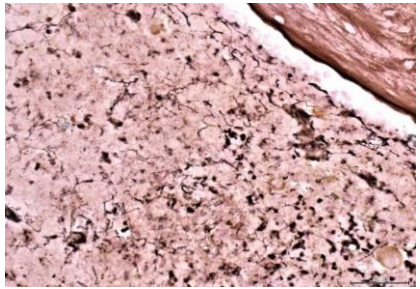
Reduction of bone marrow fibrosis

RUX



3+ reticulin fibrosis

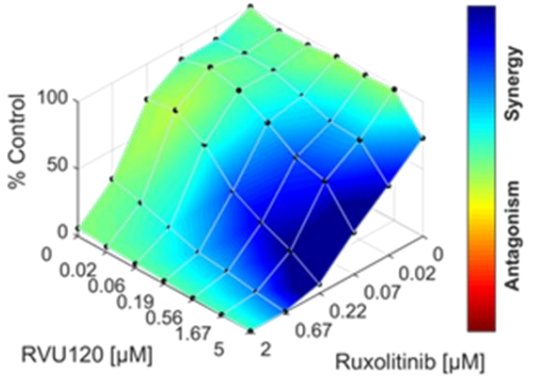
RUX + RVU120



0+ reticulin fibrosis

Memorial Sloan Kettering Cancer Center

JAK2 V617F mut Ruxolitinib-resistant cells

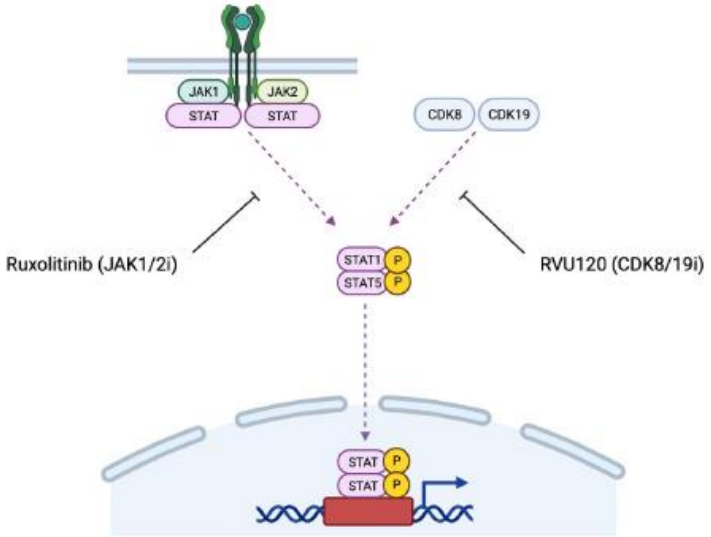


RVU120 validated as a drug candidate in MPNs/MF

Conclusions

- RVU120 alone and in combination can reduce symptoms and has disease modifying potential in MPNs/MF
- Favorable RVU120 toxicity profile may enable **targeting patients non eligible for ruxolitinib treatment**
- Preclinical results confirm RVU120's potential in ruxolitinib r/r MF patients
- **Synergy with ruxolitinib indicates potential for expansion in the frontline setting**

Mechanism of RVU120 activity in MPNs/MF



AGENDA

Summary / Q&A

HENDRIK NOGAI

Chief Medical Officer

Summary: RVU120 development in AML/HR-MDS and solid tumors
Phase II initiation planned for H2 2023

Status of dose finding

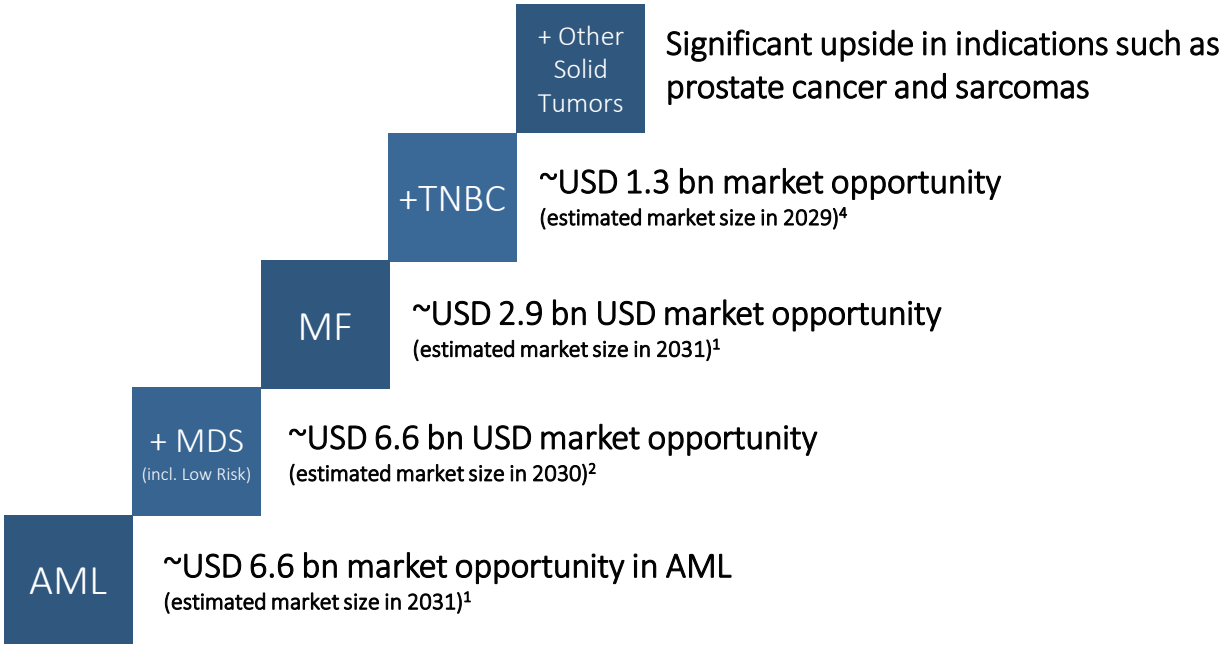
- After the data cut-off for the EHA poster, the 135 mg cohort has been fully enrolled
  - Enrollment is currently ongoing at 175 mg
- **11 of 24 evaluable patients showed clinical benefit** in the Phase I dose escalation (as of May 25, 2023)
- Additional sites in Poland are planned to be activated shortly to further support patient enrollment
- The study in patients with solid tumors is ongoing at 375 mg with no observed DLTs and consistent 70% target engagement.
- Further dose finding steps will be discussed at the next Data Review Committee Meeting on June 12th

Phase II start-up activities are on-going full speed

- Discussions with ~20 key opinion leaders and investigators in several development tracks: AML/HR-MDS, MDS-MPN, LR-MDS
- Study protocols finalized, CRO / clinical vendors contracting either finalized or at the advanced stage
- **Targeting H2 2023 for Phase II initiation in AML/HR-MDS and solid tumors**

RVU120 / Pipeline-in-a-pill: High market potential

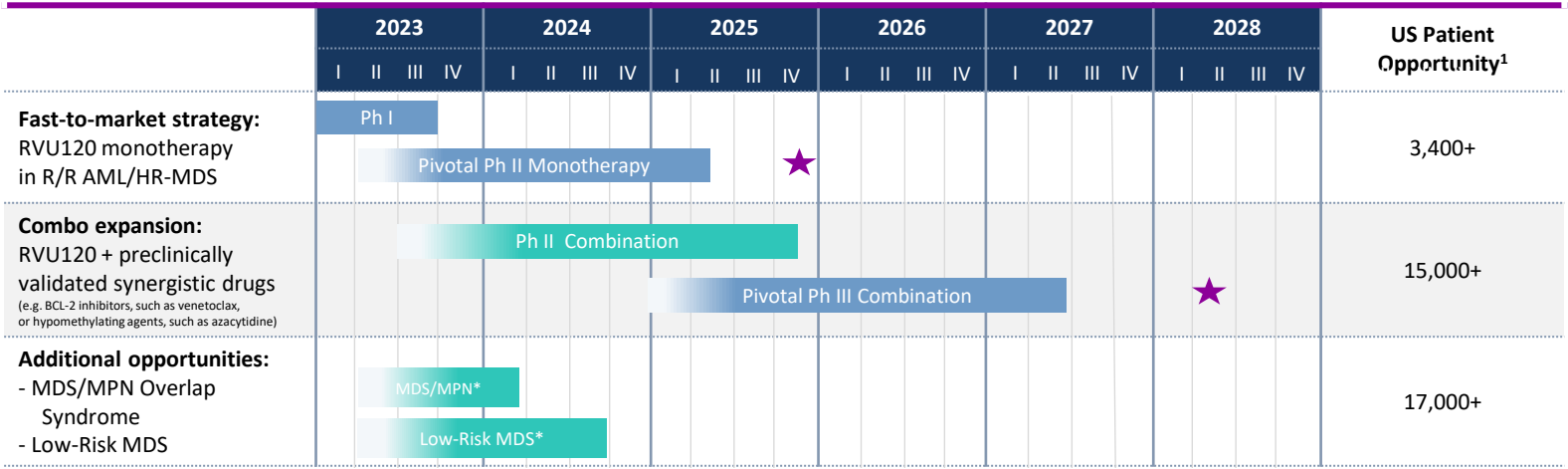
Indication Expansion to a Broad Commercial Space



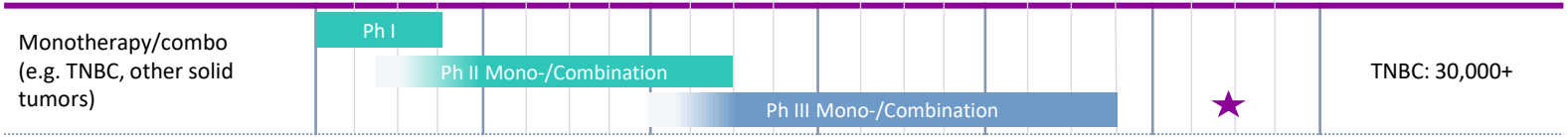
1. GlobalData
2. Coherent Market Insights, 2021
3. Allied Market Research, 2023
4. Data Bridge Market Research, 2022

Ryvu is committed to execute a broad Clinical Development Plan for RVU120

HEMATOLOGY CANCERS



SOLID TUMORS



★ Initiation of the registration process

Registration study

1 US Patient Opportunity is comprised of Datamonitor forecasts of US incident cases in 2030

* Further clinical development will be planned based on PoC

RVU120 – Potential further data disclosures in 2023

Conference name	Date of the Meeting	Location
ENA 2023 EORTC-NNCI-AACR Symposium	**Oct 11 to 15**	**Boston, USA**
ESMO 2023 Congress of the European Society of Medical Oncology	**Oct 20 to 24**	**Madrid, Spain**
ASH 2023 65th American Society of Hematology Annual Meeting	**Dec 9 to 12**	**San Diego, USA**

Q&A

RVU120 is tolerated in patients with relapsed or refractory AML/HR-MDS

Signs of clinical activity were confirmed in additional patients

New translational data support additional opportunity in myeloproliferative neoplasms

Transition into Phase 2 development is planned for H2/2023

THANK YOU

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