Targeted therapeutics
at the forefront of oncology

CORPORATE PRESENTATION

May 2021
Note on the presentation and forward looking statements

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Ryvu at a glance

Clinical Pipeline Across Heme and Solid Tumors

- Wholly owned, first-in-class, selective oral CDK8/19 inhibitor
- Clinical data in 2021 from Phase Ib study in AML/MDS
- Solid tumor Phase Ib study in start-up phase

RVU120

- First-in-class dual PIM/FLT3 kinase inhibitor for AML in Phase II
- Single agent efficacy and acceptable safety profile demonstrated in r/r AML
- Partnered with Menarini

SEL24

Small Molecule Platform with Differentiated Synthetic Lethality Targets

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

- Synthetic Lethality
  - WRN, cancers with MTAP-deletion

- Immuno-Oncology
  - HPK1, STING

Robust internal drug discovery engine (150 FTEs)
Partnerships including Galapagos and Merck

Listed on Warsaw Stock Exchange, market cap of $262m

- One of the largest drug discovery companies in the region, headquartered in Kraków, Poland
- ~$33m cash position and significant non-dilutive grant funding (>$25m secured till 2023)
## Broad pipeline addressing emerging targets in oncology

### CLINICAL PROJECTS

<table>
<thead>
<tr>
<th>PROGRAM / TARGET NAME</th>
<th>INDICATION</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PARTNER</th>
<th>ANTICIPATED MILESTONES</th>
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<tbody>
<tr>
<td>SEL24 (MEN1703) PIM/FLT3</td>
<td>AML</td>
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<td>MENARINI</td>
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<td>RVU120 CDK8/19</td>
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<td>ELLER</td>
<td>Initial Phase I data H1 2021</td>
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<td>SOLID TUMORS</td>
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<td>Initiation of Phase I 2021</td>
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### DISCOVERY & PRECLINICAL PROJECTS

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<th>PARTNER</th>
<th>ANTICIPATED MILESTONES</th>
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<td>MTAP DELETIONS</td>
<td>SOLID TUMORS</td>
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<td>NOVEL TARGETS</td>
<td>ONCOLOGY</td>
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| IMMUNO-ONCOLOGY | | | | | | | |
| HPK1 | SOLID TUMORS | | | | | | |
| STING | SOLID TUMORS | | | | | | |

| DISCOVERY COLLABORATIONS | | | | | | | |
| Galápagos | | | | | | | |
| MERCK | | | | | | | |
**Strong momentum since the focusing of Ryvu Therapeutics as a standalone oncology biotech**

- **10.2019**
  - Corporate spin-out of Selvita (CRO) from Ryvu Therapeutics completed, >$100m incremental value created for Ryvu shareholders

- **03.2020**
  - SEL24 – successfully completed Phase I in acute myeloid leukemia patients, FDA approval for Phase II
  - RVU120 – orphan drug designation in AML by FDA

- **04.2020**
  - Collaboration with Galapagos in inflammatory disorders announced

- **06.2020**
  - SEL24 Phase I data at EHA 2020, RVU120 and pre-clinical program posters at EHA and AACR 2020

- **07.2020**
  - Completed construction and move into a new fully-owned $20m research center in Krakow
  - $38m (PLN143m) raised in a follow-on public offering
  - **First patient dosed with SEL24 in Phase II study**

- **01.2021**
  - Clinical Trial Application filed for RVU120 study in solid tumors in Europe & approved for RVU120 AML/MDS Phase Ib sites in Europe

- **02.2021**
  - Secured $5.5m non-dilutive grant funding for RVU120 in solid tumors

- **05/06 2021**
  - Preliminary RVU120 Phase I clinical and preclinical data presented at EHA2021
  - SEL24(MEN1703) Phase II clinical data presented at EHA2021
Clinical Candidates in Hematology and Solid Tumors
Unmet need in acute myeloid leukemia – Ryvu’s initial clinical focus

Most common, highly aggressive type of acute leukemia in adults with poor outcomes in most patients

- ~20,000 new cases diagnosed and >11,000 deaths in the US in 2018

- AML makes up 1% of all cancers and 34% of all adult leukemia cases

- Occurs in a predominantly elderly, frail patient population; 75% of patients diagnosed with AML were aged >60 years

- Lowest survival among all blood cancers; only 26% of patients survive 5 years after diagnosis

- 30% AML patients with an ITD mutation in the FLT3 gene have a less favorable prognosis; 70% of patients are refractory to current inhibitors targeting FLT3 mutation

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1. Mayo Clinic
2. Cancer.net
3. Leukemia & Lymphoma society
4. Walter, R; Leukemia 2015
5. Evaluate Pharma

AML Market

- 2020: $1.2 billion
- 2025: $8.0 billion
- 46% CAGR

Only 20% patients aged >80 receive intensive therapy

~$1,300m
~$600m
~$500m
~$400m
~$300m
Clinical landscape: targeted small molecule therapies for AML

<table>
<thead>
<tr>
<th>FIRST-IN-CLASS</th>
<th>CDK8/CDK19</th>
<th>RYVU THERAPEUTICS</th>
<th></th>
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<tbody>
<tr>
<td>FIRST-IN-CLASS</td>
<td>FLT3</td>
<td>FUJIFILM</td>
<td>arog</td>
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<tr>
<td>Dual PIM/FLT3</td>
<td>RYVU</td>
<td>MZNARINI</td>
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<tr>
<td>PIM</td>
<td>Incyte</td>
<td>NOVARTIS</td>
<td>TOLOMA PHARMACEUTICALS</td>
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<tr>
<td>IDH1 or IDH2</td>
<td>FORMA THERAPEUTICS</td>
<td>TIBSOYO</td>
<td>IDHIFA</td>
</tr>
<tr>
<td>Others</td>
<td>BerGenBio</td>
<td>APTOS</td>
<td>ORYZON</td>
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</tbody>
</table>

| Phase 1/2 | Phase 3 | Approved |

- RVU120 is the only CDK8/CDK19 inhibitor in clinical development
- SEL24(MEN1703) is a unique, clinical-stage dual PIM/FLT3 inhibitor

RYYVU CLINICAL PROGRAMS DESIGNED TO FULFILL UNMET NEEDS IN AML

- Overcoming resistance to single-target mutation-specific inhibitors
- Efficacy in broader patient populations
- Reducing chemotherapy-based treatment regimens
- Fully oral regimen
Transcriptional deregulation is a hallmark of AML.

CDK8 is a kinase subunit of the Mediator complex serving as a bridge between basal transcription and regulatory elements involved in:
- Deregulation of super enhancers (SE)
- Affected differentiation and pro/anti-apoptotic genes

**RATIONALE FOR CDK8/CDK19 INHIBITORS IN AML**

- Transcriptional deregulation is a hallmark of AML
- CDK8 is a kinase subunit of the Mediator complex serving as a bridge between basal transcription and regulatory elements involved in:
  - Deregulation of super enhancers (SE)
  - Affected differentiation and pro/anti-apoptotic genes

**EFFICACY OF RVU120 - CDK8/CDK19 INHIBITOR - IN AML**

- Selectively targets leukemic cells, sparing normal blood cells (unaffected normal hematopoiesis)
- Promotes cell death (differential cytotoxicity on STAT5+ AML)
- Represses increased levels of anti-apoptotic proteins and induces lineage commitment genes in undifferentiated AML cells
RVU120: Highly selective first-in-class CDK8/CDK19 inhibitor with broad potential in hematological malignancies and solid tumors

<table>
<thead>
<tr>
<th>BLOOD CANCERS</th>
<th>SOLID TUMORS</th>
<th>BLOOD DISORDERS</th>
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<tbody>
<tr>
<td>AML</td>
<td>Breast</td>
<td>Diamond-Blackfan Anemia (DBA)</td>
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<td>JAK2 mut</td>
<td>Colorectal</td>
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<td>AML/MPN</td>
<td>Prostate</td>
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<tr>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
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<tr>
<td>ALL, NHL</td>
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</table>

**RVU120 Rationale/ Opportunity**

- Direct cytotoxicity (induction of apoptosis)
- Eradication of Leukemic Stem Cells (LSC), responsible for tumor relapse in AML
- Preclinical data indicate safe and synergistic combination with chemo and targeted therapies
- Targeted MOA by transcriptional regulation of cancer-dependent genes
- Preclinical data to support broad potential in multiple solid tumors
- Modulation of immune cell activity (NK cells)
- Translational data to support erythroid differentiation, reversing anemia
- High unmet need in an orphan indication

Orphan drug designation in AML in 2020

Therapy Acceleration Program (TAP) grant support

**Total funding: $3.25m**
### Initial positioning of RVU120 in AML treatment regimen and strategic expansion

#### AML TREATMENT PROTOCOL

**UNFIT PATIENTS**

<table>
<thead>
<tr>
<th>NO RELEVANT MUTATIONS</th>
<th>RVU120 Opportunity in AML/MDS</th>
<th>MUTATION-DRIVEN</th>
<th>RVU120 Opportunity in AML/MDS</th>
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<tr>
<td><strong>FIRST LINE</strong></td>
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<tr>
<td>LOW INTENSITY</td>
<td>RVU120 combination</td>
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<tr>
<td>CHEMOTHERAPY</td>
<td>(doublet or triplet) with SoC</td>
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<tr>
<td>• RVU120 combination</td>
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<td>(doublet or triplet)</td>
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<td>with SoC</td>
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<td>• Third+ Line:</td>
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<tr>
<td>RVU120 monotherapy</td>
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<td>• Second/Third Line:</td>
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<tr>
<td>RVU120 monotherapy or</td>
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<tr>
<td>combo with low intensity</td>
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<tr>
<td>chemo (e.g. azacitidine)</td>
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<tr>
<td><strong>RELAPSED/REFRACTORY</strong></td>
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<td>LOW INTENSITY</td>
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<td>RVU120 monotherapy or</td>
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<tr>
<td>combo venetoclax</td>
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</tbody>
</table>

• RVU120 combination (doublet or triplet) with SoC, e.g. venetoclax+azacitidine

• Third+ Line: RVU120 monotherapy

• Second/Third Line: RVU120 monotherapy or combo venetoclax
RVU120: Preclinical data support key clinical features

RVU120 is a potent and selective CDK8/CDK19 inhibitor

pSTAT1/pSTAT5 levels and stemness markers discriminate responders/ non-responders in vitro

Experiments performed in CD34+ AML patient-derived xenografts:

- Complete regression (peripheral blood)
- Hematologic recovery (bone marrow)

RVU120 strongly synergizes with venetoclax in vitro and in vivo

- RVU120 potentially addresses treatment resistant disease through safe, indirect MCL-1 downregulation in cancer cells
- Compelling potential for RVU120 in combination with venetoclax

Excellent **on-target** activity of RVU120 in pSTAT positive AML cell models

RVU120 induces **complete regression and bone marrow recovery** in AML PDX models in vivo
RVU120: Phase Ib study – initial data at EHA 2021

Phase Ib Study of RVU120 in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome

1. **STUDY POPULATION:**
   - Patients with relapsed/refractory AML or high risk MDS
   - No upfront patient stratification

2. **PRIMARY OBJECTIVE:**
   - To assess safety and tolerability
   - To determine the recommended dose

3. **SECONDARY OBJECTIVE:**
   - To evaluate pharmacokinetics
   - To evaluate the preliminary anti-leukemic activity

4. **EXPLORATORY OBJECTIVE:**
   - To evaluate pharmacodynamics

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**PROJECT MILESTONES**

2Q 2021
- Initial results from Phase Ib at EHA

H2 2021
- Additional results from Phase Ib

H1 2022
- Phase II in AML/MDS

2022+
- Interim results from Phase II

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**STATUS AND PLANS**

**6 SITES IN US**

Partial Clinical Hold – Enrollment Expected to Resume
- April 2021: partial clinical hold on new enrollment pending additional data to address a patient death
- Interaction with FDA ongoing to resume enrollment

**SITE EXPANSION**
- 2 sites in Poland – CTA application approval obtained in January 2021
- EU & Asia-Pacific sites under consideration
## RVU120 study design in AML/MDS and further plans

### H2 2019-2021

<table>
<thead>
<tr>
<th>Part 1: Establishing Recommended Phase 2 Dose (RP2D)</th>
<th>Evaluation</th>
<th>Part 2: Safety Expansion</th>
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</table>

**Cohort 1**

- Expansion from the single patient cohort to a 3+3 design
- DLTs evaluated at completion of cycle 1 in each cohort

**Average of 24 Patients**

- **Cohort 1**
- **Cohort 2**
- **Cohort 3**

**Up to 8 Cohorts**

### Q1-Q2 2022

- **SINGLE ORAL DOSE, EOD**
- **7 DOSES/CYCLE**
- **3 WEEKS CYCLE**

### 2022 Start

#### Phase II

- **Part 2: Safety Expansion**
  - **6 Patients**

#### AML Single Agent
- Front line: Triplet with venetoclax

#### AML Combination
- Front line: Triplet with venetoclax

#### MDS Single Agent
- Front line with SOC HMAs

#### MDS Combination
- Front line with SOC HMAs

### Timeline

- H2 2019-2021
- Q1-Q2 2022
- Start 2022
RVU120: Data at EHA 2021 demonstrate early signs of efficacy

**Early Signs of Efficacy**

Two of the first four evaluable patients demonstrated clinically relevant responses:

- **Cohort 3**: patient showed evidence of an **erythroid response**
- **Cohort 4**: patient achieved a **complete hematological recovery**.

**Phased Ib Study of SEL120 (RVU120) in Patients with AML or High Risk MDS: Preliminary Clinical and PK Results from Initial Dose Escalation Cohorts**

Angelosanto et al., EHA-3345, CL120-001

- Preliminary data from the first 4 dose escalation single patient cohorts; 6 US sites
- SEL120 was administered orally every other day, for a total of 7 doses, in a 3-week treatment cycle until disease progression/unacceptable toxicity
- Cohorts 1 to 4, each enrolled 1 DLT evaluable patient who received SEL120 at dose levels from 10 to 75 mg. 3 patients had a diagnosis of R/R AML, 1 patient had persistent high risk MDS
- No DLTs were observed, 4 SAEs were reported/assessed by the investigator as unlikely related to study drug

- **Cohort 1** patient, at 10 mg dose level, and **cohort 2** patient, at 25 mg showed **stable disease (SD) and progressive disease**, respectively at C1.
- **Cohort 3** patient, who started at 50 mg dose level, is an 81-year-old male with high risk MDS who showed **evidence of an Erythroid Response at CSD8**. He is now in C8, at 75 mg, following to a dose escalation during C7.
- **Cohort 4** patient, at 75 mg dose level, is a 62-year-old male with persistent AML and extramedullary skin leukemia, who failed prior venetoclax/decitabine. This patient achieved a **complete hematological recovery at C2 and absence of bone marrow blasts and continuous improvement of skin leukemia, now ongoing in C5**, however, the profound post ven/dec pancytopenia complicates assessments of magnitude of the contribution of SEL120 to this response.

Data cutoff date: Jan 2021
RVU120 can rescue anemia in *in vivo* models

Anemia in Chronic Hematological Diseases

- Anemia in chronic hematological diseases may occur due to ineffective erythropoiesis
- Ineffective erythropoiesis causes imbalance in various progenitor and precursors cells that proliferate, differentiate and mature into red blood cells
- Anemia is a hallmark of several diseases such as myelodysplastic syndrome and Diamond-Blackfan anemia

Mutations involving signaling molecules, epigenetic regulators, splicing factors and transcription regulators can lead to ineffective erythropoiesis and anemia

Source: [https://keepmaturationtrack.eu/ineffective-erythropoiesis/](https://keepmaturationtrack.eu/ineffective-erythropoiesis/)
In vitro, RVU120 treatment leads to erythroid differentiation in transformed (Lin-) CD34+ cells. Correlating these data with clinical results indicate potential for reversal of anemia in AML and MDS patients.

RVU120 (SEL120), A CDK8/CDK19 INHIBITOR, POSSESSES STRONG MULTILINEAGE DIFFERENTIATION POTENTIAL IN LEUKEMIC CELLS
Pakulska et al., AACR Poster 3291
- RVU120 demonstrates strong erythroid differentiation potential in (Lin-) CD34+ cells that acquired genetic abnormalities resulting in arrested erythroid commitment, a characteristic of many MDS and AML subtypes.
- Data also show commitment into myeloid lineage indicating that RVU120 possesses multilineage differentiation potential.
- Detailed transcriptomic profiling strongly associated differentiation with enrichment of genes representing regulators of erythroid commitment and hemoglobin metabolism.

RVU120/SEL120 CDK8/19 INHIBITOR - A DRUG CANDIDATE FOR THE TREATMENT OF MDS CAN INDUCE ERYTHROID DIFFERENTIATION IN TRANSFORMED CD34+ HEMATOPOIETIC PROGENITOR CELLS
Rzymski et al., EHA-3382
- Evaluated erythroid differentiation potential of RVU120 in transformed lineage depleted (Lin-) CD34+ blood cells characterized with the early block in erythroid differentiation
- RVU120 treatment leads to transcriptional reprogramming of transformed (Lin-) CD34+ cells.
- Results indicate strong erythroid differentiation potential of RVU120 in (Lin-) CD34+, that acquired genetic abnormalities resulting in arrested erythroid commitment, characteristics of many MDS and AML subtypes.
- Further studies are warranted to investigate efficacy of RVU120 in anemias associated with bone marrow failures in AML and MDS patients.
RVU120 beyond blood cancers: potential role of CDK8/CDK19 in solid tumors

RVU120: expansion plan in multiple solid tumors and other heme malignancies
Phase I start: 2021, preliminary results: 2022

CDK8/CDK19 inhibitors have potential in multiple solid tumors
- Ryvu confirmed in vitro or in vivo potential in breast, colorectal, and prostate cancer

Unique MoA differentiates CDK8/CDK19 from other CDK family members
- Do not interfere with cell cycle progression (like CDK1, CDK2, CDK4/6)
- Unique across family mediator of transcriptional reprogramming (induction of silent genes, not physiological transcription) preventing metastasis and drug-resistance
- Different stratification of responders and biomarkers of response
- First generation of CDK8/19 inhibitors unsuccessful due to toxic off-target effects and suboptimal PK/PD profile

CDK8/19 inhibitors designed to provide targeted and safer treatment options
- Selective targeting cancer cells while sparing healthy ones unlike other CDK Inhibitors (e.g., CDK4/6, CDK9 affect both normal and cancer cells – possible cytopenias, no bone marrow recovery)
- Selective regulation of transcription in a cancer gene specific context (e.g., CDK7/9 involved in general transcriptional programs of normal genes)
RVU120: expansion plan in multiple solid tumors and other heme malignancies – preliminary plan
Phase I start: 2021, preliminary results: 2022

PART 1: ESTABLISHING RECOMMENDED DOSE

A 3+3 STUDY DESIGN
18 PATIENTS
DLTs evaluated at completion of cycle 1 in each cohort

COHORT 1
COHORT 2
COHORT 3
REMAINING COHORTS

SINGLE ORAL DOSE EOD
7 DOSES/CYCLE
3 WEEK CYCLE

RP2D determined

PART 2: EFFICACY & SAFETY EXPANSION SIMON 2-STAGE

STAGE 1
14 PATIENTS

R/R mTNBC
+ 10 PATIENTS

UP TO 3 OTHER SOLID TUMORS

STAGE 2
UP TO 20 PATIENTS

+ 10 PATIENTS

SAFETY, EFFICACY, PK, PD

Go/no-go decision to enroll next 10 patients based on RECIST ORR after cycle 3

EVALUATION

H2 2020

2021

2022

SCREENING

PART 1: ESTABLISHING RECOMMENDED DOSE

PART 2: EFFICACY & SAFETY EXPANSION SIMON 2-STAGE

EVALUATION

ADULTS
R/R SOLID TUMORS + NHL
NO MORE THAN 3 PRIOR THERAPIES FOR ENTRY DISEASE

PFS at 9 months
Overall survival follow-up: 2 years

14 PATIENTS
UP TO 20 PATIENTS

2021

2022
SEL24(MEN1703) is a differentiated, first-in-class PIM/FLT3 dual kinase inhibitor

PIM and FLT3 are oncogenes involved in AML.

Dual targeting creates potential for broader activity, more durable responses than selective FLT3 inhibitors such as gilteritinib.

Potential for treating patients that have relapsed on selective FLT3 inhibitors – PIM kinases are largely responsible for the development of resistance to FLT3 inhibitors.

VALUE THROUGH GLOBAL DEAL WITH

- Partnered globally with Menarini in 2017
- Menarini is fully responsible for clinical development and funds translational research at Ryvu
- Ryvu eligible to receive >$100M in milestones and double-digit royalties

ONGOING CLINICAL TRIALS

**Study title:** A Phase I/II Study of SEL24 in Patients With Acute Myeloid Leukemia

**INITIAL RESULTS OF THE PHASE I STUDY:**
- Determined the recommended Phase II dose (RP2D), the PK profile and the single agent activity in R/R or newly diagnosed AML patients; study results published at EHA 2020 Conference in June 2020
- Ryvu has received $1.9m milestone payment for successful completion of Phase I studies

**INITIAL RESULTS OF THE PHASE II STUDY (EHA 2021):**
- As of January 21, 2021 (cut-off date), n=48 pts were treated across the dose escalation (DE, n=25) and Phase II cohort expansion (CE, n=23).
- Responses occurred in 2 pts in the CE, both with IDH1 mutant disease (naïve to IDH inhibitors) who achieved complete remission with incomplete hematologic recovery (CRi).
- Across DE and CE, 4 CR/CRi occurred, three of which in pts with IDH mutations.
- A total of 3 out of 6 pts with IDH mutations treated at doses ≥75 mg achieved CR/CRi, including a CR in a patient with IDH2 mutant AML relapsed on Enasidenib.
Initial Phase I data presented in 2020 for SEL24(MEN1703) demonstrated compelling single agent efficacy

Acceptable safety data with complete responses observed

## RESULTS

- **Establishment of recommended dose and evaluation of safety profile**
  - SEL24 has acceptable safety profile up to 125mg
  - RD defined at 125mg
  - Treatment-Emergent Adverse Events – mostly hematologic or infectious. Transient peak in transaminases was detected by C1 D14 in almost all cohorts (Grade ≤2 and reversible in the 7 days OFF treatment period up to the RP2D)

- **Objective response / single agent efficacy in patients without FLT3 mutation**
  - Complete remission at 75mg in a 81 y.o. patient, with DNMT3A/IDH2 mutant AML progressed on enasidenib
  - Complete response with incomplete hematological recovery at 125mg in a 75 y.o. patient with ASXL1/EZH2 mutant AML relapsed after chemotherapy and decitabine

- **Confirmed pS6 biomarker inhibition**

## INDIVIDUAL TREATMENT DURATION

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients Completions</th>
<th>CRI – CR with incomplete hematologic recovery</th>
<th>CR – Complete Remission</th>
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<tbody>
<tr>
<td>25mg</td>
<td>001-001 003-003</td>
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<tr>
<td>50mg</td>
<td>003-003 005-007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75mg</td>
<td>005-010 007-011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100mg</td>
<td>007-015 009-017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125mg</td>
<td>009-018 011-019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150mg</td>
<td>011-024 013-023</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **N=25 patients treated**
- 22 patients evaluable (cut-off date 11-Feb-20)
- **68 years median age** (range 25-84)

**FREQUENT MUTATIONS**
- 5 (20%) FLT3/ITD.
- 4 (16%) DNMT3A
- 4 (16%) IDH1
- 2 (8%) IDH2
- 2 (8%) NMP1

**PATIENTS**
- 2 newly diagnosed
- 11 primary refractory AML
- 12 relapsed AML
SEL24/MEN1703: Data to be presented at EHA 2021 confirm early signs of efficacy

RESULTS FROM DIAMOND-01 (CLI24-001) TRIAL: FIRST IN HUMAN STUDY OF SEL24/MEN1703, A DUAL PIM/FLT3 KINASE INHIBITOR, IN PATIENTS WITH ACUTE MYELOID LEUKEMIA
Solomon et al., EHA-1390

• **Background:** SEL24/MEN1703, a dual PIM/FLT3 kinase inhibitor shows activity in both primary Acute Myeloid Leukemia (AML) cells and AML cell lines, regardless of FLT3 status. In the dose escalation (DE) part of the First in Human, Phase I/II DIAMOND-01 trial (CLI24-001, NCT03008187, EudraCT No. 2019-000941-10), SEL24/MEN1703 demonstrated an acceptable safety profile up to the recommended dose (RD) of 125 mg along with initial evidence of single agent activity and meaningful target engagement in heavily pre-treated AML patients (pts) (Solomon et al, EHA 2020; Tomirotti et al, ASH 2020). Here we present updated data including pts enrolled in the Phase II, cohort expansion (CE) of the study.

• **Aims:** The key objectives of the CE part of the study were the confirmation of the safety profile determined in the DE part along with further investigation of the single agent activity.

• **Methods:** DIAMOND-01 trial enrolled pts unsuitable for chemotherapy having relapsed or refractory (R/R) (DE and CE) or previously untreated (DE) AML. Previous target therapies were allowed with the only exception of previous PIM inhibitors treatments. SEL24/MEN1703 was given orally, QD, 14 days ON / 7 days OFF until disease progression/unacceptable toxicity. In the DE of the study MEN1703 escalating doses ranging from 25 to 150 mg were tested, whereas in the CE the RD (125 mg) was administered. Adverse events (AEs) were graded according to NCI/CTCAE v.4.03; responses assessed as per ELN 2017 criteria.

• **Results:** As of January 21, 2021 (cut-off date), n=48 pts were treated across DE (n=25) and CE (n=23). All pts signed the informed consent form prior to undergoing any study procedure. Median age was 69 (25-84) years. Overall, 20 (43%) and 15 (32%) pts had non de novo AML and primary refractory AML, respectively. Adverse karyotype was reported in 7 (15%) pts. Most frequently reported mutations were FLT3/ITD (23%, n=11), DNMT3A (15% n=7), NPM1 (15%, n=7), IDH1 (13%, n=6) and IDH2 (4%, n=2), CEBPA (4%, n=2), FLT3/TKD (2%, n=1). Median number of cycles was 2 (1-8). At the RD (n=30), most frequent serious treatment-emergent AEs (serious TEAEs) were pneumonia (23%), sepsis and febrile neutropenia (13%) and pulmonary mycosis (10%), whereas most frequent G≥3 TEAEs were febrile neutropenia and pneumonia (23%), leukocytosis (20%) and neutrophil count decrease, platelet count decrease, lymphocyte count decrease and sepsis (13%). Responses occurred in 2 pts in the CE, both with IDH1 mutant disease (naïve to IDH inhibitors) who achieved complete remission with incomplete hematologic recovery (CRi). Both responses occurred by Cycle 3, with a duration of 79 (ongoing at cut-off date) and 43 days, respectively. Across DE and CE, 4 CR/CRi occurred, three of which in pts with IDH mutations. A total of 3 out of 6 pts with IDH mutations treated at doses ≥75 mg achieved CR/CRi, including a CR in a patient with IDH2 mutant AML relapsed on Enasidenib.

• **Summary/Conclusion:** SEL24/MEN1703 confirmed a manageable safety profile at RD and showed preliminary single agent efficacy in R/R AML, particularly clustering in pts with IDH mutant disease either naïve or previously exposed to IDH inhibitors. These results warrant further investigation of SEL24/MEN1703 in AML, with potential focus in the IDH mutated subset.
Small Molecule Platform with Focus on Synthetic Lethality
**Integrated Ryvu Discovery Engine**

**TARGET IDENTIFICATION AND VALIDATION**

- **✓ MultiDEP**: proprietary bioinformatic engine
  - Discovery of novel synthetic lethal target pairs
  - Enables multicomponent and multigene analysis to provide comprehensive, large scale analysis, unprecedented among competitors

**DRUG DISCOVERY**

- Integrated, multidisciplinary processes: rapid lead identification/optimization with deep translational biology support
- Platform has delivered 2 projects in clinical development; multiple projects in discovery/research
- Team of ~150 scientists (with ~80 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**
- • WRN, cancers with MTAP-deletion

**Immuno-Oncology**
- • HPK1, STING
Ryvu strategically utilizes synthetic lethality phenomenon to access new treatment modalities

**Loss of function mutation in Gene X leads to Gene Y addiction in cancer cells**

- **Cancer Cells**
- **Gene X**
- **Gene Y**
- **Cancer Cell Phenotype**

- **Viable**
- **Viable**
- **Lethal**

Synthetic lethal compounds selectively kill cancer cells by targeting tumor cell-essential processes, but leave healthy cells unharmed.

**Predominantly Oncogenes**
- Neomorphic activity
- Hyperactivity
- Aberrant expression

**Lack of Rational Options for Cancers Driven By:**
- Undear dominant oncogenic event
- Non-druggable oncogenes
- Mutations in tumor suppressors/loss of function mutations

**~40k Proteins in Human Genome** (Gencode/NCBI)

**~20k Protein-Coding Genes**

**~2k Druggable Genome**

**~60 Drug Targets**

**~293 Cancer Driver Genes** (Bailey, Cell 2018)

**>99% SNVs Passenger Mutations**
Small molecule inhibitors of WRN

WRN INHIBITORS PROGRAM IN RYVU

**KEY RATIONALE**
- Synthetic lethality of WRN with microsatellite instability (MSI-high)

**MoA**
- WRN inhibitors of ATPase activity selectively targeting tumors with microsatellite instability (MSI)

**NOVELTY**
- First or best-in-class potential Focus on anti-targets selectivity (RecQ)

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

**BIOMARKERS**
- Distal biomarker developed

**DEVELOPABILITY**
- Target druggable with small molecules Multiple hits identified from HTS

**STATUS**
- Hit to lead generation ongoing

WRN INHIBITORS OF ATPase ACTIVITY SELECTIVELY TARGETING TUMORS WITH MICROSATELITE INSTABILITY

HELICASE FUNCTION VALIDATED IN VITRO AS CRITICAL REQUIREMENT

- Ryvu identified several preliminary small molecule hits – first-in-class inhibitors of WRN ATPase activity

- Distal PD biomarker developed, battery of in vitro assays being developed

- Discovery engine: Rational med.-chem hit-to-lead expansion

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

- Chan 2019

**Chan 2019**
Small molecules for MTAPdel cancers

MTAP deletion PROGRAM IN RYVU

<table>
<thead>
<tr>
<th>KEY RATIONALE</th>
<th>MAT2A – the only pharmacologically validated synthetic lethal target in context of MTAP deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoA</td>
<td>Undisclosed targets being pursued</td>
</tr>
<tr>
<td>NOVELTY</td>
<td>Best-in-class potential Strong differentiation</td>
</tr>
<tr>
<td>TOP TUMOR INDICATIONS</td>
<td>MTAP deletions, up to 15% of all cancers, one of the largest genetically defined population: pancreatic, lung, DLBCL, bladder, esophageal (by %: mesothelioma, GBM)</td>
</tr>
<tr>
<td>BIOMARKERS</td>
<td>MTAP and p16 status SAM (plasma), SDMA (tissue) levels</td>
</tr>
<tr>
<td>DEVELOPABILITY</td>
<td>Target druggable with small molecules Selective inhibitors identified</td>
</tr>
<tr>
<td>STATUS</td>
<td>Hit to lead generation ongoing</td>
</tr>
</tbody>
</table>

RYVU HAS IDENTIFIED UNIQUE INHIBITORS WITH CLEAR DIFFERENTIATION AND STRATEGY VS CLINICAL COMPETITORS

1. Several patentable chemical series, confirmed biomarker inhibition
2. Full in vitro pharmacology cascade in place, crystallography and in vivo pharmacology up and running
3. MAT2A: Strong selectivity vs putative TOX TARGET identified by Ryvu (to possibly avoid Agios clinical DLT)
   - Target #2 currently at hit ID and confirmation stage

RYVU MAT2A HIT cmpd exhibits synthetic lethal phenotype: differential activity in isogenic pair in HCT116 (3D)

![Graph showing differential activity in isogenic pair in HCT116 (3D)](image)
Ryvu has selective, potent HPK1 inhibitors with anti-tumor efficacy in mice

**RYVU APPROACH**

**STATUS**

**APPROACH**

- Small molecule, selective, orally bioavailable inhibitors of HPK1 kinase activity

**CURRENT DIFFERENTIAL FACTORS**

- High selectivity against kinases from TCR pathway
- Immunostimulatory activity in immunosuppressed, resistant hPBMC and T cells across species

**MILESTONES FOR HPK1 INHIBITOR**

<table>
<thead>
<tr>
<th>Year</th>
<th>Lead Optimization</th>
<th>Preclinical Development</th>
<th>Initiation of IND-Enabling Studies</th>
<th>IND Filing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2 2022</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2023</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2023+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EFFICACY IN CT26 (MOUSE MODEL OF COLON CANCER)**

- Controls
- UHN Reference
- RVU-293

**COMBINATION WITH ANTI-mPD-1**

- 75 mg/kg BID, 21 days
- TGI = 60.9%

- 100 mg/kg BID, 21 days
- TGI = 69.8%

*Currently Treadwell Therapeutics, in phase I clinical trials

**RYVU SMALL MOLECULE HPK1 INHIBITORS SHOW EFFICACY IN MOUSE SYNGENEIC MODEL COMPARABLE TO CLINICAL REFERENCE COMPOUND**

<table>
<thead>
<tr>
<th></th>
<th>RVU-518</th>
<th>RVU-293</th>
<th>UHN</th>
<th>Takeda/Ariad</th>
<th>Genentech</th>
<th>Incyte</th>
<th>Bayer</th>
</tr>
</thead>
<tbody>
<tr>
<td>hHPK1</td>
<td>1.0</td>
<td>1.4</td>
<td>2.7</td>
<td>0.55</td>
<td>4.5</td>
<td>33</td>
<td>2.9</td>
</tr>
<tr>
<td>Ki[nM]</td>
<td>0.1</td>
<td>0.3</td>
<td>0.7</td>
<td>0.1</td>
<td>1.6</td>
<td>20.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* RVU-918
* RVU-293
* UHN Reference

**HPK1 IC50 [nM]**

- 1.0
- 1.4
- 2.7
- 0.55
- 4.5
- 33
- 2.9

**HPK1 Ki [nM]**

- 0.1
- 0.3
- 0.7
- 0.1
- 1.6
- 20.7
- 0.4
Small molecule, direct, systemic STING agonists with strong anti-tumor efficacy

RYVU APPROACH

STATUS

Approach

CURRENT DIFFERENTIAL FACTORS

IP RIGHTS STATUS

PRECLINICAL CANDIDATE

- Small molecule, systemic, direct STING agonists amenable to ADC technology
- Superior in vitro activity and anti-tumor efficacy
- Suitable either for systemic or targeted delivery
- Several patent applications covering broad chemical estate filed, initial FTO confirmed

KEY DIFFERENTIATION

Small molecule, direct, systemic STING agonists with multiple routes of administration (IV, SC, IT) allowing two tracks of development:

- standalone systemic treatment
- using targeted delivery as payload for antibodies (antibody-drug conjugates ADC approach)

Systemic efficacy in mouse models on par with GSK reference (IV) and outperforming Aduro/Novartis agonist (IT) accompanied with favorable safety profile

Active across multiple STING haplotypes to target broad patient population

Well protected IP and confirmed initial FTO space

Selected properties of Ryvu STING agonists

<table>
<thead>
<tr>
<th>Generation</th>
<th>III generation</th>
<th>II generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example compounds</td>
<td>Ryvu-24024</td>
<td>Several candidates</td>
</tr>
<tr>
<td>ChemoType</td>
<td>Non CDN small molecule</td>
<td>Non CDN small molecule</td>
</tr>
<tr>
<td>Development approach</td>
<td>SINGLE AGENT, With functional handle ADC-AMENABLE</td>
<td>SINGLE AGENT</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>~600</td>
<td>~300</td>
</tr>
<tr>
<td>drugP/drugD</td>
<td>3.7 / 3.4</td>
<td>2.9-4.0 / 2.4-3.5</td>
</tr>
<tr>
<td>FTS Atn [°C] 50pM</td>
<td>11 / 17</td>
<td>28-30 / 16-21*</td>
</tr>
<tr>
<td>human/mouse STING</td>
<td>0.051</td>
<td>0.24-0.31</td>
</tr>
<tr>
<td>HMDC IFN EC50 [µM]</td>
<td>0.39</td>
<td>0.017-0.027</td>
</tr>
<tr>
<td>TMF IRF EC50 [µM]</td>
<td>0.24</td>
<td>0.030*</td>
</tr>
<tr>
<td>In vovo antTumor efficacy</td>
<td>confirmed</td>
<td>confirmed</td>
</tr>
<tr>
<td>General characteristic</td>
<td>Potent human STING agonist; lower potency on murine STING protein</td>
<td>Highly potent mouse STING agonist; lower potency on human STING</td>
</tr>
</tbody>
</table>

* Data currently available for selected compounds
## Broad pipeline addressing emerging targets in oncology

Ryu drives value creation from its multiple data readouts

<table>
<thead>
<tr>
<th>Program/target name</th>
<th>Indication</th>
<th>Discovery and preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Partners / Collaborators</th>
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</thead>
<tbody>
<tr>
<td>SEL24 (MEN1703) PIM / FLT3</td>
<td>AML</td>
<td></td>
<td></td>
<td></td>
<td>• Ph. II interim data</td>
</tr>
<tr>
<td>RVU120 CDK8</td>
<td>AML / MDS</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td>• Initial Ph. Ib data</td>
</tr>
<tr>
<td>MTAP</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>• Hit-to-lead</td>
</tr>
<tr>
<td>WRN</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>• Hit-to-lead</td>
</tr>
<tr>
<td>HPK1</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>• Lead optimization</td>
</tr>
<tr>
<td>STING</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>• IND-enabling studies</td>
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</table>

### Anticipated Milestones

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<tr>
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<th>2021</th>
<th>2022+</th>
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</thead>
<tbody>
<tr>
<td>Clinical stage assets</td>
<td>2</td>
<td>3+</td>
</tr>
<tr>
<td>Human PoCs</td>
<td>2</td>
<td>3+</td>
</tr>
<tr>
<td>Early pipeline programs</td>
<td>7+</td>
<td>10+</td>
</tr>
</tbody>
</table>
# Ryvu R&D Center for Innovative Drugs

## Move completed in July 2020

<table>
<thead>
<tr>
<th>2017</th>
<th>August 2018</th>
<th>April 2020</th>
<th>June 2020</th>
<th>July 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparations for the investment; obtaining a grant from the Ministry of Development</td>
<td>Initiation of construction works</td>
<td>Completion of major construction works</td>
<td>Obtained occupation permits, first laboratories launched</td>
<td>All labs and offices fully operational</td>
</tr>
</tbody>
</table>

- **Usable area of the Center**: > 86,000 sq. ft
- **# workplaces**: ~300 associates
- **Investment budget**: > $20m
- **Value of the grant from the Polish Ministry of Development**: ~$9m

- Investment initiated in 2017 – before the corporate split from Selvita CRO
- Provides Ryvu with adequate and consolidated research infrastructure
- Has enabled the spin-out of Selvita (CRO) and value creation of >$100m for Ryvu shareholders
- Ryvu has secured funds for investment from joint pre-split cash balance

---

*Exchange rate used – average NBP for 2019 – 1 USD = 3.8395 PLN*
### Financial results & employment

<table>
<thead>
<tr>
<th></th>
<th>$ million</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2020</td>
</tr>
<tr>
<td><strong>Revenues</strong></td>
<td>9.6</td>
</tr>
<tr>
<td><strong>Partnering</strong></td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Grants</strong></td>
<td>5.5</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>18.7</td>
</tr>
<tr>
<td><strong>EBIT</strong></td>
<td>-9.2</td>
</tr>
<tr>
<td><strong>EBITDA</strong></td>
<td>-6.0</td>
</tr>
<tr>
<td><strong>CAPEX</strong></td>
<td>-9.5</td>
</tr>
</tbody>
</table>

**Cash position**  
May 5, 2021  
$32.6M  

**Available grant funding**  
>$25M  

**Financing secured until**  
Q1 2023
### Ryvu investment highlights and near term milestones

- **Developing small molecule therapies which address high value emerging targets and pathways in oncology**
- **Diverse pipeline targeting kinases, synthetic lethality and immuno-oncology**
- **First-in-class selective CDK8 inhibitor (RVU120) with potential across multiple indications**
- **Validation from strategic collaborations including partnership with Menarini on SEL24(MEN1703)**
- **Extensive early stage pipeline delivering near term clinical candidates**
- **Robust internal drug discovery engine and partnership options for early-stage candidates**
- **Limited cash burn thanks to non-dilutive grants and cost-efficient discovery platform, significant resources located in Poland**

---

![Diagram](image)

**SEL24(MEN1703)**
- Phase II PoC data at EHA 2021

**RVU120**
- Phase I interim data at EHA 2021

**New programs expected to enter the clinic in 2022**
- Additional near-term PC and late discovery targets
- Partnering deals in the early pipeline
Excellent on-target activity of SEL120 in pSTAT positive AML cell models

SEL120 is a potent and selective CDK8/CDK19 inhibitor

Low nM activity on CDK8/CDK19 and excellent kinase selectivity (broad kinome)

- Spares CDK2, CDK4, CDK6, CDK7, CDK9, etc.
- Type I, ATP-competitive mechanism of binding and inhibition of CDK8/19 activity
- Lack of binding to off-targets potentially associated with toxicity of pre-clinical EMD Serono CDK8/19 inhibitors (such as JNK1 or GSK3b)\(^1\)
  - Higher selectivity based on comparison of gene expression effects\(^2\)
- Composition of matter patents granted in 2017

pSTAT1/pSTAT5 levels discriminate responder/ non-responder

1Chen et al. 2019
2Rzymski et al. 2017
SEL120 induces complete regression and bone marrow recovery in AML
In CD34+ AML patient-derived xenografts

PDX cells → NSG mice
Vehicle / SEL120
Dose: 45mg/kg
17 days latency
Daily treatment 29/30 days
Leukemia burden analysis

<table>
<thead>
<tr>
<th>COMPLETE REGRESSION (PERIPHERAL BLOOD)</th>
<th>HEMATOLOGIC RECOVERY (BONE MARROW)</th>
<th>REDUCED SPLENOMEGALY</th>
</tr>
</thead>
</table>

- **TUMOR GROWTH KINETICS**
  PERIPHERAL BLOOD

- **BODY WEIGHT CHANGE**

- **BONE MARROW**

- **SPLEEN**

Research performed at: RYUU THERAPEUTICS
SEL120 strongly synergizes with Venetoclax

**Compelling potential for SEL120 in combination with Venetoclax**

**SEL120 potentially addresses treatment resistant disease through safe, indirect MCL-1 downregulation in cancer cells**

**MV-4-11 cells**

**Venetoclax, 100 mg/kg QD, po + SEL120, 40 mg/kg QD, po**

**NSG mice**

**SEL120+Venetoclax Daily, PO, 21 days**

**Leukemia burden analysis**

**COMPLETE REGRESSION**

**HEMATOLOGIC RECOVERY (BONE MARROW)**

**Human cells in bone marrow**

**Murine cells in bone marrow**