Targeted therapeutics at the forefront of oncology

CORPORATE PRESENTATION

July 2021
Note on the presentation and forward looking statements

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**Clinical Pipeline Across Heme and Solid Tumors**

<table>
<thead>
<tr>
<th>RVU120</th>
<th>SEL24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wholly owned, first-in-class, selective, oral CDK8/19 inhibitor</td>
<td>First-in-class dual PIM/FLT3 kinase inhibitor for AML in Phase II</td>
</tr>
<tr>
<td>Clinical data in 2021 from Phase Ib study in AML/MDS</td>
<td>Single agent efficacy and acceptable safety profile demonstrated in r/r AML</td>
</tr>
<tr>
<td>Solid tumor Phase Ib study in start-up phase</td>
<td>Partnered with Menarini</td>
</tr>
</tbody>
</table>

**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, PRMT5, Novel SL targets
- **Immuno-Oncology**
  - HPK1, STING

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

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**Listed on Warsaw Stock Exchange, market cap of $290m**

- 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)

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1 09 June 2021. Exchange rate (NBP): 1$=PLN3.67
2 05 May 2021
# 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>
</tr>
</thead>
<tbody>
<tr>
<td>SEL24 (MEN1703) PIM/FLT3</td>
<td>AML</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II interim data 2021</td>
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<tr>
<td>RVU120 CDK8/19</td>
<td>AML/MDS</td>
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<td>Initial Phase I data H1 2021</td>
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<tr>
<td></td>
<td>SOLID TUMORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Initiation of Phase I 2021</td>
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## DISCOVERY & PRECLINICAL PROJECTS

### SYNTHETIC LETHALITY

<table>
<thead>
<tr>
<th>PROGRAM / TARGET NAME</th>
<th>INDICATION</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
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<th>PHASE II</th>
<th>PARTNER</th>
<th>ANTICIPATED MILESTONES</th>
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<tbody>
<tr>
<td>PRMT5</td>
<td>SOLID TUMORS</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>WRN</td>
<td>SOLID TUMORS</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NOVEL TARGETS</td>
<td>ONCOLOGY</td>
<td></td>
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</tbody>
</table>

### IMMUNO-ONCOLOGY

<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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</thead>
<tbody>
<tr>
<td>HPK1</td>
<td>SOLID TUMORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pre-clinical candidate 2022</td>
</tr>
<tr>
<td>STING</td>
<td>SOLID TUMORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IND filing 2022</td>
</tr>
</tbody>
</table>

## 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
- RVU120 — orphan drug designation in AML by FDA

04.2020
- Collaboration with Galapagos in inflammatory disorders announced

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 approved for RVU120 AML/MDS Phase Ib sites in Europe

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

05.2021
- Clinical Trial Application approved for RVU120 study in solid tumors

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
### Clinical landscape: targeted small molecule therapies for AML

<table>
<thead>
<tr>
<th>Clinical Programs</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVU120 is the only CDK8/CDK19 inhibitor in clinical development</td>
<td>✔</td>
</tr>
<tr>
<td>SEL24(MEN1703) is a unique, clinical-stage dual PIM/FLT3 inhibitor</td>
<td>✔</td>
</tr>
</tbody>
</table>

**RYVU 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

<table>
<thead>
<tr>
<th>Target</th>
<th>Phase 1/2</th>
<th>Phase 3</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK8/CDK19</td>
<td>RYVU Therapeutics</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>FLT3</td>
<td>Hanmi</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Dual PIM/FLT3</td>
<td>RYVU Therapeutics</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PIM</td>
<td>Novartis, Incyte, Forma Therapeutics</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>IDH1 or IDH2</td>
<td>Tibsoyo, IDHIFA</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Others</td>
<td>APTOS, Oryzon, GlycoMimetics, Inc., AstraZeneca, MEI, Rafael, Syros, Venclexta</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
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>
</tr>
</thead>
<tbody>
<tr>
<td>• AML</td>
<td>• Breast</td>
<td>• Diamond-Blackfan Anemia (DBA)</td>
</tr>
<tr>
<td>• JAK2 mut AML/MPN</td>
<td>• Colorectal</td>
<td></td>
</tr>
<tr>
<td>• MDS</td>
<td>• Prostate</td>
<td></td>
</tr>
<tr>
<td>• ALL, NHL</td>
<td>• Other</td>
<td></td>
</tr>
</tbody>
</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

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**Orphan drug designation in AML in 2020**

**Therapy Acceleration Program (TAP) grant support**

**Total funding: $3.25m**
RVU120: Preclinical data support key clinical features

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

RVU120 is a potent and selective CDK8/CDK19 inhibitor

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

**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

RVU120 induces **complete regression and bone marrow recovery** in AML PDX models in vivo

Experiments performed in CD34+ AML patient-derived xenografts:

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

RVU120 induces complete regression and bone marrow recovery in AML PDX models in vivo

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
RVU120: Phase Ib study – initial data at EHA 2021
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

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

STATUS AND PLANS

5 SITES IN US

SITE EXPANSION in EUROPE
2 sites in Poland – CTA application approval obtained in January 2021
RVU120 Phase I AML/MDS study (CLI120-001) design

**PART 1: ESTABLISHING RECOMMENDED PHASE 2 DOSE (RP2D)**

**H2 2019-2021**

- **COHORT 1**
  - Average of 24 PATIENTS
- **COHORT 2**
- **COHORT 3**
- **UP to 8 COHORTS**

**ORAL DOSE**

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

**EXPANSION FROM THE SINGLE PATIENT COHORT TO A 3+3 DESIGN**

DLTs evaluated at completion of cycle 1 in each cohort

**PART 2: SAFETY EXPANSION**

**Q1-Q2 2022**

- **6 PATIENTS**

**SAFETY, EFFICACY, PK, PD**

**RP2D MTD**

**SAFETY EXPANSION**

**2022 START**

**PHASE II**

- **PART 1: ESTABLISHING RECOMMENDED PHASE 2 DOSE (RP2D)**
- **PART 2: SAFETY EXPANSION**

**AML SINGLE AGENT**

- AML COMBINATION
  - Front line: Triplet with venetoclax

**MDS SINGLE AGENT**

- MDS COMBINATION
  - Front Line with SOC HMAs

**PHASE II**

- **H2 2019-2021**
  - **Q1-Q2 2022**

**2022 START**

- Average of 24 PATIENTS

**EVALUATION**
RVU120/SEL120 PRELIMINARY RESULTS FROM INITIAL DOSE ESCALATION COHORTS of CLI120-001 TRIAL: A PHASE1b STUDY OF SEL120/RVU120, SELECTIVE CDK 8/19 INHIBITOR, IN PATIENTS WITH AML OR HIGH RISK MDS

N.Angelosanto,1 C.Abboud,2 G.Borthakur,3 S.Solomon4, W. Donnellan,5 J. Bendell,5 A. Nazha,6 A.Gerds,6 T. Bradley,7 J. M.Zaucha,6 E. Lech Maranda 8 K.Brzózka,1 T.Rzymski,1 J.Dow,1 E. Mouhayar,3 S.Shamsili1

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Cohort No</th>
<th>Patient ID</th>
<th>Dose (mg)</th>
<th>Diagnosis</th>
<th>Age (yrs)</th>
<th>ECOG (PS)</th>
<th>Risk category/ Karyotype/Mutations</th>
<th>Previous line of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100-003</td>
<td>10</td>
<td>HR-MDS</td>
<td>78</td>
<td>1</td>
<td>Poor/IPSS-R &amp; S</td>
<td>2 (Aza/tcydine/ CD33-CD3 bispic ab)</td>
</tr>
<tr>
<td>1</td>
<td>101-001</td>
<td>10</td>
<td>AML</td>
<td>74</td>
<td>1</td>
<td>Adverse/ Complex/ TPS3mut()</td>
<td>3 (Cytabrane / Dectabrine, Cytabrane / Cladrbrine/ CD33-CD3 bispic ab)</td>
</tr>
<tr>
<td>2</td>
<td>102-001</td>
<td>25</td>
<td>AML</td>
<td>54</td>
<td>2</td>
<td>Adverse/ inv3+14 trisyomy</td>
<td>3 (Flag/iداء, Dectabine, Cytabrane/ Venetoclax)</td>
</tr>
<tr>
<td>3</td>
<td>103-001</td>
<td>50</td>
<td>HR-MDS</td>
<td>81</td>
<td>2</td>
<td>Normal/ IPSS-R 6</td>
<td>2 (Aza/tcydine, Dectabine/ Venetoclax)</td>
</tr>
<tr>
<td>4</td>
<td>103-002</td>
<td>75</td>
<td>AML</td>
<td>62</td>
<td>0</td>
<td>Intermediate/ Normal/ NPM1, FLT3-ITD</td>
<td>3 (Cytabrane / Idarubicin / Midostaurin, Giltertinib, Dectabine/ Venetoclax)</td>
</tr>
</tbody>
</table>

SAFETY

• No DLTs were observed, 4 SAEs were reported/assessed by the investigator as unlikely or not related to study drug

PK ANALYSIS

➢ PK analysis performed using plasma samples collected at C1D1 and C1D13
➢ Relatively rapid absorption, linear exposure with doses between 10-75 mg, plasma half-life from 22 to 40 hr
➢ Low accumulation, based on half-life or the ratio of AUC D13/ D1;
➢ Low within patient variability of plasma concentrations of RVU 120, over at least 6 cycles
**RVU120 Phase I data show early signs of efficacy in AML and MDS**

Of the first five patients enrolled (across the first four dose cohorts), clinically relevant responses were seen in patients in the two higher dose cohorts:

- **Cohort 3 patient** (50mg, escalated to 75mg): HRMDS, demonstrated an **erythroid response**
- **Cohort 4 patient** (75mg): R/R AML, response in C2 improved to **Complete Response (CR)** in C7

<table>
<thead>
<tr>
<th>Cycles completed/Response/Reason for discontinuation</th>
<th>Data cutoff: 20 May 2021</th>
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<tbody>
<tr>
<td>Cohort # 1: 1-10 mg q2 100-003 (HR: MDS)</td>
<td>SD</td>
</tr>
<tr>
<td>Cohort # 1: 1-10 mg q2 100-001 (AML)</td>
<td>SD PD</td>
</tr>
<tr>
<td>Cohort # 2: 25 mg q2 100-001 (AML)</td>
<td>SD</td>
</tr>
<tr>
<td>Cohort # 3: 50 mg q2 100-001 (HR: MDS)</td>
<td>SD + ER</td>
</tr>
<tr>
<td>Cohort # 4: 75 mg q2 100-002 (AML)</td>
<td>+ ER</td>
</tr>
</tbody>
</table>

**Treatment Status**
- Discontinued due to progressive disease (PD)
- Discontinued due to relapsed disease (R)
- Discontinued for reasons other than progressive/relapsed disease (e.g. unacceptable toxicity, PI Decision/Death)
- Treatment ongoing

SD = Stable Disease, PD = Progressive Disease, *CRI = Complete Remission with incomplete hematological recovery and skin leukemia, *CR = Complete Remission except for skin leukemia, C R = Complete Remission, ER = Erythroid Response, R = Relapsed Disease.
**Case Focus: Cohort 4 AML patient achieved CR despite poor prognostics**

**COHORT 4 AML PATIENT:**

- FLT3+ and NPM1+ AML
- Failed 3 prior lines of therapy, including 2 FLT3 inhibitors and venetoclax+decitabine – known to be associated with poor prognosis (median OS 2.4 months\(^1\))
- Received 75mg dose
- Showed **fast clearance of bone marrow blasts** at C1D17, and **recovery in platelets and absolute neutrophil count (ANC) from C2**, but due to skin leukemia lesions, no CR was reportable at that time
- Skin leukemia gradually improved under RVU120 treatment up to **complete resolution in C7**, achieving a CR
- Patient progressed at the end of C8.


Case Focus: Cohort 3 HRMDS patient achieved erythroid response, and remains on study in Cycle 14

- Failed 3 prior lines of therapy, including previous HMA, associated with median OS of 4.5 months
- Received 50mg dose and escalated to 75mg from C7
- Achieved an **erythroid response** according to Cheson Criteria\(^1\) from C5 and maintained *the difference in the number of Red Blood Cells (RBC) units of at least 4 units in 8-week interval period vs baseline requirement* up to C7, with a new increase (but lower than baseline) in transfusion requirement after D15 of C7
- Patient was first dosed on August 26, 2020 and remains on treatment after more than 10 months (C14) with SD

Anemia in chronic hematological diseases may occur due to ineffective erythropoiesis, causing an imbalance in various progenitor and precursor 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.

RVU120 induces erythroid differentiation measured by increasing number of CD47+/CD71+ erythroid lineage cells and gradual decrease of CD34+/CD38- undifferentiated hematopoietic progenitor cells. Erythroid master regulators such as GATA1 are transcriptionally induced by RVU120 by the mechanism involving displacement of CDK8 from TSS, which can be occupied by Pol2.

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

CDK8/19 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: development in solid tumors and other heme malignancies
CTA approved on 28 May 2021; first site activation planned for June
Expecting first patient in Q3 2021; preliminary results in 2022

**PART 1: ESTABLISHING RECOMMENDED DOSE**

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

**PART 2: EFFICACY & SAFETY EXPANSION SIMON 2-STAGE**

STAGE 1
14 PATIENTS
R/R mTNBC

STAGE 2
UP TO 20 PATIENTS

- UP TO 3 OTHER SOLID TUMORS
- +10 PATIENTS

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

**EVALUATION**

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

**SCREENING**

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

**2021**

**2022**

H2 2020

- SINGLE ORAL DOSE EOD
- 7 DOSES/CYCLE
- 3 WEEK CYCLE

- SAFETY, EFFICACY, PK, PD

- RP2D determined

**RP2D determined**
SEL24(MEN1703) is a differentiated, first-in-class PIM/FLT3 dual kinase inhibitor

1. PIM and FLT3 are oncogenes involved in AML
2. Dual targeting creates potential for broader activity, more durable responses than selective FLT3 inhibitors such as gilteritinib
3. Potential for treating patients that have relapsed on selective FLT3 inhibitors – PIM kinases are largely responsible for the development of resistance to FLT3 inhibitors

PHASE I/II CLINICAL STUDY

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 I/II STUDY (ASH 2020, 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).
- Confirmed pS6 biomarker inhibition
- Across DE and CE, 4 CR/CRi occurred, three of which in pts with IDH mutations.
- A total of 3 out of 5 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.
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

SCOTT SOLOMON,1 PAU MONTESINOS,2 AZIEM NAZHA,3 STEPHEN STRICKLAND,4 GIOVANNI MARTINELLI,5 ARMANDO SANTORO,6 ROLAND WALTER,7 RACHEL COOK,8 SUSANA VIVES,10 SALMAN FAZAL,11 KRZYSZTOF BRZÓZKA,12 SETAREH SHAMSILI,12 SIMONE BALDINI,13 ANDREA PELLACANI,13 FARHAD RAVANDI,14

DEMOGRAPHICS AND BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>All (n=48)</th>
<th>125 mg (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>69 (25-84)</td>
<td>69.5 (38-83)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for inclusion, n (%)</th>
<th>All</th>
<th>125 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed AML</td>
<td>3 (6.3%)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Primary refractory AML</td>
<td>16 (33.3%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Relapsed AML</td>
<td>29 (60.4%)</td>
<td>21 (70.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AML status, n (%)</th>
<th>All</th>
<th>125 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo AML</td>
<td>27 (56.3%)</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td>Non De novo AML</td>
<td>21 (43.7%)</td>
<td>14 (46.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytogenetics, n (%)</th>
<th>All</th>
<th>125 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>7 (14.6%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>6 (12.5%)</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>22 (45.8%)</td>
<td>15 (50.0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (22.9%)</td>
<td>8 (26.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most frequent mutations, n (%)</th>
<th>All</th>
<th>125 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3/ITD</td>
<td>12 (25.0%)</td>
<td>8 (26.7%)</td>
</tr>
<tr>
<td>FLT3/TKD</td>
<td>1 (2.1%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>7 (14.6%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>IDH1</td>
<td>6 (12.5%)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>IDH2</td>
<td>2 (4.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>NPM1</td>
<td>7 (14.6%)</td>
<td>5 (16.7%)</td>
</tr>
</tbody>
</table>

48 patients were treated: in DE (n = 25) and in CE (n = 23) part

Data cut-off date: April 19, 2021

At RD, SEL24/MEN1703 showed a manageable safety profile with most Grade ≥3 treatment-emergent AEs (TEAEs) being hematologic or infectious

Grade ≥3 TEAEs (incidence >10%) at RD (125 mg, N=30)

<table>
<thead>
<tr>
<th>Preferred Term (PT)</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>9/30(30.0%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9/30(30.0%)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>6/20(30.0%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4/3(13.3%)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>4/3(13.3%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>4/3(13.3%)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>4/3(13.3%)</td>
</tr>
</tbody>
</table>
SEL24 (MEN1703) showed single agent efficacy in R/R AML patients, in particular in IDH+ population

- Objective responses have been reported in 4 out of 48 patients (8%) across DE and CE phases, with 3 out of 4 responders harboring IDH mutations
- Median number of cycles in responding patients was 7 (Range 7-8)
- 3 out of 5 patients with IDH mutations treated at doses 75-125 mg achieved CR/CRi, including a CR in a patient relapsed on enasidenib
- 1 patient with IDH1 mutation achieved CRi and underwent allogeneic-HSCT

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Dose Level</th>
<th>AML Status</th>
<th>Reason for inclusion</th>
<th>Cytogenetics</th>
<th>Mutations</th>
<th>No of cycles</th>
<th>Response by cycle #</th>
</tr>
</thead>
<tbody>
<tr>
<td>004-012</td>
<td>81</td>
<td>75 mg</td>
<td>de novo AML</td>
<td>Relapsed AML</td>
<td>Intermediate</td>
<td>DNMT3, IDH2, ASXL1, CUX1, DDX41 (C.3G&gt;A, R525H), EZH2, PRPF8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>004-022</td>
<td>75</td>
<td>125 mg</td>
<td>AML post MDS</td>
<td>Relapsed AML</td>
<td>Unfavourable</td>
<td>IDH1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>401-031</td>
<td>63</td>
<td>125 mg</td>
<td>AML post MDS</td>
<td>Relapsed AML</td>
<td>Unfavourable</td>
<td>IDH1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>401-034</td>
<td>55</td>
<td>125 mg</td>
<td>de novo AML</td>
<td>Relapsed AML</td>
<td>Unfavourable</td>
<td>IDH1</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

SEL24 (MEN1703) as single agent showed preliminary efficacy in R/R AML, particularly clustering in patients with IDH mutant disease

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

✓ **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

✓ 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

✓ 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, PRMT5, Novel SL targets

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

- PREDOMINANTLY ONCOGENES
  - Neomorphic activity
  - Hyperactivity
  - Aberrant expression

- LACK OF RATIONAL OPTIONS FOR CANCERS DRIVEN BY:
  - Unclear dominant oncogenic event
  - Non-druggable oncogenes
  - Mutations in tumor suppressors/loss of function mutations

- LOSS-OF-FUNCTION MUTATION IN GENE X LEADS TO GENE Y ADDICTION IN CANCER CELLS
  - Synthesis lethal compounds selectively kill cancer cells by targeting tumor cell-essential processes, but leave healthy cells unharmed.
Small molecule inhibitors of WRN

WRN INHIBITORS PROGRAM IN RYVU

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

WRN INHIBITORS OF ATPase ACTIVITY SELECTIVELY TARGETING TUMORS WITH MICROSATELITE INSTABILITY

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

Helicase function validated in vitro as critical requirement

Ryuv 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

Chan 2019
MTAPdel cancers – PRMT5 SL inhibitors

<table>
<thead>
<tr>
<th>KEY RATIONALE</th>
<th>PRMT5 MTA-cooperative inhibitors exert synthetic lethal phenotype in MTAP deleted cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoA</td>
<td>MTA-cooperative inhibitors</td>
</tr>
<tr>
<td>NOVELTY</td>
<td>Best-in-class potential (vs Mirati, Tango)</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, oesophageal (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 Ryvu SL PRMT5 inhibitors identified</td>
</tr>
</tbody>
</table>
| VALUE INFLECTION POINTS | 2021: Hit-to-lead  
2022: Lead, in vivo PoC  
2023: Preclinical candidate |

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

RYVU HIT cmpd exhibits synthetic lethal phenotype: differential PD biomarker inhibition in isogenic pair in HCT116 (3D)

- Patetable chemical series, confirmed biomarker inhibition
- Immediate program kick-off: full in vitro pharmacology cascade in place, PRMT5 crystallography and in vivo pharmacology up and running
- Fast progress possible due to fully developed cascade and chemical properties of hit series.

DATA FROM COMPETITORS

- AACR 2021
- SEC 2021
Ryvu has selective, potent HPK1 inhibitors with anti-tumor efficacy in mice

**RYVU APPROACH**

### STATUS
- LEAD OPTIMIZATION
  - Small molecule, selective, orally bioavailable inhibitors of HPK1 kinase activity

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

**CURRENT MILESTONES FOR HPK1 INHIBITOR**

- **2021**: LEAD OPTIMIZATION
- **2022**: DEVELOPMENT CANDIDATE
- **2023**: IND

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

<table>
<thead>
<tr>
<th>hPK1</th>
<th>RVU-918</th>
<th>RVU-293</th>
<th>TAKEDA/ARAD</th>
<th>GENENTECH</th>
<th>INCYTE</th>
<th>BAYER</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 (nM)</td>
<td>1.0</td>
<td>1.4</td>
<td>2.7</td>
<td>0.55</td>
<td>4.5</td>
<td>33</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>
</tr>
</tbody>
</table>

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

- **CONTROLS**
- **UHN REFERENCE**
- **RVU-293**

**COMBINATION WITH ANTI-mPD1**

- 75 mg/kg BID, 21 days + anti-mPD1 5 mg/kg
  - TGI = 60.9%
- 100 mg/kg BID, 21 days + anti-mPD1 5 mg/kg
  - TGI = 69.8%

*currently Treadwell Therapeutics, in phase I clinical trials*
Small molecule, direct, systemic STING agonists with strong anti-tumor efficacy

**RYVU APPROACH**

<table>
<thead>
<tr>
<th>STATUS</th>
<th>APPROACH</th>
<th>CURRENT DIFFERENTIAL FACTORS</th>
<th>IP RIGHTS STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECLINICAL CANDIDATE</td>
<td>▪ Small molecule, systemic, direct STING agonists amenable to ADC technology</td>
<td>▪ Superior <em>in vitro</em> activity and anti-tumor efficacy</td>
<td>▪ Several patent applications covering broad chemical estate filed, initial FTO confirmed</td>
</tr>
</tbody>
</table>

**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>II generation</th>
<th>III generation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example compounds</strong></td>
<td>Ryvu-24024</td>
<td>Several candidates</td>
</tr>
<tr>
<td><strong>Chemotype</strong></td>
<td>Non-CDN small molecule</td>
<td>Non-CDN small molecule</td>
</tr>
<tr>
<td><strong>Development approach</strong></td>
<td>SINGLE AGENT</td>
<td>SINGLE AGENT, with functional handle ADC-AMENABLE</td>
</tr>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>( &lt;500 )</td>
<td>( &gt;600 )</td>
</tr>
<tr>
<td>( \log P/\log D )</td>
<td>( 3.7 / 3.4 )</td>
<td>( 2.9-4.8 / 2.4-3.5 )</td>
</tr>
<tr>
<td><strong>FTS ATR [(^{\circ})C] 50pM</strong></td>
<td>11 / 17</td>
<td>26-30 / 16-21*</td>
</tr>
<tr>
<td><strong>human/mouse STING</strong></td>
<td>0.051</td>
<td>0.24-0.31</td>
</tr>
<tr>
<td><strong>THP IRI EC50 [( \mu M )]</strong></td>
<td>0.39</td>
<td>0.017-0.027</td>
</tr>
<tr>
<td><strong>HMDI IFN EC50 [( \mu M )]</strong></td>
<td>0.24</td>
<td>0.003*</td>
</tr>
<tr>
<td><strong>In vivo antitumor efficacy</strong></td>
<td>confirmed</td>
<td>confirmed</td>
</tr>
<tr>
<td><strong>General characteristic</strong></td>
<td>Highly potent mouse STING agonist; lower potency on human STING</td>
<td>Potent human STING agonist; lower potency on mouse STING protein</td>
</tr>
</tbody>
</table>

* Data currently available for selected compounds
### Financial results & employment

<table>
<thead>
<tr>
<th></th>
<th>$ million</th>
<th>2020</th>
<th>Q1 2020</th>
<th>Q1 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Revenues</strong></td>
<td></td>
<td>9.6</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Partnering</strong></td>
<td></td>
<td>4.0</td>
<td>2.0</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Grants</strong></td>
<td></td>
<td>5.5</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td>18.7</td>
<td>4.7</td>
<td>5.9</td>
</tr>
<tr>
<td><strong>EBIT</strong></td>
<td></td>
<td>-9.2</td>
<td>-1.3</td>
<td>-4.1</td>
</tr>
<tr>
<td><strong>EBITDA</strong></td>
<td></td>
<td>-6.0</td>
<td>-0.6</td>
<td>-3.4</td>
</tr>
<tr>
<td><strong>CAPEX</strong></td>
<td></td>
<td>-9.5</td>
<td>-1.6</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

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

**Available grant funding**  
>$25M

**Financing secured until**  
Q1 2023
**Broad pipeline addressing emerging targets in oncology**

**Ryvu 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>
</tr>
</thead>
<tbody>
<tr>
<td>SEL24 (MEN1703)</td>
<td>AML</td>
<td></td>
<td></td>
<td></td>
<td>Ph. II interim data</td>
</tr>
<tr>
<td>PIM / FLT3</td>
<td>AML / MDS</td>
<td></td>
<td></td>
<td></td>
<td>Ph. II complete</td>
</tr>
<tr>
<td>RVU120 CDK8</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>Initial Ph. I b data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ph. II initiation</td>
</tr>
<tr>
<td>MTAP</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>Ph. I Initiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ph. I Interim data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ph. II initiation</td>
</tr>
<tr>
<td>WRN</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>Hit-to-lead</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lead optimization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-GLP tox</td>
</tr>
<tr>
<td>HPK1</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>Hit-to-lead</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lead optimization</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Non-GLP tox</td>
</tr>
<tr>
<td>STING</td>
<td>Solid tumors</td>
<td></td>
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<td></td>
<td>Lead optimization</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-GLP tox</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IND-enabling studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ph. I initiation</td>
</tr>
</tbody>
</table>

**Anticipated Milestones**

<table>
<thead>
<tr>
<th>2021</th>
<th>2022+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage assets</td>
<td>Clinical stage assets</td>
</tr>
<tr>
<td>Human PoCs</td>
<td>Human PoCs</td>
</tr>
<tr>
<td>Early pipeline programs</td>
<td>Early pipeline programs</td>
</tr>
</tbody>
</table>
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

---

**SEL24(MEN1703)**
- Phase II PoC data at EHA2021
- Initiation of studies in IDHm subset

**RVU120**
- Phase I interim data in AML at EHA2021
- Initial solid tumor data in H1 2022
- 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

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

- **Complete Regression (Peripheral Blood)**
- **Hematologic Recovery (Bone Marrow)**
- **Reduced Splenomegaly**

**Research performed at:**

- **PDX cells**
- **NSG mice**
- **Vehicle / SEL120**
  - Dose: 45mg/kg
  - 17 days latency
  - Daily treatment 29/30 days

**Leukemia burden analysis**

**Tumor Growth Kinetics**

- Peripheral Blood
- Days: 0 to 30
- %CD45+

**Body Weight Change**

- Days: 0 to 30
- Mean body weight change [% ± SEM]
- Vehicle, QD, po
- SEL120, 45 mg/kg QD, po

**Bone Marrow**

- %CD34+
- Days: 0 to 30
- Control vs SEL120

**Spleen**

- Weight [mg]
- Days: 0 to 30
- Control vs SEL120
SEL120 strongly synergizes with Venetoclax

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

Compelling potential for SEL120 in combination with Venetoclax

MV-4-11 cells IV 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

No of murine BM cells

% hCD45 cells

No of murine BM cells

% hCD45 cells