

CURRENT REPORT 11/2024

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Preclinical data on RVU120 and Synthetic Lethality Programs to be presented at the 2024 AACR Annual Meeting

The Management Board of Ryvu Therapeutics S.A. with its registered office in Krakow, Poland ("Company", "Ryvu") announces that it will present preclinical data from its synthetic lethality pipeline and RVU120 project, at the 2024 AACR Annual Meeting, which takes place April 5-10 in San Diego, California, USA.

The poster presentations include an updated preclinical data from Ryvu's synthetic lethality pipeline, including PRMT5 program in MTAP-Deficient cancers, WRN inhibitors in the treatment of microsatellite unstable (MSI-H) tumors, and its cutting-edge synthetic lethality platform based on primary cancer cells. Furthermore, poster presentations highlight the synergistic effects of RVU120 in combination with ruxolitinib in myeloproliferative neoplasms.

Also, during 2024 AACR Annual Meeting a data on MEN1703 (SEL24), demonstrating promising anti-tumor activity in preclinical models of myelofibrosis both as a single agent and combined with ruxolitinib will be presented by the Company's partner from Italian Menarini Group.

Details on the poster presentations are as follows:

Abstract Title: "Discovery of novel MTA-cooperative PRMT5 inhibitors as targeted therapeutics for MTAP-deleted cancers."

Session Name: HDAC and Methyltransferase Inhibitors

Session date and time: Tuesday, April 9, 9:00 AM - 12:30 PM EST

Poster Number: 4598

Co-deletion of MTAP is observed in approximately 80-90% of tumors with homozygous deletion of CDKN2A, representing 10-15% of all human tumors. These tumor types, including non-small cell lung cancer, pancreatic adenocarcinoma, glioblastoma, and mesothelioma, have a poor prognosis, highlighting the significant unmet medical need in

this area. Deletion of MTAP leads to a significant accumulation of methylthioadenosine (MTA) in cells. MTA, at high concentrations, selectively inhibits the PRMT5 methyltransferase enzyme. As a result, the overall level of symmetric arginine dimethylation throughout the proteome is reduced, which makes cells with MTAP deletion more susceptible to therapeutic targeting of PRMT5. Ryvu has developed potentially best-in-class MTA-cooperative PRMT5 inhibitors showing favorable drug-like properties and effective PRMT5 inhibition dependent on MTA binding. Structure-based lead optimization has enabled rapid expansion and delivery of two independent chemical series with novel intellectual property, characterized by high target engagement in cells, and selective potency in MTAP-deleted cell lines, along with favorable DMPK profiles allowing an oral administration. The antitumor activities were compared *in vitro* and *in vivo* in MTAP null tumors. The correlation between compound exposure and on-target effect was confirmed in PK/PD and efficacy studies. Performed studies confirm that MTA-cooperative PRMT5 inhibitors exert a strong synthetic lethal phenotype in MTAP-deleted cancers, offering an exciting therapeutic opportunity for a large patient population.

Abstract Title: "A comprehensive platform for identification of KRAS-specific synthetic lethal targets using patient-derived cells."

Session Name: New Targets, Technologies, and Drug Delivery Systems

Session date and time: Tuesday, April 9, 9:00 AM - 12:30 PM EST

Poster Number: 4684

Ryvu's cutting-edge drug discovery platform uniquely combines high throughput capabilities with the precision and translational impact traditionally associated with later, lower throughput stages. Our approach taps into the power of primary cells to transform cancer treatment, focusing especially on colorectal cancer (CRC). By leveraging human stem cell derived model cells (PDC), patient-derived xenografts (PDXs) and clinical samples we have created a groundbreaking approach to identify synthetic lethal (SL) targets specific to oncogenic pathways. We integrate CRISPR/Cas9 technology, phenotypic screening, RNA-seq, and whole-exome sequencing (WES), enabling rapid identification of molecular vulnerabilities. We present results obtained in engineered intestinal primary models which represent frequently altered genes in CRC, including KRAS G12D mutation. Notably, our use of normal hISCs facilitates the identification of genes essential only for transformed cells, amplifying the precision tumor targeting of our novel discoveries. Beyond CRC, our platform could extend to personalized medicine approaches in various cancer types. By spearheading the identification of KRAS-specific SL inhibitors, we pave the way for novel, targeted therapies, offering hope to patients battling this heterogeneous malignancy and beyond.

Abstract Title: "Discovery of WRN inhibitors as targeted therapy in the treatment of microsatellite unstable (MSI-H) tumors."

Session Name: Novel Antitumor Agents 4

Session date and time: Tuesday, April 9, 1:30 PM – 05:00 PM EST

Poster Number: 5942

The synthetic lethality resulting from the inhibition of the WRN helicase protein has been observed in tumors characterized by high levels of microsatellite instability (MSI-H). This instability stems from a deficiency in the DNA mismatch repair (MMR) mechanisms, leading to the accumulation of DNA damage. This phenomenon is notably prevalent in 10-30% of colorectal, gastric, endometrial, and ovarian cancers.

Structure-based optimization performed at Ryvu facilitated the rapid expansion and delivery of a compound library with novel intellectual property (IP), demonstrating target engagement in cells and selective potency over other RecQ family members. The pharmacokinetic properties of these compounds were favorable and allowed progressing to *in vivo* studies which confirmed efficacy of our compounds in xenograft MSI-H cancer models. These data provide pharmacological proof-of-concept for the synthetic lethal effect of our inhibitors and support WRN inhibition as a new, targeted oncological therapy.

Abstract Title: "Combination JAK1/2 and CDK8/19 inhibition demonstrates enhanced efficacy in myeloproliferative neoplasms."

Session Name: Targeted, Combination, and Differentiation Therapies

Session date and time: Wednesday, April 10, 9:00 AM - 12:30 PM EST

Poster Number: 7225

The presentation, prepared in collaboration with Prof. Rajit Rampal's group from Memorial Sloan Kettering Cancer Center, includes the assessment of RVU120, a highly selective and potent CDK8/19 inhibitor, both in monotherapy and combination with ruxolitinib (RUX), a JAK1/2 inhibitor, for the treatment of myeloproliferative neoplasms (MPN) and hydroxyurea-resistant/intolerant polycythemia vera (PV). The combination of RVU120 and RUX demonstrated biochemical synergy and differential inhibition of STAT5 phosphorylation *in vitro*. Further, *in vivo* treatment with RVU120/RUX+RVU120 resulted in significant reductions in disease manifestation (splenomegaly, WBC, fibrosis scoring, hematopoiesis) compared to VEH/RUX. These data suggest that JAK1/2 and CDK8/19 inhibition could be a potential novel therapeutic strategy in MPNs. Additional work on nascent RNA expression and cytokine profiles aims at elucidating the exact mechanism of synergy between tested compounds .

Abstract Title: "MEN1703/SEL24 exhibits promising antitumoral activity in preclinical models of myelofibrosis both as single agent and combined with ruxolitinib."

Session Name: Novel Antitumor Agents 2

Session date and time: Sunday April 7, 01:30 AM – 0500 PM EST

Poster Number: 665

MEN1703 (SEL24) is an oral, first-in-class, dual PIM/FLT3 kinase inhibitor in development for hematologic malignancies. The presented study aims to investigate the efficacy of MEN1703 alone and in combination with the JAK inhibitor ruxolitinib (RUX) in preclinical models of myelofibrosis (MF) and to elucidate the underlying signaling pathways. MEN1703 demonstrated anti-tumoral efficacy in MF preclinical models, exhibiting *in vitro* activity at clinically relevant concentrations. Importantly, the combination of MEN1703 with the standard of care, RUX, exhibited synergistic effects, and molecular analyses confirmed the inhibition of downstream targets of PIM. The results support the therapeutic potential and relevance of MEN1703 in the treatment strategies for myelofibrosis.

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Legal basis: Article 17.1 of MAR

Representatives of the Issuer:

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