Phase I/II trial of RVU120, a CDK8/CDK19 inhibitor, in patients with relapsed/refractory metastatic or advanced solid tumors.

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INTRODUCTION

CDK8 and its paralog CDK19 are cyclin-dependent kinases involved in transcriptional regulation via the mediator complex. A variety of cancer cells hijack CDK8/19 to maintain stemness and an undifferentiated state to prevent apoptotic cell death. Targeting cancer-specific gene transcription via CDK8/19 inhibition has the potential to be the effective treatment against solid tumors.

RVU120 is a first-in-class CDK8/19 inhibitor with high selectivity and potency. Preclinical data indicate efficacy of RVU120 in hematologic malignancies and a variety of solid tumor types (Rzymski et al. 2017). RVU120 has shown clinical activity in two currently ongoing Phase I trials in patients with relapsed/refractory AML or HR-MDS (NCT04021368) and in patients with metastatic or advanced solid tumors (NCT05052255).

Here, we provide an update with newly available data collected from both ongoing and newly enrolled patients with solid tumors treated with RVU120 at doses up to 400 mg.

OBJECTIVES

The study is designed to consist of 2 seamless parts:

Part 1 (Phase I) dose escalation study with relapsed/refractory solid tumor patients who have exhausted available standard of care (SOC).

Part 2 (Phase II) safety/efficacy study expansion with continuing dose escalation, schedule adjustment and food effect assessment; single agent study in up to five patient groups with simultaneous enrollment of relapsed/refractory patients progressing after at least 1 line of systemic therapy.

Part 1 study objectives: primary objective is to characterize the safety and tolerability of RVU120 as single agent in patients with solid tumors; secondary objectives are to determine the preliminary anti-tumor response to RVU120 and to determine PK profile of RVU120.

Part 2 study objectives: primary objective is to further evaluate safety and tolerability of RVU120 and to explore its anti-tumor activity as single agent in patients with selected tumor types; secondary objective is to determine the PK profile of RVU120, including food effect (in a subgroup of patients).

METHODS

RVU120-SOL-021 [AMNYS-51] is a Phase I/II, open-label, multi-center, multi-national, single group assignment, dose-escalation study using the 3+3 design in patients with relapsed/refractory solid tumors

The study is currently enrolling at 2 sites in Poland and 3 sites in Spain.

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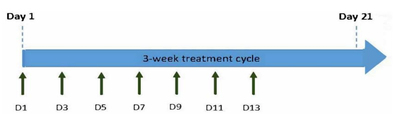
RVU120 is administered orally every other day (QoD) in the fasted state for a total of 7 doses in a 3-week treatment cycle, until disease progression, death, unacceptable toxicity or discontinuation for other reason such as consent withdrawal.

3 weeks in total
2 weeks **on** treatment
1 week **off** treatment — 7 doses of RVU120 over period of 14 days



Pharmacokinetic data and parameter variables will be summarized using descriptive statistics. Pharmacodynamic activity of RVU120 is evaluated by measuring changes in levels of STAT5 phosphorylation using flow cytometry in the ex vivo plasma inhibitory assay. In this assay, cancer cells are exposed to plasma samples collected from patients at baseline and C1D13, when steady state was established. Molecular response to RVU120 is assessed by transcriptional profiling of tumor biopsies using NanoString technology.

EFFICACY & SAFETY

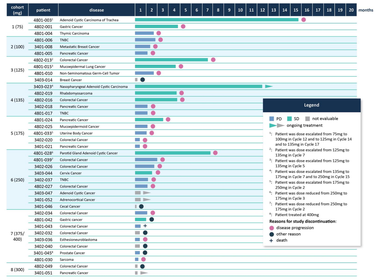
At the data cut-off on 26 Sep 2023, 39 patients have had IMP administered, and 4 patients were ongoing. Median patient age is 58 years, median count of previous lines of therapy is 5 lines (heavily pre-treated group).

TEAEs incidence per cohort (intra-patient dose changes).

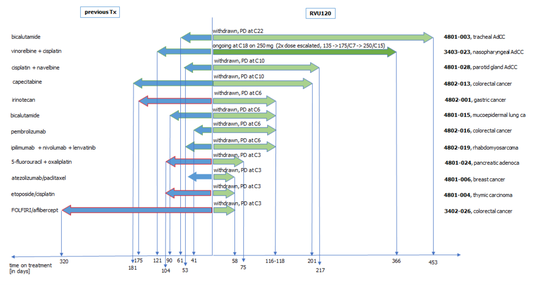
Treatment Emergent Adverse Event (incidence)	75 mg	100 mg	125 mg	135 mg	175 mg	250 mg	300 mg	375 mg	400 mg	Total
Number of patients per cohort (+dose escalated patient)	3	3 (+1)	4 (+1)	5 (+3)	5 (+1) (-2)	8	2	7	1	38
Nausea	0%	25%	40%	75%	50%	100%	0%	86%	100%	68%
Vomiting	0%	0%	20%	63%	25%	75%	0%	43%	100%	53%
Fatigue	0%	0%	40%	25%	63%	75%	0%	29%	0%	37%
Constipation	33%	25%	40%	25%	13%	13%	0%	14%	100%	26%
NT-proBNP increase	33%	25%	40%	25%	13%	25%	0%	29%	0%	26%
AST increase	0%	0%	0%	13%	38%	25%	0%	43%	0%	21%
ALT increase	0%	0%	0%	13%	13%	25%	0%	43%	0%	18%
ALP increase	33%	0%	0%	13%	0%	25%	0%	29%	0%	16%
Abdominal pain	0%	0%	40%	25%	0%	0%	0%	14%	0%	13%
Appetite lost	33%	0%	0%	0%	25%	13%	0%	14%	100%	13%
CRP increase	33%	0%	20%	13%	13%	13%	0%	0%	0%	13%
Diarrhea	33%	0%	20%	13%	13%	0%	0%	0%	100%	13%
Hypoalbuminemia	0%	25%	0%	25%	0%	0%	0%	29%	0%	13%
Insomnia	33%	0%	0%	25%	13%	13%	0%	0%	0%	13%
Asthenia	0%	0%	0%	13%	0%	13%	0%	14%	100%	11%
Creatinine increase	0%	0%	20%	0%	13%	25%	0%	14%	0%	11%
Dyspepsia	0%	0%	20%	13%	0%	13%	0%	14%	0%	11%
GGTP increase	0%	0%	20%	13%	0%	25%	0%	0%	0%	11%
Infection NOS	0%	25%	0%	13%	13%	0%	0%	14%	0%	11%
Pruritus	0%	25%	20%	0%	0%	25%	0%	0%	0%	11%
UTI	0%	0%	20%	38%	0%	13%	0%	0%	0%	11%
Weakness	33%	0%	20%	13%	13%	0%	0%	0%	0%	11%

Most frequent AEs were GIT-related (nausea / vomiting) occurring shortly after initial RVU120 dosing (average time to onset slightly over 1 hour).

Swimmer-plot, all patients treated with at least 1 dose.



Total of 49 patients were screened and 39 enrolled in the study. Current data are consistent with expected RVU120 safety profile although treatment duration was short in Cohort 7 due to, at least partially, adverse GIT effects (nausea and vomiting).



Efficacy assessment:
Last previous treatment line vs. RVU120 response duration in patients who reached stable disease as best response.

Out of 12 patients who achieved disease stabilization on RVU120, 8 lasted longer than the last line of previous therapy. The trend to longer treatment duration was specifically observed in patients with adenoid cystic carcinoma (AdCC).

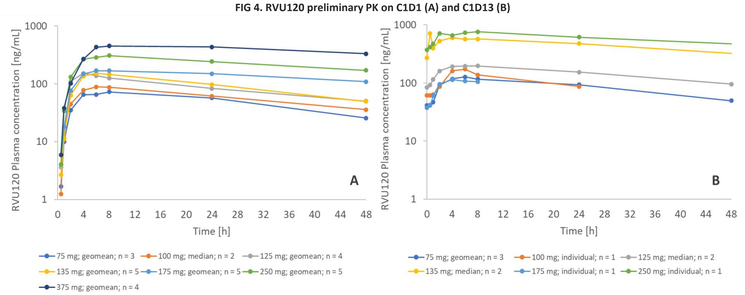
PHARMACOKINETICS

RVU120 PK was characterized across the dose interval on C1D1 and after multiple doses on C1D13 (FIG 4).

Plasma exposure of RVU120 was observed to increase with dose across the dose range investigated for patients evaluable for PK.

Median t_{max} for RVU120 was observed approximately 6 hours post dose, with half-life of approximately 40 hours.

FIG 4. RVU120 preliminary PK on C1D1 (A) and C1D13 (B)



PHARMACODYNAMICS AND MECHANISM OF ACTION

Treatment with RVU120 results in effective inhibition of pharmacodynamic marker (PD) in solid tumor patients in the ongoing dose-escalation trial.

Our goal is to achieve plasma levels of RVU120 that can effectively block CDK8 activity and trigger anti-tumor effects. To assess the PD response of RVU120, we developed a flow cytometry assay that measures changes in CDK8-dependent STAT5 phosphorylation levels (pSTAT5 S725). Analysis of cells exposed to patient plasma samples after treatment with RVU120 revealed that inhibition of pSTAT5 in patients closely correlated with achieved exposures (C_{max} – FIG1A, and AUC – FIG1B), reaching a biologically significant range of more than 50% at doses 250 mg and above (FIG 2).

FIG 1. pSTAT5 inhibition tightly correlates with RVU120 exposure (A - C_{max}; B - AUC)

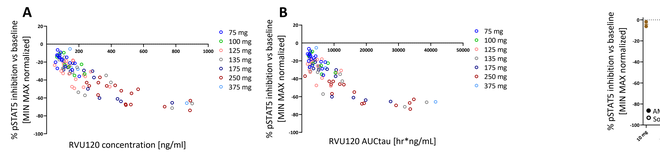
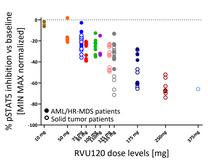


FIG 2. pSTAT5 inhibition tightly correlates with RVU120 dose (data from both ongoing Phase I studies)



We used nanostring technology to assess the effects of RVU120 treatment on gene expression profiles in tumor samples from patients. In the pancreatic carcinoma patient 4801024 we detected broad mRNA changes after 3 cycles of RVU120 treatment (FIG 3) that were related to RVU120 mode of action and potential resistance pathways. The observed suppression of JAK-STAT-dependent genes in this patient was in line with the nonclinical cancer models and indicated on-target activity of RVU120 (FIG 4).

FIG 3. RVU120 treatment in pt 4801024 results in vast gene expression changes

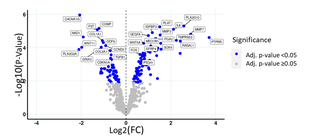
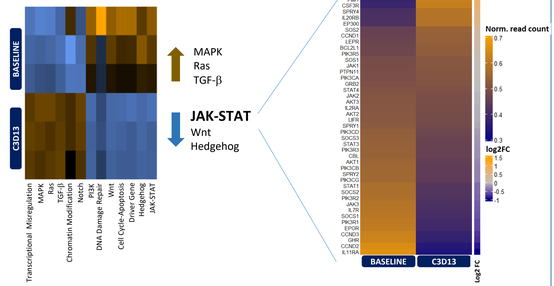


FIG 4. JAK-STAT pathway is downregulated after RVU120 treatment



CONCLUSION(S)

- RVU120 demonstrates a favorable safety profile in a heavily pretreated, unselected all-comer patient population. No dose limiting toxicities (DLTs) or other safety signals were observed confirming CDK8/19 inhibition as a viable approach for cancer therapies.
- Low grade nausea and vomiting were the most frequent AEs reported, contributing to suboptimal tolerability in Cohort 7.
- A robust relationship between exposure to RVU120 and inhibition of PD marker has been observed. Doses of 250 mg QoD result in exposure in the pharmacologically active range and are expected to result in robust efficacy in selected patients, both as single agent and in synergistic combinations.
- Nanostring analysis in one patient confirms on-target activity of RVU120 in tumor tissue.
- Disease stabilization (SD) was observed in 12 patients with previously progressing disease, with treatment durations exceeding the most recent previous therapy line in 8 patients. A potential signal in patients with AdCC requires further confirmation.
- Dose optimization and efforts to improve GI tolerability are ongoing to increase RVU120 exposure to fully exploit the opportunity space of CDK8/19 inhibition.

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