Safety and efficacy Results from CLI120-001 a Phase 1 Study in RR-AML and HR-MDS: Update from Higer Dose Levels

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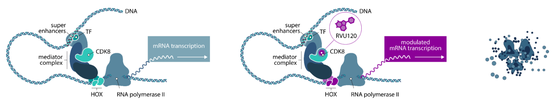
INTRODUCTION

- CDK8 and its paralog CDK19 are cyclin-dependent kinases involved in transcriptional regulation via the mediator complex.
- **RVU120** is a first in class inhibitor of the Mediator Complex kinases CDK8/19 with anti-leukemic activity. The efficacy of RVU120 is mediated by changes in the expression of stemness and lineage commitment genes[1] (Fig 1).
- CLI120-001 is the ongoing phase 1 study of RVU120 in patients with relapsed/refractory AML and HR-MDS (NCT04021368).
- The current poster reports data from patients treated at doses up to 250 mg

Fig 1. RVU120 Mechanism of Action



CDK8/19 mediator promotes AML growth

CDK8/19 inhibition by RVU120 triggers differentiations and apoptosis

OBJECTIVES AND METHODS

- Primary objective of the study is to determine the safety profile and the recommended phase 2 dose (RP2D) of RVU120 as a single agent in patients with R/R AML and HR-MDS.
- Secondary objectives include the characterization of PK, antitumor activity, and exploratory pharmacodynamic (PD) effects.
- RVU120 is administered orally until disease progression or unacceptable toxicity according to the following schedule:

21 day-cycle: 1 oral dose of RVU120 every other day (EOD) for a total of 7 doses/cycle followed by 1 week off.

- Dose escalation applies a standard 3+3 design. Adverse events are graded according to NCI-CTCAE v5.0. DLTs are assessed at the completion of C1.
- Disease evaluation is performed according to Dohner 2017 and Cheson 2006 criteria for AML and MDS, respectively.
- Target engagement is evaluated by measuring STAT5 phosphorylation changes by flow cytometry through ex vivo plasma inhibitory assay.

SAFETY

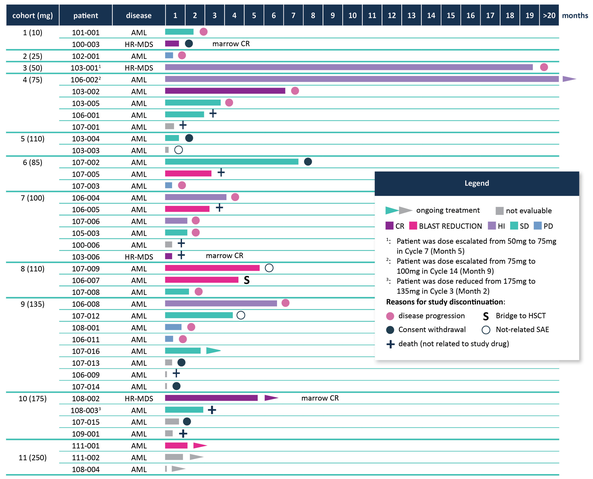
- At the data cut-off of 10 Nov 2023, 38 patients (34 with AML and 4 with HR-MDS) have been treated in the trial at doses up to 250 mg.
- The median age was 72 years and patients received a median of 3 prior lines of treatment.
- No DLTs occurred.
- No serious adverse events leading to permanent study discontinuation.
- Most frequent Treatment Emergent Adverse Events (TEAE) (Table 1) were: Nausea and vomiting manageable with common antiemetics.

Most common TEAE	RVU120 (10-250 mg)	
	Any grade n of pts (%)	Grade 3-5 n of pts (%)
Nausea	24 (60%)	0
Vomiting	16 (40%)	1 (2%)
Thrombocytopenia	11 (28%)	8 (20%)
Febrile neutropenia	9 (22%)	8 (20%)
Decreased appetite	7 (18%)	1 (2%)
Pneumonia	7 (18%)	7 (18%)
Cough	6 (15%)	0
Hypokalemia	6 (15%)	0

Table 1. TEAEs that occurred in ≥15% of patients

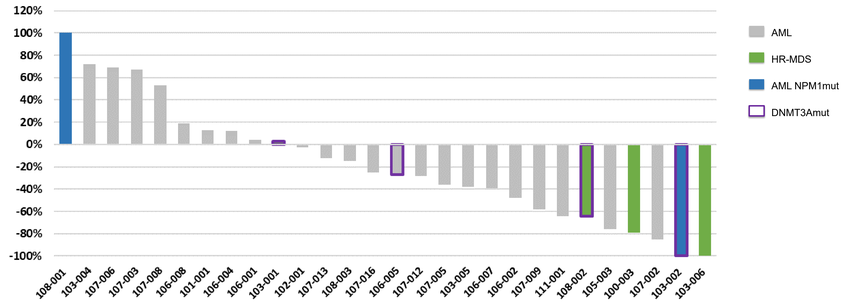
EFFICACY

Fig 2. Swimmer plot and best response. 14 out of 28 evaluable patients showed signs of clinical activity:



- 5 patients showed **erythroid hematological improvement** (HI-E), 4 of them (106-002, 106-004, 107-006, 106-008) became RBC transfusion independent (RBC-TI) and 1 pt (103-001) achieved an absolute difference of >4 RBC Units compared to baseline, as per Cheson 2006 criteria,
- 2 of those patients with RBC-TI (pt 106-004 and 107-006) resolved also their Grade 3 thrombocytopenia to **normal platelet values[2]**,
- 8 experienced a clinically significant **BM blast reduction** (1 CR, 3 marrow CR, and 4 clinically relevant BM blast reduction). Of relevance, 2 patients with TP53 mutation reduced BM blasts of 36% and 58% and remained on treatment for >2 months and 5 months, withdrawn for reason other than PD
- 1 patient with double leukemic clones received transplant after nearly 4 months of treatment,
- the first evaluable patient at 250 mg, showed significant blast reduction (64%) at the end of cycle 2.

Fig 3. BM blasts % change from baseline at the moment of the best response



An NPM1 mutation was identified in 2 pts who received RVU120 at 75 and 175mg respectively:
- pt 103-002 achieved a CR with skin leukemia resolution,
- pt 108-001, who was under controlled disease at the beginning of C2 and progressed after missing 4 doses in cycle 2 due to SAE (cholecystitis) not related to study drug.

A DNMT3A mutation was identified in 4 pts. All of them experienced BM blast reduction or control:
- pt 103-001 with HR-MDS maintained 0-4% Blasts in the BM up to C25 (≥ 18 months of treatment) in addition to erythroid hematological improvement,
- pt 103-002 (NPM1mut, DNMT3Amut) achieved a CR in C7,
- pt 106-005 showed 37% BM blast reduction in C2,
- pt 108-002 achieved a marrow CR in C2 and is currently ongoing in C7 with BM fibrosis reduction and RBC transfusion reduction (Fig 4).

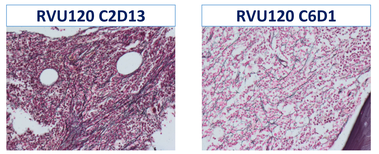
HR-MDS
- 4 pts with HR-MDS treated were failing 1-5 prior lines of treatment, including hypomethylating agents, and were heavily transfused prior to study entry.
- 3 of these pts had >10 % blasts at baseline, all of them met the Cheson criterion of marrow CR during treatment with RVU120.

EFFICACY, CONT.

Myeloproliferative neoplasia/ myelofibrosis: 2 patients with BM fibrosis, 1 pt with AML secondary to myelofibrosis (106-002) and 1 pt with HR-MDS and BM fibrosis (108-002), showed clinically relevant response to RVU120:

- pt 106-002 is ongoing after 22 months of treatment with both HI-E and HI-P;
- pt 108-002 achieved a marrow CR with reduction of fibrosis from grade 3 to grade 2 (Fig 4).

Fig 4. Trephine biopsy of patient 108-002 during treatment with RVU120



PHARMACODYNAMICS

1. Pharmacodynamic (PD) activity of RVU120 was assessed by measuring changes to baseline in the CDK8-specific phosphorylation site of STAT5 (S725) from patient-derived leukemic cells ex vivo. pSTAT5 percentage change at steady state (CxD13) represents the target engagement of RVU120.
2. Results of RVU120-induced pSTAT5 changes from patients enrolled in CLI120-001 (NCT04021368) and from the concomitant phase 1 study in patients with solid tumors (NCT05052255) show a tight correlation between pSTAT5 inhibition and drug exposure at doses up to 375 mg (Fig 5). At a dose of 250 mg, a target engagement level between 50%-70% is achieved, that is expected to result in robust antileukemic efficacy (Fig 6).

Fig 5. pSTAT5 inhibition per dose level

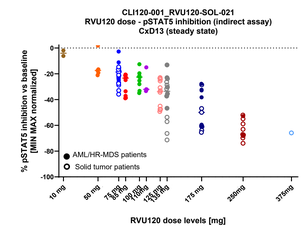
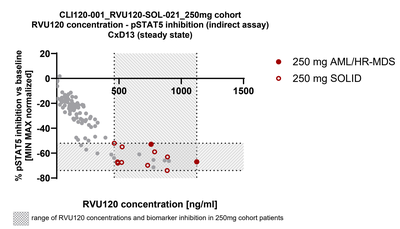


Fig 6. pSTAT5 inhibition correlation with drug exposure



CONCLUSIONS

- Doses up to 250 mg have shown a favorable safety profile of RVU120 in patients with AML or HR-MDS.
- Target engagement of 50%-70% is achieved at 250 mg, which is predicted to result in robust antileukemic efficacy in selected populations and in combinations based on preclinical data.
- RVU120 as a single agent shows signs of clinical activity including a complete response, and several patients with blast reductions, hematologic improvement, or reduction of bone marrow fibrosis.
- In particular, early signs of efficacy were observed in patients with NPM1 mutation, DNMT3a mutation, and in patients with HR-MDS.
- The observed effect on bone marrow fibrosis are in line with previously reported data in murine models of myelofibrosis.
- Subsequent clinical trials investigating RVU120 as a single agent and in combination with SoC in patients with hematologic disorders are being initiated.

REFERENCES

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LEUKEMIA & LYMPHOMA SOCIETY

The concept of RVU120 has been validated through the support of The Leukemia and Lymphoma Society, the largest blood cancer foundation in the world which has supported multiple breakthrough therapies through its highly competitive Therapy Acceleration Program.

This work was financed by Smart Growth Operational Programme 2014-2020/European Regional Development Fund (Project no. POIR.01.02.00-00-0032/15 co-financed by the European Union)of innovative medicine".

European Funds Smart Growth | European Union European Regional Development Fund | NCBR National Centre for Research and Development