3920

CLI24-001 (DIAMOND-01): First in Human Study of SEL24/MEN1703, First in Class, Orally Available Dual PIM/FLT3 Kinase Inhibitor, in Patients with Acute Myeloid Leukemia

S. R. Solomon[1] , A. Nazha[2], S. Strickland[3], R. Walter[4], I. Valimberti[5], A. Tagliavini[5], P. Mazzei[5], C. Fiesoli[5], S. Scartoni[5], D. Bellarosa[6], M. Binaschi[6], P. Chrom[7*], S. Baldini[5], K. Brzozka[7], A. Capriati[5], A. Pellacani[8] And F. Ravandi[9]

[1]Northside Hospital Cancer Institute. Atlanta, GA, USA; [2]Cleveland Clinic. Cleveland OH, USA; [3]Vanderbilt University Medical Center. Nashville, TN, USA; [4]Fred Hutchinson Cancer Research Center. Seattle, WA, USA; [5]Clinical Sciences, Menarini Ricerche SpA. Firenze, Italy; [6]Menarini Ricerche SpA. Pomezia, Italy; [7]Ryvu Therapeutics S.A. Krakow, Poland; [8]Menarini Ricerche SpA. Firenze, Italy, [9]MD Anderson Cancer Center. Houston, TX, USA; [*] not currently employed at Ryvu

Background

- PIM kinases are thought to be major drivers of resistance to FLT3 inhibitors and their inhibition in relapsed samples restores cell sensitivity to these agents.
- SEL24/MEN1703 is a potent, first in class, orally available dual PIM/FLT3 inhibitor.
- When compared to either FLT3 or PIM single inhibitors, SEL24/MEN1703 shows increased activity in both primary Acute Myeloid Leukemia (AML) cells and AML cell lines, irrespectively of FLT3 mutational status.
- The broader spectrum of activity of SEL24/MEN1703, which goes beyond PIM/FLT3 inhibition, warrants the compound investigation in AML patients regardless of FLT3 aberrations.

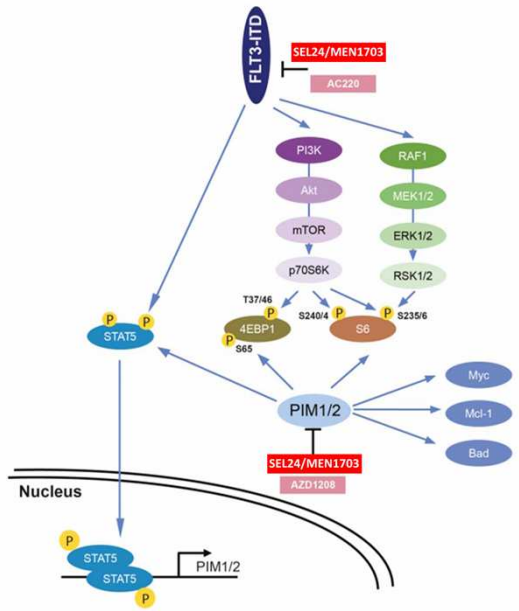

Figure 1. SEL 24/MEN1703 on FLT3/PIM pathway (adapted from Czardybon W *et al.*, Oncotarget 2018; 9(24):16917-16931)

Methods

CLI24-001 (DIAMOND-01) is a First-in-Human, Phase I/II, open label, non-randomized, multi-center, dose-escalation (DE) and cohort expansion (CE) study of SEL24/MEN1703 in newly diagnosed, relapsed or refractory AML (excluding acute promyelocytic leukemia) patients who are unsuitable for intensive chemotherapy.

Objectives:

- Primary objective: Identification of the recommended dose (RD) of SEL24/MEN1703 given as single agent in patients with AML.
- Key secondary objectives:
  - Characterization of the pharmacokinetics (PK) of SEL24/MEN1703;
  - Assessment of single agent activity of SEL24/MEN1703 in AML.
- Exploratory objectives:
  - Assessments of relevant biomarkers (e.g. pS6) in peripheral blood and bone marrow, and their correlation with PK at different time points;
  - Correlation of CD25 expression and clinical activity.

Study design:

- After 5 incremental dose levels using a 3+3 design, a Bayesian modified Toxicity Probability Interval model (mTPI) was implemented in the Dose Escalation part to provide the most accurate identification of the RD.
- the Cohort Expansion part will start once the RD is determined.

Treatment outline:

SEL24/MEN1703 is given orally, QD, for 14 days in a 21-day cycle to be repeated until disease progression/unacceptable toxicity.

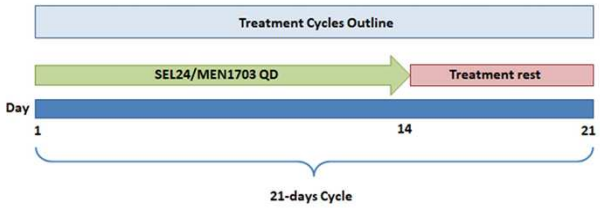

Figure 2. Treatment cycles outline

Main eligibility criteria:

- Patients aged ≥ 18 years with (a) newly diagnosed AML, (b) relapsed AML or (c) primary refractory AML who are not suitable for intensive chemotherapy;
- In both study parts, *patients are eligible regardless of mutational status and/or prior exposure to FLT3 inhibitors;*
- Prior treatment with PIM inhibitors is not allowed;
- White blood count (WBC) ≤ 30 x 10^9/L prior to start study treatment (hydroxyurea/Leuko-apheresis permitted to lower WBC);
- Main exclusion criteria include hematopoietic stem cell transplant within 4 months of first dose of study drug and systemic immune-modulating therapy for the prophylaxis or treatment of graft versus host disease.

Current Status:

- The study is running at 5 US sites and is planned to be extended to additional sites both in the US and EU.
- As of Nov 21th, 2019, 24 patients have received SEL24/MEN1703 at dose levels ranging from 25 to 150 mg.
- Patients have a median age of 69 (25-84) years and a median of 4 (1-8) prior treatments for AML. Adverse prognostic factors such as primary refractory AML, unfavourable cytogenetics and prior MDS history accounted for 45.8%, 41.7%, 33% of study patients, respectively.
- The most frequently reported mutations are:
  - FLT3-ITD (20.8% of patients)
  - DNMT3A (16.7%)
  - IDH1 (16.7%)

Conclusions

- This is the first trial testing a dual PIM/FLT3 inhibitor with the potential to overcome FLT3 inhibitor resistance, but also to be active in AML regardless of FLT3 mutational status.
- Ongoing adjustment of the DE by applying a Bayesian mTPI design has been performed to obtain more robust data on the RD.

References

1. Green AS et al. Pim kinases modulate resistance to FLT3 tyrosine kinase inhibitors in FLT3-ITD acute myeloid leukemia. Science Advances 2015; Vol. 1, no. 8, e1500221
2. Czardybon W et al. A novel, dual pan-PIM/FLT3 inhibitor SEL24 exhibits broad therapeutic potential in acute myeloid leukemia. Oncotarget 2018; 9(24):16917-16931

American Society of Hematology, Orlando, FL; December 7-10, 2019

DIAMOND-01

Clinical Trial Information:
NCT03008187

sbaldini@menarini-ricerche.it