Background

- FLT3-ITD is one of the most common genetic lesions in acute myeloid leukemia (AML).
- PIM kinases are oncogenic FLT3-ITD targets expressed in AML.
- Increased PIM kinase expression is found in relapse samples from AML patients treated with FLT3 inhibitors.
- Inhibition of PIM kinases restores sensitivity to FLT3 inhibitors.
- Dual FLT3/PIM inhibition eradicates FLT3-ITD+ cells including primary AML cells.
- SEL24/MEN1703, a potent PIM/FLT3 dual inhibitor, demonstrates a significantly broader spectrum of activity in AML cell lines and primary AML blasts, irrespective of FLT3 status, compared to monotherapy with either FLT3 or PIM inhibitors such as quizartinib or AZD1208 (Sci Adv. 2015;1:e1500221; Oncotarget. 2018 Mar 30;9(24):16917-16931).

Methods

• SEL24/MEN1703 is a First-in-Human, Phase I/II, open-label, non-randomized, multi-center, dose-escalation and cohort expansion study of SEL24/MEN1703 in AML patients (excluding acute promyelocytic leukemia) not suitable for intensive chemotherapy.

Study design and Treatment:

- The study is running the Dose Escalation Phase under a 3+3 design, with the exception of the starting dose.
- Once the Recommended Dose (RD) is determined, the Cohort Expansion Phase will start opening the recruitment in patients with or without FLT3 mutations and/or CD25 expression.
- SEL24/MEN1703 dose levels range from 25 mg to 150 mg QD. Exploration of higher dose levels will be subjected to a safety assessment and potential subsequent protocol amendment.
- SEL24/MEN1703 is formulated as oral capsule to be given once daily, for 14 consecutive days over a 21-day treatment cycle, to be repeated until disease progression or unacceptable toxicity.

Main eligibility criteria:

- Patients aged ≥ 18 years with (a) newly diagnosed AML, (b) relapsed AML or (c) primary refractory AML and that have no standard therapeutic options available
- 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.
- A white blood count (WBC) ≤ 30 x 10^9/L is required 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.

Objectives:

- Primary objective: Identification of the RP2D of SEL24/MEN1703 given as single agent in patients with AML
- Key secondary objectives include:
  - Pharmacokinetics
  - Pharmacodynamic activity
  - Single agent efficacy of SEL24/MEN1703.
- Exploratory objectives include the assessment of relevant biomarkers (e.g. pS6) in peripheral blood and bone marrow.

Current Status:

- Recruitment start date: March 2017
- New formulation introduced at dose level 100mg
- Dose level 125mg ongoing
- The study is enrolling at 5 US sites and will be extended both in US and EU.

References

- Cyzdarbon W et al., Oncotarget 2018; 9(24):16917-16931

Correspondence

sbaldini@menarini-ricerche.it

CLI24-001 (DIAMOND-01) is the first trial testing a dual PIM/FLT3 inhibitor with the potential to be active in AML regardless of FLT3 status and to overcome FLT3 inhibitor resistance