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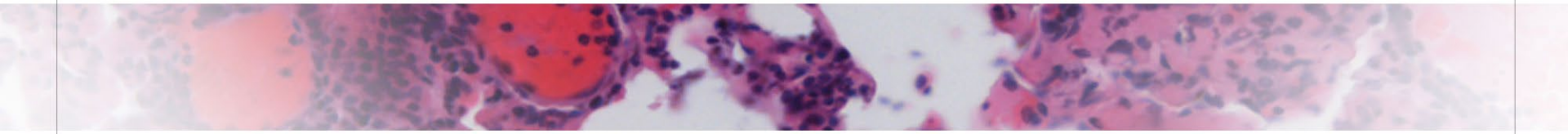

SEL24/MEN1703 provides PIM/FLT3 Downstream Pathway Inhibition in Acute Myeloid Leukemia (AML) Blast Cells: Results of the Pharmacodynamic (PD) Assay in the Dose Escalation Part of First-in-Human DIAMOND-01 Trial

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Conflict of Interest Disclosure

- A.M.Tomirotti, D.Bellarosa, M.Binaschi,M.Salerno, S.Baldini, A.Pellacani are or were Menarini Ricerche employees
- D.Laurent is Menarini Ricerche /BerlinChemie AG, Berlin, Germany employee
- K.Brzozka is Ryvu Therapeutics, Krakow, Poland employee, board member and shareholder, Ardigen, Krakow, Poland supervisory board member and shareholder, Nodthera Ltd. Cambridge, UK shareholder
- M.Mazan is Ryvu Therapeutics, Krakow, Poland employee
- For other authors there are no relationships to disclose

Background

- SEL24/MEN1703 is a first-in-class, orally available, dual PIM/FLT3 kinase inhibitor investigated in unselected AML patients in the First-in-Human, Dose Escalation (DE) and Cohort Expansion CLI24-001 (DIAMOND-01) trial[1]
- The recently completed DE part showed an acceptable safety profile up to the recommended dose (RD), with initial evidence of single agent efficacy[2]
- **AIM:** To assess the target engagement by evaluating phosphorylation of S6 (pS6), a downstream effector of the PIM/FLT3 pathway, and its preliminary correlation with the anti-leukemic effect of SEL24/MEN1703

1: Clinicaltrials.gov identifier: NCT03008187
2: Solomon *et al.*, EHA 2020

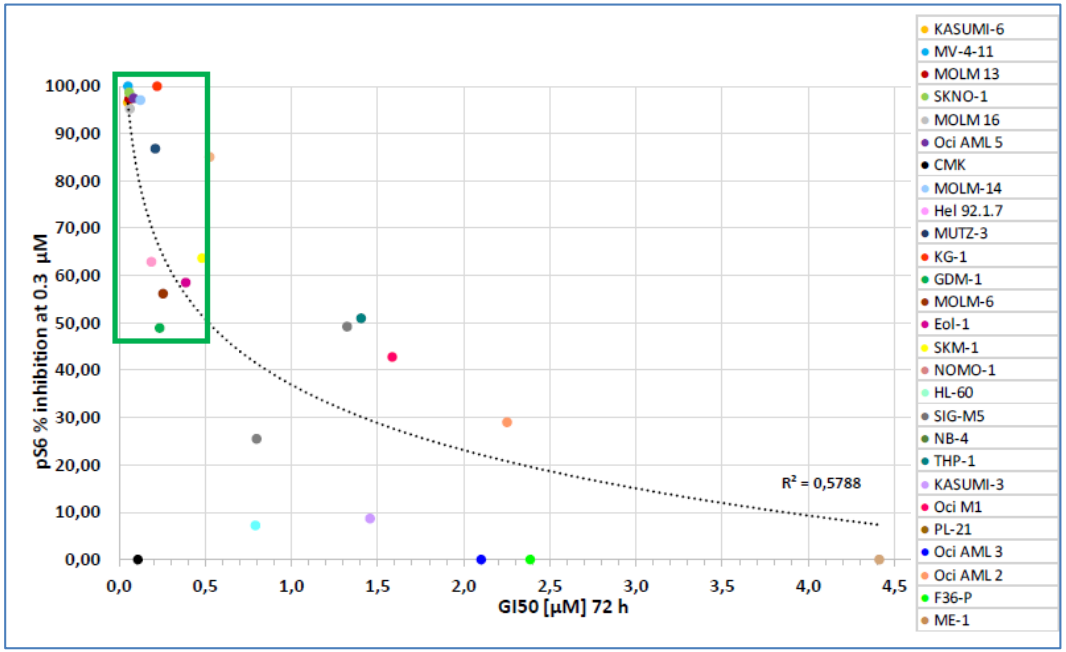
Methods

- S6 phosphorylation has been longitudinally monitored in the DIAMOND-01 study through a flow cytometric assay both on peripheral blood (PB) and bone marrow (BM) samples
- Percentage of pS6 inhibition was calculated considering the data from screening to the last day of dosing in the first treatment cycle (C1D14)
- A total of N=9 PB and N=7 BM samples, collected from patients belonging to 100 mg and 125 mg (RD) dose levels, were analyzed
- Blast counts were monitored to assess their possible correlation with target engagement

In vitro pS6 Inhibition vs Cytotoxic Activity

- *In vitro* studies with 26 AML cell lines bearing various genetic alterations showed a direct correlation between SEL24/MEN1703 activity and pS6 inhibition

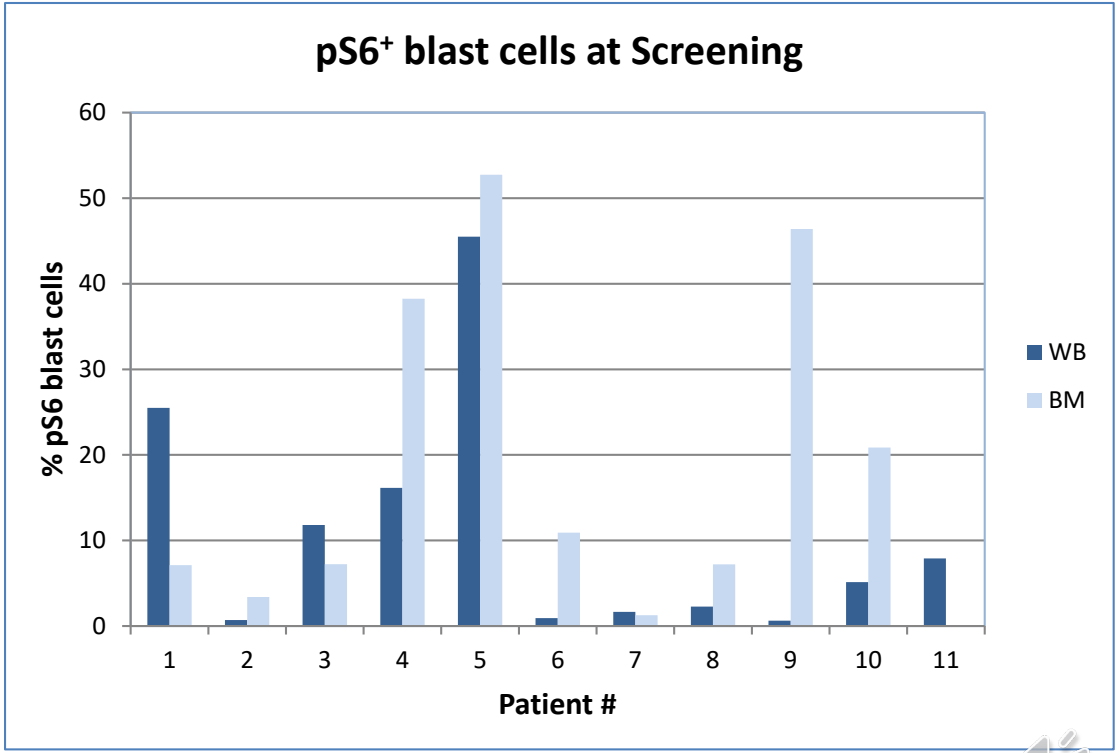
- pS6 inhibition levels ranges from 50% to 100% in cells showing higher growth inhibition degree (GI_{50} < 0,5 µM, green box)



GI_{50}: Concentration causing 50% cell growth inhibition

pS6 levels at Screening

At screening, PB and BM samples showed heterogenous levels of pS6⁺ blast cells (range: 1-53%), consistent with the unselected AML patient population recruited in the DIAMOND-01 trial



% of pS6 inhibition assessed at C1D14

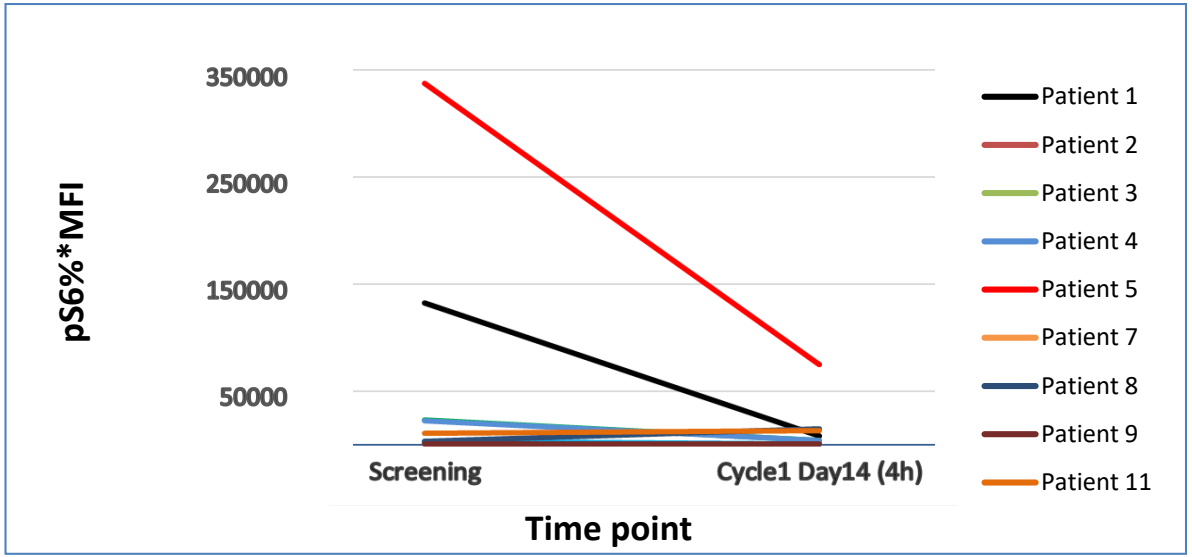
Following SEL24/MEN1703 treatment, blast pS6 inhibition was observed at the end of Cycle 1 in:

- 7 out of 10 PB samples (70%), range: 70-94%
- 4 out of 7 BM samples (57%), range: 26-76%

Patient #	Dose level (mg)	PB % pS6 inhibition*	BM % pS6 inhibition*
1	100	94	-64
2	100	70	77
3	100	83	26
4	100	82	-122
5	125	78	76
6	125	-211	N/A
7	125	89	40
8	125	-415	-234
9	125	75	N/A
10	125	N/A	N/A
11	125	-23	N/A

*pS6 inhibition (%)= $100 - \left(\frac{pS6\ test}{pS6\ screening}\right) \times 100$

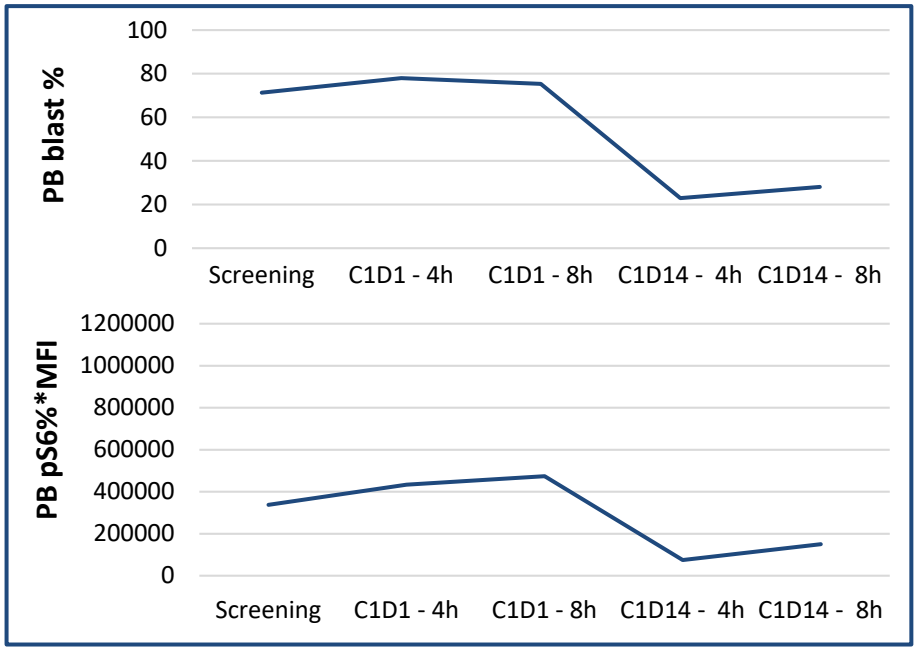
pS6 levels at Screening and C1D14 in PB

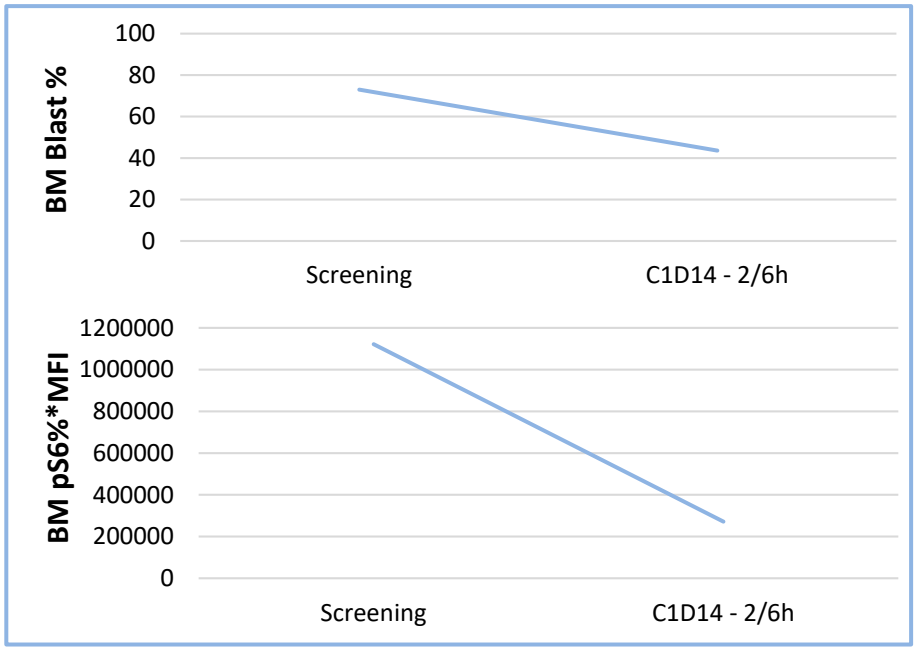


pS6 levels (determined as % of pS6 blast cells × MFI) were measured in PB blasts at screening and after the first cycle of dosing in patients treated at 100 and 125 mg

MFI: Median Fluorescence Intensity

Patient 5 blast/pS6 assesment in PB and BM





Patient 5 (125 mg cohort, >40-50% $pS6^{+}$ blasts) showed direct correlation between inhibition of pS6 and blast count reduction both in PB (left) and BM(right)

Conclusions

- The longitudinal pharmacodynamic (PD) study, performed through the assessment of S6 phosphorylation status by flow cytometry, confirmed that target engagement of patients treated with SEL24/MEN1703 at 100 and 125 mg was achieved, both in PB and BM

- Preliminary data suggest that the FLT3/PIM pathway inhibition might be associated with blast count reduction, particularly in patients with high pS6 values at baseline

- Longitudinal monitoring of PD will continue in the CE part of the DIAMOND-01 trial