Phase 1/2 study of SEL24/MEN1703, a first-in-class dual PIM/FLT3 kinase inhibitor, in patients with *IDH*1/2-mutated acute myeloid leukemia: The DIAMOND-01 trial

AML-389

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INTRODUCTION

- Acute myeloid leukemia (AML) is a highly aggressive condition with high mortality rates
- Increased understanding of the molecular and cytogenetic aspects of AML has facilitated the development of targeted therapies for different AML subsets
- The FMS-like tyrosine kinase 3 (FLT3) receptor tyrosine kinase is overexpressed on most AML blasts[1]
  - Mutations in FLT3 are the most frequently observed in AML patients (21–34% of de novo AML) and are associated with poor prognosis[2]
- Isocitrate dehydrogenase (*IDH*) *1* and *IDH2* mutations (collectively *IDH*m) are also observed in patients with AML and co-occur with FLT3 tyrosine kinase mutations in up to 30% of cases[3]
- Proviral integration site for Moloney murine leukemia virus (PIM) kinases may also be overexpressed in AML and PIM overexpression is thought to drive resistance to FLT3 inhibitors[4,5]
  - Preclinical data suggest that PIM inhibition restores sensitivity to FLT3 inhibitors in relapsed AML samples[6]
- Together, these data provide a strong rationale for dual targeting of the PIM and FLT3 kinase pathways
- SEL24/MEN1703 is an orally available, pan-PIM/FLT3 dual kinase inhibitor
- The phase 1/2 first-in-human DIAMOND-01 trial (NCT03008187) evaluated single-agent SEL24/MEN1703 in adults with AML
  - Preliminary data demonstrated promising antitumor activity in patients with relapsed/refractory (R/R) *IDH*m AML, where 3/8 patients had a response
- Herein, we report the safety and efficacy results from an additional expansion cohort of the DIAMOND-01 trial, which specifically enrolled patients with R/R *IDH*m AML, a population with an unmet need

METHODS

- This is a phase 1/2 study consisting of dose escalation (part 1) and cohort expansion (part 2) with an additional expansion cohort (*IDH*m) that is ongoing
- For the *IDH*m cohort, adult patients (≥18 years) with R/R AML who harbored *IDH* mutations and who had no standard therapeutic options were eligible
- The recommended dose of 125 mg SEL24/MEN1703 (as determined in part 1) was given orally, once daily for 14 days over a 21-day cycle until disease progression, withdrawal of consent, or unacceptable toxicity
- The primary endpoint was to further characterize the safety profile of single-agent SEL24/MEN1703; adverse events (AEs) were graded according to NCI CTCAE v4.03
- The secondary endpoint assessed the antileukemic activity of single-agent SEL24/MEN1703, including overall response rates (ORR), defined as complete remission (CR), CR with incomplete hematologic recovery (CRi), CR with partial hematologic recovery (CRh), and morphologic leukemic-free state

RESULTS

Patients

- As of 21 April 2022, 25 patients were enrolled in the *IDH*m expansion cohort
- Patient demographics and baseline characteristics are reported in **Table 1**
- In total, 5 patients remain on study and 20 patients have discontinued
  - The reasons for discontinuation were death (35% due to unrelated AEs, 5% due to disease progression), disease progression (25%), 'other' (20%), and investigator's decision (15%)

Table 1. Patient Demographics (N=25)

Age (years)	
Median (range)	**68** (33-79)
Sex, n (%)	
Male	**16** (64)
Female	**9** (36)
AML type, n (%)	
De novo	**18** (72)
Secondary to MDS	**6** (24)
Not reported*	**1** (4)
Cytogenetic risk category n, (%)	
Favorable	**2** (8)
Intermediate	**13** (52)
Unfavorable	**1** (4)
Not reported*/unknown	**9** (36)
AML status, n (%)	
Refractory	**6** (24)
Relapsed	**18** (72)
Not reported*	**1** (4)
Prior lines of therapy, n (%)	
1	**9** (36)
2	**9** (36)
3+	**5** (20)
Not reported*	**2** (8)
***IDH* mutation status, n (%)**	
IDH1	**9** (36)
IDH2	**14** (56)
IDH1/2	**1** (4)
Not reported*	**1** (4)
Concomitant mutational status, n (%)	
NPM1	**7** (28)
FLT3-ITD	**4** (16)
DNMT3A	**4** (16)
RUNX1	**3** (12)
ASXL1	**2** (8)
EZH2	**2** (8)
TP53	**1** (4)
CEBPA	**1** (4)
BAALC	**1** (4)
SRSF2	**1** (4)
WT1	**1** (4)
No additional	**9** (36)

*Data not available in the electronic case report form.

SEL24/MEN1703, a dual PIM/FLT3 inhibitor, has a tolerable safety profile and single-agent activity in patients with R/R *IDH*m AML

Table 2. Summary of Any Grade TEAEs (≥20% patients)

Preferred Term	All, n (%)	Related to MEN1703, n (%)
Asthenia	**8** (36)	**4** (18)
Nausea	**7** (32)	**6** (27)
Pneumonia	**6** (27)	**0**
Vomiting	**5** (23)	**5** (23)

Table 3. Summary of Grade ≥3 TEAEs (≥10% patients)

Preferred Term	All, n (%)	Related to MEN1703, n (%)
Pneumonia	**6** (27)	**0**
Asthenia	**4** (18)	**1** (5)
Thrombocytopenia	**3** (14)	**0**

Table 4. Summary of Serious TEAEs (≥5% patients)

Preferred Term	All, n (%)	Related to MEN1703, n (%)
Pneumonia	**6** (27)	**0**
Sepsis/Septic shock	**2** (9)	**0**

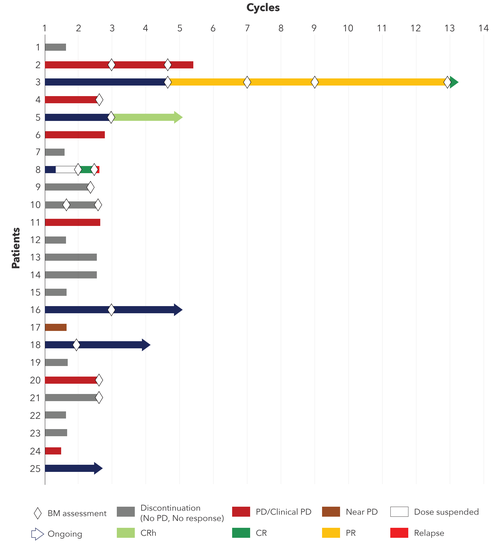
Safety

- The safety population consisted of 22 patients
- The most common any-grade treatment-emergent AEs (TEAEs) were asthenia (8/22) and nausea (7/22), reported as related to SEL24/MEN1703 in 4 and 6 patients, respectively (Table 2)
- Pneumonia (6/22, all unrelated), asthenia (4/22, 1 related), and thrombocytopenia (3/22, all unrelated) were the most common grade ≥3 TEAEs (**Table 3**)
- Serious TEAEs were pneumonia (6/22) and sepsis/septic shock (2/22), both unrelated to the study drug (**Table 4**)
  - One drug-induced liver injury occurred and was reported as possibly related to MEN1703 and other concomitant medications with known hepatotoxic potential (posaconazole, simvastatin, and paracetamol)
    - The extent of the contribution of each suspected drug cannot be defined, although it is well known that co-administration of posaconazole and simvastatin is contraindicated per label
- Three of 22 patients had a drug interruption as a result of treatment-related AEs (TRAEs), which were drug-induced liver injury, hyponatremia, and asthenia
- There were no drug discontinuations or deaths due to TRAEs
- No differentiation syndrome was observed

Efficacy

- The median duration of treatment was 2 cycles (range 1–13)
  - The **Figure** below displays the treatment duration and response by individual patient
- In total, 15 patients completed ≥1 treatment cycle and were efficacy evaluable
  - The ORR was 13%
  - One patient with *IDH2* and *NPM1* mutations had a partial remission at cycle 4 and achieved a CR at cycle 13. Treatment is ongoing in this patient and duration of response (DOR) is 177 days
  - One patient with an *IDH1* mutation achieved a CRh at cycle 3 and underwent hematopoietic stem cell transplant. Treatment is ongoing in this patient, with a DOR of 133 days

Figure. Individual Patient Treatment Duration



CONCLUSIONS

- Promising efficacy was seen, with an ORR and CR/CRi/CRh of 13% for the *IDH*m cohort, which is similar to monotherapy activity of other drugs in R/R AML
- SEL24/MEN1703 was well tolerated, with only asthenia, nausea, and vomiting reported as the most frequent TEAEs (any grade) possibly related to study drug
- No drug discontinuations or deaths occurred as a result of TRAEs
- The majority of grade ≥3 TEAEs were hematologic or infectious, and were mostly unrelated to study drug
- SEL24/MEN1703 may be a feasible therapy in this difficult-to-treat population of patients with R/R AML who harbor *IDH* mutations
- Clinical trials are planned in order to better explore the potential of SEL24/MEN1703 in combination with standard-of-care therapies in different AML patient populations

Abbreviations in Tables/Figure: AE, adverse event; AML, acute myeloid leukemia; BM, bone marrow; CR, complete response; CRh, CR with partial hematologic recovery; IDH, isocitrate dehydrogenase; mDOT, median duration of treatment; MDS, myelodysplastic syndrome; PD, progressive disease;PR, partial response; TEAE, treatment-emergent adverse event.

REFERENCES: 1. Carow CE, et al. Blood. 1996;87:1089-1096. **2.** Papaemmanuil E, et al. N Engl J Med. 2016;374:2209-2221. **3.** DiNardo CD, et al. Am J Hematol. 2015;90:732-736. **4.** Keeton EK, et al. Blood. 2014;123:905-913. **5.** Cheng H, et al. J Transl Med. 2017;15:179. **6.** Green AS, et al. Sci Adv. 2015;1:e1500221.

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