**ALICE: AN AML STUDY WITH LSD1i IN COMBINATION WITH AZACITIDINE IN THE ELDERLY**

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**Introduction**

Acute Myeloid Leukemia (AML) is primarily a disease of older people. Outcomes for the elderly remain poor, with less than 20% 5-year overall survival rates. Azacitidine (Aza) is approved for AML with 20-30% blasts. Lysine-specific demethylase (LSD1) has been shown to be a target in some gene transformations in AML and contributes to sustain the oncogenic process. Iadademstat is a highly potent and selective LSD1 inhibitor that has been shown to be effective in preclinical models (both alone or in combination with other compounds, including Aza). A Phase I FIM study supported that it is remarkably safe, and demonstrated preliminary anti-leukemic activity as monotherapy. Thus, iadademstat in combination with Aza may offer a novel treatment option for a patient group with limited therapeutic options.

**Study design and objectives**

ALICE is a Phase IIa, multicenter, open label clinical trial assessing the safety, tolerability and dose finding (DF) of iadademstat in combination with Aza, Depending on the dose limiting toxicities (DLTs), iadademstat may be escalated or de-escalated. Once the Recommended Phase II Dose (RP2D) is identified, an expansion cohort of 18 patients will include determination of specific biomarkers, morphological differentiation in blasts, determination of minimal residual disease (MRD) and PK/PD measures. ALICE is including subjects with AML diagnosis ≥60 years of age with AML ineligible for intensive chemotherapy (MRD) and PK/PD measures. ALICE is a two-stage trial. The dose finding (DF) stage will dose 12-18 patients with a starting dose of iadademstat of 90 μg/m²/d in combination with Aza. Depending on the dose limiting toxicities (DLTs), iadademstat may be escalated or de-escalated. Once the Recommended Phase II Dose (RP2D) is identified, an expansion cohort of 18 patients will be enrolled and treated with iadademstat in combination with Aza in this second stage. ALICE is including subjects with a 60 years of age with AML according to WHO classification, ineligible for intensive chemotherapy regimen at that time, or who refused standard chemotherapy, and have not received prior treatment for AML other than hydroxyurea.

**Results**

Six subjects have been recruited as per May cut-off into the DF stage. All of them have been treated with iadademstat at 90 μg/m²/d in combination with Aza. Depending on the dose limiting toxicities (DLTs), iadademstat may be escalated or de-escalated. Once the Recommended Phase II Dose (RP2D) is identified, an expansion cohort of 18 patients will be enrolled and treated with iadademstat in combination with Aza in this second stage. ALICE is including subjects with a 60 years of age with AML according to WHO classification, ineligible for intensive chemotherapy regimen at that time, or who refused standard chemotherapy, and have not received prior treatment for AML other than hydroxyurea.

**Highlights**

- Combination of iadademstat and azacitidine shows a good safety profile in elderly AML patients.
- Preliminary signals of clinical efficacy are encouraging, with 80% of ORs (4 out of 5; 3 CR and 1 PR).
- Rapid clinical responses (median time to first response 1.5 months).
- Recommended Phase II dose (90 μg/m²/d) established for the expansion stage of the trial.

**Study design**

- **Part 1:** Finding dose stage
  - iadademstat/5′-azacytidine (Aza) (starting dose) (4 subjects)
  - iadademstat/5′-azacytidine (Aza) (next dose) (4 subjects)
  - iadademstat/5′-azacytidine (Aza) (next dose) (2 subjects)

- **Part 2:** Expansion stage
  - iadademstat/5′-azacytidine (Aza) (RP2D) (6 subjects)

**Demographics: Enrolled patients**

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<td>80.00-60.50</td>
<td>162.50-160.00</td>
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**Preliminary Results: Efficacy**

Blood samples were used to assess treatment-induced cell differentiation. Cellular smears were visualized by standard optical microscopy after HE staining. RNA was extracted from peripheral blood cells and analyzed by qRT-PCR. ΔCt values were calculated relative to the pre-treatment sample and to the endogenous control gene HPRT1. PD biomarkers assayed include LIN12, S100A12, VCAN, CD66, among others.

**Preliminary Conclusions**

This Phase II study aims to explore the safety and efficacy of iadademstat in combination in elderly AML patients as a first line treatment, as a prelude of a broader application in other leukemia patients. Data to-date support that iadademstat has a good safety profile compared with other anti-leukemic or epigenetic agents and is a meaningful candidate for selective combinations with other agents in this and future leukemia studies. Added toxicity appears to be manageable. Based on safety data and TE evaluation, a RP2D has been selected.

Preliminary efficacy data in this limited sample is encouraging, with 80% of OR (of which 75% CR, 25% PR), and short time to responses. These preliminary results will be expanded in the coming months with additional patients and longer clinical observation times to better assess the frequency, consolidation and duration of the responses. LSD1 has a mechanistic role that been extensively characterized in MLL leukemia and erythroleukemia subtypes. However, these data support that the therapeutic applicability of LSD1 inhibition, alone or in combo, extends beyond these leukemia niches.

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