Iadademstat Shows Efficacy in Elderly AML Patients in Combination with Azacitidine. ALICE Trial

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Introduction

Acute Myeloid Leukemia (AML) is predominantly a disease of the elderly with an increasing incidence in the past decades. The probability of achieving complete remission and survival rates decrease with age, and there is rather limited treatment success with standard (chemotherapy) leading to 5-year survival rates of 20% or lower. It has been shown that Lysine-specific demethylase 1 ( LSD1) adds to malignant transformation in AML. Iadademstat is a potent and selective LSD1 inhibitor that has shown to be effective in preclinical models, both alone and in combination with other compounds, including azacitidine (Aza). A Phase I FIM study in AML showed that iadademstat exhibits a good safety profile and preliminary anti-leukemic activity as monotherapy. Iadademstat in combination with Aza may thus offer an alternative option for elderly AML patients, a population with limited therapeutic options.

Methods

ALICE is a Phase IIa clinical trial to assess the safety, tolerability and recommended dose of iadademstat in combination with Aza, and also to measure the clinical activity of the combination, including objective responses (OR) assessed by BM aspirates, along with PK/PD measures (including a set of 6 blood biomarkers).

In the dose finding Part (1) of the trial a maximum of 18 patients were to be treated with a starting dose of iadademstat of 90 μg/m² in combination with Aza at 75 mg/m². Iadademstat could be escalated or de-escalated depending on the observed dose limiting toxicities. After definition of the Recommended Dose (RD) in Part 1, an expansion cohort of 18 patients will be enrolled (Part 2). AML patients ≥ 60 years of age (diagnosis according to WHO classification), considered to be ineligible for intensive chemotherapy without prior treatment for AML other than hypoxaemia, can be enrolled. Later on, the study protocol was amended to allow dosing variations of Aza and iadademstat to manage possible hematological events, as well as to contemplate the opportunity to re-escalate the dose of iadademstat (to 90 μg/m²) in case of good tolerability but where no CR/CRI had been achieved.

Results and Discussion

SAFETY: The Safety Monitoring Committee (SMC) of the study initially selected a RD of iadademstat of 90 μg/m² in combination with Aza 75 mg/m². This decision was made based on data from the first 6 subjects, where this dose was well tolerated and only 1 DLT (differentiation syndrome; Patient #10) was observed, and based on the fact that the selected dose: i) was able to saturate LSD1 target engagement in PBMCs after 5 days of treatment; ii) was well tolerated (11 treatment cycles were completed at the moment of decision) and iii) demonstrated initial signs of efficacy. After recruitment of additional patients at the same dose, there was one patient who withdrew consent after experiencing severe fatigue (Patient #5; CD42B), and another patient (Patient #11) died due to an intracranial hemorrhage on CD115. The SMC then decided to reduce the dose of iadademstat to 60 μg/m², a dose level also able to saturate LSD1 target engagement and with a clear biomarker effect, but with a potential better tolerability and therefore a better adherence to treatment schedule. The combination appears to be safe and well tolerated and, up to date, no clinically relevant non-hematological adverse events have been reported.

EFFICACY: At the date of writing, 13 patients have been enrolled in ALICE: 8 have had ≥ 1 BM evaluation (evaluable patients as per protocol), 3 died before their first BM evaluation (one of them by an accidental fall not related to disease progression (Patient #9)), and 2 were just starting treatment (cycle 1) at the time of data cut. The mean follow up time amongst the evaluable patients was 20 weeks, with a Mean Time to Response (TTR) of only 32 days (in those patients who respond). Six of the 8 evaluable patients (75 %) achieved OR responses: 2 CR, 3 CRI and 1 PR. Two of the 5 patients (40%) that have received more than 3 cycles of treatment have also become transfusion independent (not requiring subsequent red cell transfusions). Excluding Patient #9, who died from a domestic accident without BM assessment, and not considering patients #12 and #13 still in CR1, the OR rate in Intention-to-treat patients was 60% (6 of 10 patients).

Acknowledgements

We thank the investigators and teams and, most importantly, the patients who participate in the study and their families. This study is partially funded thanks to the Retos program RTC-2017-6407-1.