Preliminary Results of the Stapled Peptide ALRN-6924, a Dual Inhibitor of MDMX and MDM2, in Two Phase IIa Dose Expansion Cohorts/Refractory TP53 Wild-Type Peripheral T-Cell Lymphoma

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Objective

A study to evaluate the safety and tolerability of ALRN-6924 in patients with relapsed or refractory PTCL who have received at least one prior systemic therapy regimen. ALRN-6924, a first-in-class stapled peptide dual inhibitor of MDMX and MDM2, is designed to engage with ≥2 targets, e.g. MDMX + MDM2. It shows enhanced binding properties at the interface of protein-protein interactions, displaying a larger surface area of interaction with its target, and providing superior binding properties and clinical activity relative to unmodified peptides due to increased stability and increased drug exposure, allowing for once-weekly dosing. ALRN-6924 has shown antitumor activity in patients with head and neck squamous cell carcinoma, melanoma, and breast cancer.

Background

Peripheral T-cell lymphomas (PTCL) are a rare and heterogeneous group of NHL with poor prognosis. Frontline therapy yields a 40-50% overall response rate, but the majority of patients will relapse, which translates to poor overall survival. An ongoing durable CR (≥2.5 years) has been reported in a patient with an angioimmunoblastic subtype of PTCL in the first-in-human study of ALRN-6924, providing the rationale to evaluate the activity of ALRN-6924 in PTCL patients.

Methods

- Patients with relapsed or refractory PTCL are receiving treatment with 3.1 mg/kg of ALRN-6924 IV over 1 hour on every other week (QW) or every three weeks (TIW), with TIW as the preferred term for both treatment arms. 
- TIW dosing is expected to be used for up to 12 weeks, followed by QW dosing if stable disease is achieved.
- Treatment duration will be determined based on the patient's response to therapy, with the goal of maintaining durable responses over time.
- Treatment with ALRN-6924 is not to exceed 12 weeks in CR, PR, or SD patients, and up to 24 weeks in those achieving a partial response with disease stabilization.
- The main reasons for treatment discontinuation include clinical or objective disease progression (70.8%) and treatment-related adverse events (25.0%).
- Mean/median duration of treatment was 166/45 days for Cohort A (QW dosing) and 50/28 days for Cohort B (TIW dosing).
- The tumor burden in target lesions is evaluated every 4 weeks using modified Cheson 2007 and IWG 2014* criteria. A total of 10 cycles is planned for each cohort.

Results

- Preliminary activity observed in Cohort A (QW dosing) of this early phase clinical trial is similar to that observed in the phase I study in patients with solid tumors and lymphomas, based on data. No Aileron-sponsored pivotal trial planned for strategic reasons.
- ALRN-6924 as single agent has shown an acceptable safety profile on both QW and TIW dosing schedules, with no treatment-related fatalities, with only 7.5% of patients discontinued due to adverse events.
- ALRN-6924 therapy is well tolerated and demonstrates clinical activity in patients with relapsed/refractory PTCL.
- The primary objective of safety and tolerability of ALRN-6924 given once-weekly and three times per week was met.
- The secondary objective of antitumor activity was also met, as ALRN-6924 has shown an acceptable safety profile and clinical activity in patients with relapsed/refractory PTCL.

Conclusions and Study Statistics

- ALRN-6924 as single agent has shown an acceptable safety profile on both QW and TIW dosing schedules, with better treatment compliance with QW dosing.
- Preliminary activity observed in Cohort A (QW dosing) of this early phase clinical trial is similar to that reported with other available agents in relapsed/refractory PTCL patients.
- Despite encouraging data from FDG-PET models, TIW dosing schedule is logistically challenging. Reduced response rates observed with TIW dosing are likely due to poor treatment compliance resulting in shorter treatment duration.
- The potential for pseudoprogression was not initially recognized, hence raising the possibility that the response rate for QW may be higher had treatment with ALRN-6924 been continued.
- Enrollment expected to complete by year-end 2018; future development path for PTCL to be decided based on data.
- ALRN-6924’s favorable safety profile will facilitate exploration of combination therapy in this and other difficult-to-treat diseases.

References