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

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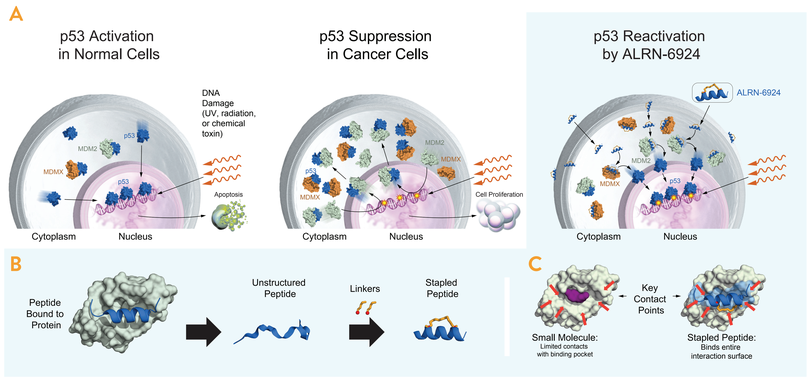
Background

Figure 1: The Cell-Permeating α-helical Peptide, ALRN-6924, is a First-in-Class Dual Inhibitor of MDMX and MDM2



A) The tumor suppressor p53 is one of the most pursued targets in oncology, playing a central role inducing cell cycle arrest, apoptosis, senescence, autophagy, cellular metabolism and immune surveillance in response to cellular stresses such as DNA damage and oncogenic signals[1]. B) ALRN-6924, a cell-permeating, stapled α-helical peptide that has demonstrated anticancer activity as monotherapy in clinical trials[2], mimics the p53 tumor suppressor protein to disrupt its interactions with both its endogenous inhibitors, MDMX and MDM2[3,4]. Stapled peptides mimic natural peptide sequences at the interface of protein-protein interactions, displaying a larger surface area of interaction with its target, and providing superior binding properties which reduce off-target effects and the risk of acquiring mutations associated with resistance. C) Furthermore, like natural protein sequences, a peptide can engage with ≥2 targets, e.g. MDMX + MDM2.

- Peripheral T-cell lymphomas (PTCL) are a rare and heterogeneous group of NHL with poor prognosis. Frontline therapy yields a 50-70% 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[2].
- ALRN-6924 was tested once a week, then 3 times per week based on preclinical data that suggested more frequent dosing may enhance efficacy[3,4].

Primary Objectives of the Two Expansion Cohorts

- Assess overall response rate.
- Evaluate the safety and tolerability of ALRN-6924 given once weekly and three times per week .

Methods

- Patients with relapsed or refractory PTCL are receiving treatment with 3.1 mg/kg of ALRN-6924 IV over 1 hour on:
  - Cohort A (QW dosing): Days 1, 8, and 15 of a 28-day cycle
  - Cohort B (TIW dosing) Days 1, 3, and 5 of a 21-day cycle
- Response is evaluated by investigators according to IWG 2014. Additionally, an independent radiologist reviews response using IWG 2014 and Cheson 2007, modified due to absence of bone marrow biopsies.
- Adverse events (AEs) are assessed per CTCAE V4.03.

Key Inclusion Criteria

- A histologically confirmed diagnosis of PTCL based on pathology review at the local institution, using the most recent edition of the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues as guidance.
- Relapsed or refractory disease after at least one but not more than 7 prior systemic anticancer regimens.
- WT TP53 status of T-cell lymphoma cells.

Table 1: Patient Characteristics

	QW (n=16)	TIW (n=13)
Age in years, median (range)	63 (31, 82)	60 (35, 80)
Gender		
Male (%)	56%	54%
Female (%)	44%	46%
Race		
White (%)	56%	54%
Black (%)	31%	31%
Asian (%)	13%	15%
ECOG		
0	25%	46%
1	75%	39%
2	0%	15%
Prior systemic therapies, median (range)	3.5 (1, 9)	2.0 (1, 4)
PTCL subtype		
PTCL NOS	7	3
AITL	4	3
ALCL, ALK-	2	3
ATLL	2	3
Other	1	1

Data cut: 08Oct2018. * Includes patient from Phase 1

Table 2: Related Non-Hematologic TEAE (≥ 10% in All Patients)

	QW (n=16)			TIW (n=13)		
	All Grades	Grade 3	Grade 4/5	All Grades	Grade 3	Grade 4/5
Patients Reporting at Least One Related TEAE	94%	50%	0%	69%	38%	0%
Nausea	56%	0%	0%	54%	15%	0%
Fatigue	62%	12%	0%	38%	8%	0%
Constipation	12%	0%	0%	15%	0%	0%
Diarrhea	12%	0%	0%	15%	0%	0%
Headache	25%	0%	0%	0%	0%	0%
Vomiting	19%	0%	0%	8%	8%	0%
Hyperbilirubinemia	6%	6%	0%	15%	8%	0%
Infusion-related reaction	12%	0%	0%	8%	0%	0%

Data cut: 08Oct2018. *Hyperbilirubinemia associated with ALRN-6924 has been transient and not associated with evidence of liver injury. No patients met "Hy's Law Criteria."

Table 3: Related Hematological Adverse Events

	QW (n=16)			TIW (n=13)		
	All Grades	Grade 3	Grade 4/5	All Grades	Grade 3	Grade 4/5
Anemia	19%	12%	0%	15%	0%	0%
Thrombocytopenia	12%	6%	0%	0%	0%	0%
Neutropenia	6%	6%	0%	8%	0%	0%
Decreased WBC count	0%	0%	0%	0%	0%	0%
Lymphocytopenia	0%	0%	0%	0%	0%	0%

Data cut: 08Oct2018. Eligibility for trial included ANC ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L, unless patient had autoimmune destruction and/or splenomegaly and/or hepatic disease infiltration.
+Grade 1 baseline thrombocytopenia; ++Grade 2 baseline neutropenia.

Table 4: Related SAEs

Cohort	Preferred Term
QW	Grade 3 pneumonia*
TIW	Grade 3 hyperbilirubinemia+
TIW	Grade 3 hyponatremia
TIW	Grade 3 nausea/vomiting

Data cut: 08Oct2018. *secondary to obstruction by a lymph node.
+an expected side effect of ALRN-6924 due to inhibition of OATBi & B3 biliary transporters.

Table 5: AEs leading to Discontinuation (Regardless of Relationship)

Cohort	Preferred Term	Relationship
QW	Grade 1 infusion-related reaction	Definite
QW	Grade 3 hemophagocytic lymphohistiocytosis	Unrelated
QW	Grade 1 neck pain	Unrelated
TIW	Grade 2 hypokalemia/Grade 3 hyponatremia	Unlikely
TIW	Grade 3 fatigue/Grade 3 nausea	Probable
TIW	Grade 2 nausea/Grade 1 fatigue	Possible

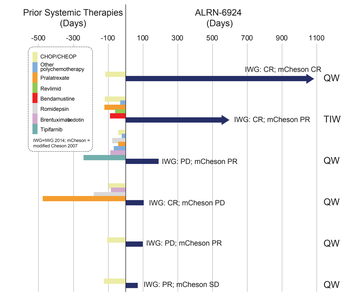
Data cut: 08Oct2018.

Table 6: Efficacy

QW+ (n=16 enrolled)	IWG 2014* (n=14 evaluable)	Modified-Cheson 2007** (n=15 evaluable)
Overall Response Rate (CR, PR)	21%	27%
Disease Control Rate (CR, PR, SD)	36%	47%
TIW (n=13 enrolled)	**IWG 2014* (n=7 evaluable)**	**Modified-Cheson 2007** (n=7 evaluable)**
Overall Response Rate (CR, PR)	14%	0%
Disease Control Rate (CR, PR, SD)	14%	14%

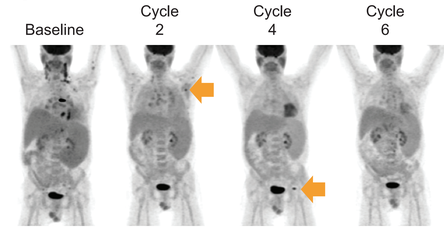
Data cut: 08Oct2018. + Includes patient from Phase 1.
*IWG per investigator (primary objective).
** Modified-Cheson per independent radiologist read (exploratory objective).
Evaluable patients include those with p53 WT, at least one dose of ALRN-6924, and had at least one post-baseline scan or non-radiographic disease progression.

Figure 2: Treatment Duration



Duration of ALRN-6924 and prior therapies in responding patients

Figure 3: Example of Pseudoprogression in QW Patient



64 year old male with PTCL, NOS, s/p 7 prior lines of therapy. Marked reduction in target lesion volume (reduction of 73% after 2 cycles and 88% after 6 cycles). Newly FDG PET avid lesions transiently appear (arrows) despite continued reduction in target lesions. Similar response patterns were identified subsequently in additional patients.

Treatment Exposure

- Over the first 2 cycles of treatment, adherence to treatment schedule was 89% in Cohort A patients (QW dosing) and 35% in Cohort B patients (TIW dosing).
- Mean/median duration of treatment was 166/45 days for Cohort A (QW dosing) and 50/28 days for Cohort B (TIW dosing). 12.5% (or 2 out of 16) of patients in Cohort A and 23% (or 3 out of 13) in Cohort B remain on treatment.

Results

- Responses have been seen across multiple PTCL subtypes including ALK- ALCL, AITL, PTCL-NOS, and ATLL*.
- Main reasons for treatment discontinuation include clinical or objective disease progression (70.8%) and AE (12.5%).

*per ATLL criteria[5], IWG response pending

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 schedule.
- 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 PDX 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. No Aileron-sponsored pivotal trial planned for strategic reasons.
- ALRN-6924's favorable safety profile will facilitate exploration of combination therapy in this and other difficult-to-treat diseases.

References

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