Phase 1/1b Study of the Stapled Peptide ALRN-6924, a Dual Inhibitor of MDMX and MDM2, as Monotherapy or in Combination with Cytarabine for the Treatment of Relapsed/Refractory AML and Advanced MDS with TP53 Wild-Type

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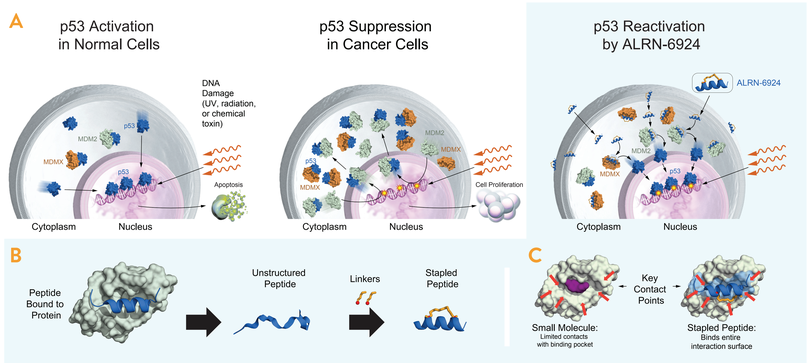
Background

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, mimics the p53 tumor suppressor protein to disrupt its interactions with both its endogenous inhibitors, MDMX and MDM2[2,3]. 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.

- In preclinical studies, ALRN-6924 inhibited the proliferation of AML cell lines and primary human AML cells alone and in combination with cytarabine.
- ALRN-6924 exerted leukemia cell-specific on-target pharmacodynamic activity *in vivo* in a patient treated with ALRN-6924 for compassionate use[3].
- Preclinical data demonstrated antiproliferative effects against leukemic stem cells, and complete responses that translated into cures in approximately 40% of mice in xenotransplantation studies. These data also suggested that more frequent dosing may enhance efficacy, and this hypothesis is now being evaluated in the ongoing clinical trial[3].

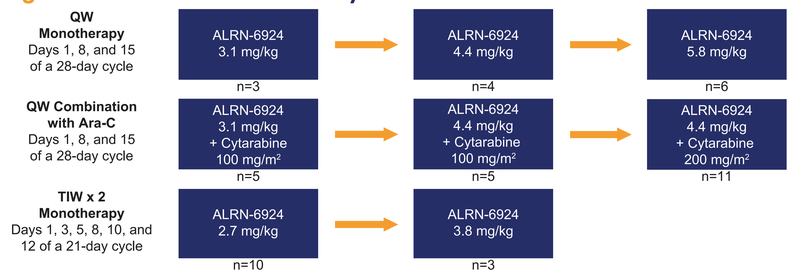
Primary Objectives

- Evaluate the safety and tolerability of ALRN-6924 alone and in combination with cytarabine (Ara-C) in adult patients with acute myeloid leukemia (AML) or advanced myelodysplastic syndrome (MDS) with wild-type (WT) TP53 who are relapsed/refractory to or intolerant of standard therapy, or for whom no standard therapy exists.
- Determine the dose limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of ALRN-6924 alone and in combination with cytarabine in adult patients with AML or advanced MDS.

Methods

- ALRN-6924 is being evaluated alone and in combination with low-dose cytarabine, using a 3+3 dose escalation design.
- Adverse events (AEs) are assessed per CTCAE V4.03.
- Responses are evaluated by the investigators according to IWG (Cheson 2006) and AML Response Criteria (Dohner 2010), for MDS and AML, respectively.

Figure2: ALRN-6924-1-02 Study



Key Inclusion Criteria

- AML: Relapsed or refractory acute myeloid leukemia according to WHO criteria.
- MDS: Diagnosis of MDS according to WHO criteria; not responsive to, intolerant to, or progression after hypomethylating agents.
- Confirmed or anticipated WT TP53 status by Next Generation Sequencing assay.
- ECOG performance status 0-2.

Table 1: Patient Characteristics

	QW mono (n=13)	QW combo (n=21)	TIW (n=13)
Age in years, median (range)	75 (42-90)	75 (38-86)	70 (47-86)
Gender			
Male (%)	62%	62%	62%
Female (%)	38%	38%	38%
Race			
White (%)	77%	91%	100%
Black (%)	15%	0%	0%
Other (%)	8%	9%	0%
ECOG			
0	8%	5%	23%
1	92%	90%	69%
2	0%	5%	8%
Prior systemic therapies, median (range)	2 (1, 10)	2 (1, 9)	2 (1, 4)
MDS	46%	48%	8%
De novo AML	39%	24%	46%
Secondary AML	15%	29%	46%
History of MDS	50%	83%	100%
Therapy-related AML	50%	17%	0%

Data cut: 08Oct2018.

Table 2: Patient Disposition

	QW mono (n=13)	QW combo (n=21)	TIW (n=13)
Discontinued from study	100%	81%	92%
Disease progression/ Treatment failure	31%	53%	58%
Consent withdrawn	39%	18%	8%
Adverse event	15%	6%	17%
Death	15%	6%	8%
Other	0%	12%	8%
Continued to transplant	0%	6%	0%

Data cut: 08Oct2018.

Table 3: Related TEAE (≥ 10% in All Patients)

	QW mono (n=13)	QW combo (n=21)	TIW (n=13)
Patients reporting at least one related TEAE	84.6%	47.6%	38.5%
Patients reporting at least one ≥ Grade 3 TEAE	30.8%	38.0%	38.5%
Nausea	38.5%	19.0%	15.4%
Vomiting	46.2%	14.3%	7.7%
Thrombocytopenia	23.1%	23.8%	0.0%
Fatigue	23.1%	9.5%	15.4%
Diarrhea	15.4%	14.3%	7.7%
Hyperbilirubinemia	30.8%	9.5%	0.0%

Data cut: 08Oct2018.

Table 4: Related SAEs

Cohort	Preferred Term	DLT in C1
4.4 mg/kg QW + 200mg/m2 Ara-C	Grade 3 pain in extremity	No
4.4 mg/kg QW + 200mg/m2 Ara-C	Grade 3 nausea	No
5.8 mg/kg QW	Grade 4 angioedema	No
3.8 mg/kg TIW	Grade 3 asthenia	Yes
3.8 mg/kg TIW	Grade 5 tumor lysis syndrome	Yes

Data cut: 08Oct2018.

Table 5: AEs leading to Discontinuation or Death

Cohort	Preferred Term	Relationship
3.1 mg/kg QW	Grade 3 fatigue	Possible
3.1 mg/kg QW + 100 mg/m² Ara-C	Grade 5 pneumonia	Unrelated
4.4 mg/kg QW + 200 mg/m² Ara-C	Grade 4 thrombocytopenia	Unrelated
5.8 mg/kg QW	Grade 4 angioedema	Probable
5.8 mg/kg QW	Grade 5 sepsis	Unrelated
2.7 mg/kg TIW	Grade 4 lung infection	Unrelated
3.8 mg/kg TIW	Grade 3 asthenia	Probable
3.8 mg/kg TIW	Grade 5 tumor lysis syndrome	Probable

Data cut: 08Oct2018.

Figure 3: Patients Show Anti-Cancer Activity

All MDS patients dosed with Combo of 4.4 mg/kg ALRN-6924 + Ara-C with disease evaluations: 5/6 evaluable patients show anti-cancer activity.

Table 6: Efficacy

ALRN-6924 as single agent:

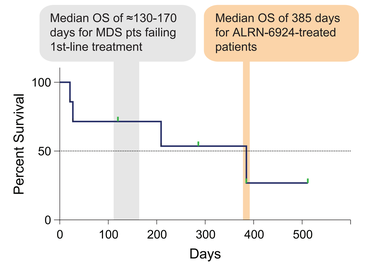
- No formal responses were seen across 11 efficacy-evaluable AML or MDS patients who received ALRN-6924 at 3.1, 4.4, and 5.8 mg/kg, QWx3 every 28 days; enrollment has been completed in this dosing arm.
- No formal responses have been seen across 8 efficacy-evaluable AML or MDS patients who received ALRN-6924 at 2.7, and 3.8 mg/kg, TIWx2 every 21 days; enrollment is still ongoing in this dosing arm.

ALRN-6924 in combination with Ara-C:

QW combo therapy (evaluable patients)	3.1 mg/kg + 100 mg Ara-C (n=4)	4.4 mg/kg + 100 mg Ara-C (n=4)	4.4 mg/kg + 200 mg Ara-C (n=8)
Response rate	0%	25%	25%
HI (MDS only)	0%	100%	20%

Data cut: 08Oct2018.
Response rate = CR/CRi or PR or a marrow CR (MDS, only).
HI = hematological improvement, calculated out of MDS patients in cohort.

Figure 4: Preliminary Analysis of Overall Survival Among a Subset of MDS Patients



Unplanned analysis of OS among MDS patients treated with 4.4 mg/kg ALRN-6924 in combination with cytarabine during dose escalation.

Conclusions and Study Statistics

- ALRN-6924 QW and TIW monotherapy and in combination in cytarabine have acceptable safety profiles in relapsed/refractory AML and MDS.
  - No DLTs with QW monotherapy.
  - DLTs of fatal TLS and Grade 3 asthenia at 3.8 mg/kg TIW.
  - No DLTs in combination with cytarabine.
- Dose escalation of QW monotherapy concluded at maximum planned dose of 5.8 mg/kg; no MTD reached.
- Dose optimization of TIW monotherapy continues.
- ALRN-6924 in combination with low-dose Ara-C has shown preliminary clinical activity in MDS patients, including marrow CRs and hematological improvement, with one patient bridged to transplant.
- Accrual to the ALRN-6924 + Ara-C combination cohort and the TIW monotherapy cohort continues.

References

1. Bieging KT et al., Unravelling mechanisms of p53-mediated tumour suppression, *Nat Rev Cancer*. 2014; 14 (5):359-70
2. Meric-Bernstam F.et al., Phase I trial of a novel stapled peptide ALRN-6924 disrupting MDMX and MDM2-mediated inhibition of WT p53 in patients with solid tumors and lymphomas, *J Clin Oncol*. 2017; 35 (15):2505-2505
3. Carvajal L.A. et al. Dual inhibition of MDMX and MDM2 as a therapeutic strategy in leukemia, *Sci Transl Med*. 2018; 10 (436)

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