ALRN-6924 is a Dual MDMX/MDM2 Inhibitor and Can Protect the Bone Marrow of Cancer Patients Treated with Chemotherapy

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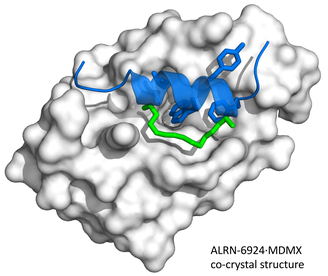
Abstract

ALRN-6924 is a cell-permeating, stabilized alpha-helical peptide that binds with high affinity to endogenous p53 inhibitors MDM2 and MDMX. In cancer patients with tumors harboring p53 mutations ALRN-6924 is expected to selectively induce cell cycle arrest in normal cells with wildtype p53 and reduce chemotoxicity, thus increasing the therapeutic index of chemotherapy.

In an ongoing Phase 1 study in heathy volunteers ALRN-6924 given at 0.3 mg/kg demonstrated excellent tolerability and preferential, p53-mediated induction of p21 in bone marrow cells, without concurrent induction of apoptosis. In a chemoprotection clinical study in patients with extensive disease SCLC treated with topotecan, ALRN-6924 given at the 0.3 mg/kg dose 24h prior to topotecan showed a strong signal of chemoprotection, reducing NCI CTC Grade 3/4 anemia and thrombocytopenia by 70% and 29%, respectively, and reducing Grade 4 neutropenia by 42%, relative to historic controls (Hart et al. ASCO 2019). Platelet and RBC transfusion rates were decreased by 83% and 85%, respectively, relative to historic controls.

ALRN-6924 has the potential to significantly reduce hematological toxicity in cancer patients receiving chemotherapy.

1: Structure And Key Design Properties Of ALRN-6924

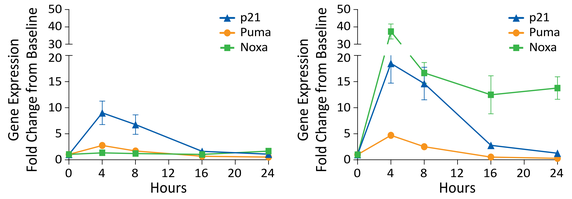


ALRN-6924-MDMX co-crystal structure

Structure is based on the α-helical N-terminal domain of p53, with a hydrocarbon staple and other chemical modifications to ensure:

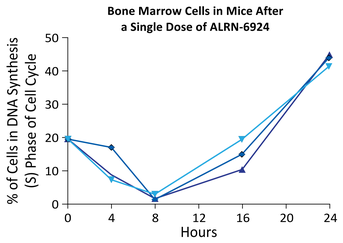
- I Protection from proteolytic cleavage
- II Permeation of cell membranes and cell entry
- III High affinity binding to its targets
- IV Preclinical and clinical on-target, on-mechanism effects

2: ALRN-6924 Induces Expression of Genes for Cell Cycle Arrest or Apoptosis in Mouse Bone Marrow in a Dose-Dependent Manner



Low-dose ALRN-6924 (2.5 mg/kg) induces cell cycle arrest marker p21, while high-dose ALRN-6924 (10 mg/kg) also induces pro-apoptotic markers Noxa and Puma in mouse bone marrow. ALRN-6924 dosed IV in C57BL/6 mice at t=0, then blood, bone marrow, and serum sampled at 4, 8, 16, 24 hours post-dose.

3: ALRN-6924 Induces Cell Cycle Arrest in Bone Marrow of Mice *in vivo*



Cell cycle arrest in the bone marrow of ALRN-6924-treated C57BL/6 mice was measured by flow cytometry using EdU incorporation in lineage negative, c-Kit positive hematopoietic stem and progenitor cells. ALRN-6924 dosed with IV at t=0, then blood, bone marrow, and serum sampled at 4, 8, 16, 24 hours post-dose.

4: Clinical Study to Evaluate ALRN-6924 in Healthy Human Volunteers

PART 1 — Determination of Optimal Dose

Three groups of subjects were treated with a single dose of placebo (n=6), ALRN-6924 0.3 mg/kg (n=4), or ALRN-6924 0.6 mg/kg (n=4)

PART 2 — Kinetics of Pharmacodynamic Effects in the Bone Marrow

23 subjects were treated with a single dose of 0.3 mg/kg ALRN-6924, with bone marrow sampled from **3** subjects each at successive time points 4-48 hrs post-dose

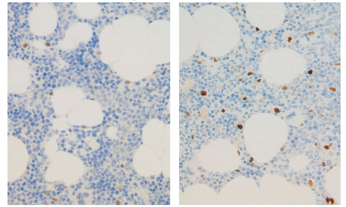
PART 3 — Confirmation of a Universal Treatment Schedule for ALRN-6924

16 subjects were treated in groups of **4**, each receiving 1, 2, 3, or 4 doses of ALRN-6924, bone marrow sampled 18 hrs after each dose

5: Effects of ALRN-6924 on p21 (Cell Cycle Arrest) and Cleaved-PARP (Apoptosis) in Bone Marrow of Healthy Human Volunteers

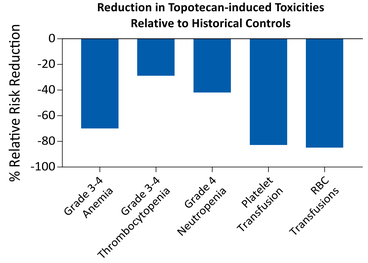
		p21, % at Differential Intensities				cPARP
Subject	Group	0	1+	2+	3+	# cells per HPF
1	Plac.	100	0	0	0	2
2	"	100	0	0	0	1
3	"	100	0	0	0	19
4	"	100	0	0	0	12
5	"	100	0	0	0	19
6	"	100	0	0	0	21
7	0.3 mg/kg	94	0	2	4	19
8	"	96	0	2	2	21
9	"	96	0	1	3	7
10	"	95	0	1	4	85
11	0.6 mg/kg	94	0	1	5	17
12	"	93	0	2	5	61
13	"	97	0	3	0	70
14	"	95	3	2	0	96

Representative p21 Staining



Analysis by immunohistochemistry of bone marrow cores sampled 8 hrs post-dose. Scoring was conducted by a pathologist blinded to experimental conditions. HPF = high-power field.

6: ALRN-6924 is an Effective Chemoprotection Agent for Small-cell Lung Cancer Patients Receiving Topotecan[1]



ALRN-6924 given at a 0.3 mg/kg dose 24 hr prior to topotecan reduced NCI-CTC Grade 3/4 anemia and thrombocytopenia by 70% and 29%, respectively, and reduced Grade 4 neutropenia by 42% relative to historic controls.[2] Platelet and RBC transfusion rates were decreased by 83% and 85%, respectively, relative to historic controls.

Conclusions

- ALRN-6924 is a potent and specific p53 agonist; this activity is achieved by its binding to p53 endogenous inhibitors MDM2 and MDMX.
- In healthy volunteers ALRN-6924 has demonstrated excellent tolerability and preferential, p53-mediated induction of p21 in bone marrow cells.
- SCLC patients treated with ALRN-6924 experienced reduced bone marrow toxicity relative to historic controls.
- Clinical development of ALRN-6924 is ongoing with a recently initiated randomized, placebo-controlled trial in NSCLC patients receiving chemotherapy or immunochemotherapy.

References

1. Prevention of Chemotherapy-induced Myelosuppression in SCLC Patients Treated with the Dual MDMX/MDM2 Inhibitor ALRN-6924. Andric et al., EJC 138, Suppl 2, S5 Oct 01, 2020. ClinicalTrials.gov Identifier: NCT04022876

2. Effect of Trilaciclib, a CDK 4/6 Inhibitor, on Myelosuppression in Patients with Previously Treated Extensive-Stage Small Cell Lung Cancer. Hart et al. ASCO Annual Meeting 2019

Acknowledgments

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