A Phase 1b Study of the Dual MDMX/MDM2 Inhibitor, ALRN-6924, for the Prevention of Chemotherapy-induced Myelosuppression

#1654P

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Summary

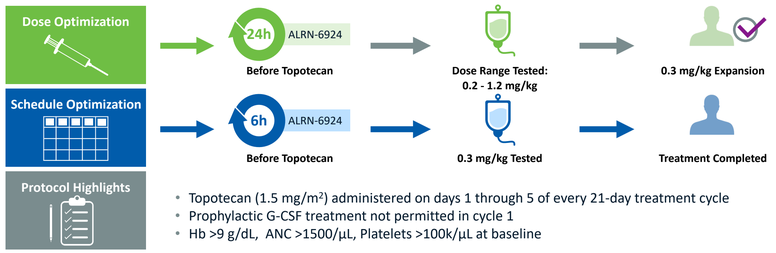
Background: ALRN-6924 is a cell-permeating, stabilized alpha-helical peptide that binds with high affinity to endogenous p53 inhibitors MDM2 and MDMX. Treatment with ALRN-6924 initiates p53 transcriptional activity, leading to cell cycle arrest. This effect is limited to cells with wild-type, functional p53; therefore, for cancer patients with tumors harboring mutated p53, pre-treatment with ALRN-6924 selectively induces cell cycle arrest in normal cells, thus allowing chemotherapy to preferentially target p53-mutant cancer cells that are actively cycling.

Materials and Methods: A Phase 1b study was conducted in extensive disease small-cell lung cancer (ED SCLC) patients with ECOG performance status (PS) 0-2 receiving treatment with five daily doses of topotecan (topo). ALRN-6924 was given either 24 hr or 6 hr prior to each 1.5 mg/m² topo infusion. The objective was to evaluate ALRN-6924 at different dose levels and two treatment schedules for the mitigation of chemotherapy-induced myelosuppression. Hematology assessments occurred on treatment days 1-5 and on day 12 of each 21-day therapy cycle, with laboratory values coded as AEs based on NCI CTC v5.0.

Results: 39 (38 evaluable) patients with ED SCLC were enrolled. 31 patients were treated on the 24 hr schedule: 0.2 mg/kg (N=4), 0.3 mg/kg (N=16), 0.6 mg/kg (N=6; 5 evaluable) and 1.2 mg/kg (N=6). 7 patients were treated with 0.3 mg/kg of ALRN-6924 at 6 hr prior to topo. Median patient age was 67 years, 74% males, ECOG PS 0 59% / PS 1 39%, baseline LDH ≥ULN 56%, chemosensitive population 51%. Median number of completed topo treatment cycles was 3. 13% of patients required topo dose reduction. No patients reported NCI CTC Grade ≥3 events of nausea, vomiting, diarrhea; 5% had Grade 3 fatigue.

The 0.3 mg/kg ALRN 6924 dose level 24 hr prior to topo showed the most favorable chemoprotection results, with NCI CTC Grade 3/4 anemia and thrombocytopenia limited to 19% and 44% of patients, respectively, and a 31% rate of Grade 4 neutropenia in the first cycle of treatment. Those results compare favorably to recent historical results of 63%, 70% and 76%, respectively.[1] None of the patients treated at the 0.3 mg/kg, 24 hr dose level had a related SAE; 6% required RBC and platelet transfusions (historical result: 41% and 36%, respectively).

Figure 1: ALRN-6924 Phase 1b Study Schema



- Topotecan (1.5 mg/m²) administered on days 1 through 5 of every 21-day treatment cycle
- Prophylactic G-CSF treatment not permitted in cycle 1
- Hb >9 g/dL, ANC >1500/µL, Platelets >100k/µL at baseline

Table 1: Demographics and Key Baseline Disease Characteristics

		24H SCHEDULE				6H SCHEDULE	TOTAL
		0.2 N=4	0.3 N=16	0.6 N=6	1.2 N=6	0.3 N=7	N=39
AGE, MEDIAN		65	68.5	66.5	58	69	67
GENDER N (%)	MALE	2 (50)	16 (100)	3 (50)	4 (67)	4 (57)	29 (74)
	FEMALE	2 (50)	0	3 (50)	2 (33)	3 (43)	10 (26)
BASELINE LDH N (%)	<ULN	1 (25)	9 (56)	2 (33)	4 (67)	1 (14)	17 (44)
	≥ULN	3 (75)	7 (44)	4 (67)	2 (33)	6 (86)	22 (56)
TIME SINCE COMPLETION OF PREVIOUS THERAPY N (%)	<60 DAYS	1 (25)	8 (50)	1 (17)	5 (83)	3 (43)	18 (46)
	≥60 DAYS	3 (75)	7 (44)	5 (83)	1 (17)	4 (57)	20 (51)
	MISSING	0	1 (6)	0	0	0	1 (3)
BASELINE ECOG STATUS N (%)	0	3 (75)	12 (75)	3 (50)	3 (50)	2 (29)	23 (59)
	1	1 (25)	4 (25)	3 (50)	3 (50)	4 (57)	15 (39)
	2	0	0	0	0	1 (14)	1 (2)
	≥3	0	0	0	0	0	0
STAGE AT SCLC DIAGNOSIS N (%)	LIMITED	0	0	0	0	0	0
	EXTENSIVE	4 (100)	16 (100)	6 (100)	6 (100)	7 (100)	39 (100)
p53 MUTATION STATUS N (%)	MUTATED	4 (100)	16 (100)	6 (100)	6 (100)	7 (100)	39 (100)
	WILD TYPE	0	0	0	0	0	0

Table 2: Study Drug Exposure

	24H SCHEDULE				6H SCHEDULE	TOTAL
	0.2 N=4	0.3 N=16	0.6 N=6	1.2 N=6	0.3 N=7	N=39
TREATMENT DURATION, MEDIAN (DAYS)	64.5	72	16.5	41.5	44	55
# OF CYCLES STARTED, MEDIAN	3.5	4	1.5	2.5	2	3
# OF CYCLES COMPLETED, MEDIAN	5	4	1	2.5	3	3
TOPOTECAN DOSE REDUCTIONS	0	3 (19)	0	1 (17)	1 (14)	5 (13)
ALRN-6924 DOSE REDUCTIONS	0	0	0	0	0	0

Table 3: Grade ≥3 TEAEs

	24H SCHEDULE				6H SCHEDULE	TOTAL
	0.2 N=4	0.3 N=16	0.6 N=6	1.2 N=6	0.3 N=7	N=39
ALL TEAES (ALL CYCLES)	3 (75)	14 (88)	5 (83)	6 (100)	7 (100)	35 (90)
NEUTROPENIA	3 (75)	13 (81)	5 (83)	6 (100)	7 (100)	34 (87)
THROMBOCYTOPENIA	2 (50)	7 (44)	2 (33)	2 (33)	5 (71)	18 (46)
LEUKOPENIA	2 (50)	3 (19)	4 (67)	4 (67)	3 (43)	16 (41)
ANEMIA	0	3 (19)	1 (17)	1 (17)	1 (14)	6 (15)
FATIGUE	0	1 (6)	1 (17)	0	0	2 (5)

Table 4: All SAEs (None Were Deemed Related to ALRN-6924 Treatment)

	24H SCHEDULE				6H SCHEDULE	TOTAL
	0.2 N=4	0.3 N=16	0.6 N=6	1.2 N=6	0.3 N=7	N=39
NEUTROPENIA	0	0	1 (17)	2 (33)	3 (43)	6 (15)
THROMBOCYTOPENIA	0	0	0	2 (33)	1 (14)	3 (8)
ANEMIA	0	0	0	1 (17)	1 (14)	2 (5)
COVID-19	0	1 (6)	0	0	1 (14)	2 (5)
LEUKOPENIA	0	0	0	1 (17)	1 (14)	2 (5)
ANGINA PECTORIS	0	1 (6)	0	0	0	1 (3)
CEREBROVASCULAR ACCIDENT	0	0	0	0	1 (14)	1 (3)

Table 5: Neutropenia NCI CTC Grade 4 in First Treatment Cycle

	24H SCHEDULE				6H SCHEDULE	TOTAL
	0.2 N=4	0.3 N=16	0.6 N=6	1.2 N=6	0.3 N=7	N=39
NEUTROPENIA GRADE 4 - N (%)	1 (25)	5 (31)	4 (67)	1 (17)	3 (43)	14 (36)

Table 6: Key Toxicities Relative to Recent Historical Control with AEs Graded by Objective Laboratory Values

	Phase 1b Clinical Trial of ALRN-6924 in SCLC Patients		Topotecan ± Trilaciclib in SCLC Patients[1]	
	AEs NCI CTC Grade ≥3		AEs NCI CTC Grade ≥3	
	ALRN-6924 0.3 mg/kg 24 h + Topotecan	ALRN-6924 + Topotecan All Patients	Placebo + Topotecan	Trilaciclib + Topotecan
	N (%) N=16	N (%) N=39	N (%) N=28	N (%) N=32
ALL AEs	14 (88)	35 (90)	27 (96)	28 (88)
NEUTROPENIA	13 (81)	34 (87)	24 (86)	22 (69)
THROMBOCYTOPENIA	7 (44)	18 (46)	20 (70)	22 (69)
ANEMIA	3 (19)	6 (15)	18 (63)	10 (39)
FEBRILE NEUTROPENIA	0	1 (3)	5 (17)	2 (6)
FATIGUE	1 (6)	2 (5)	2 (7)	3 (9)
NAUSEA	0	0	1 (4)	0
NEUTROPENIA NCI CTC GRADE 4[†]	5 (31)	14 (36)	21 (76)	13 (41)

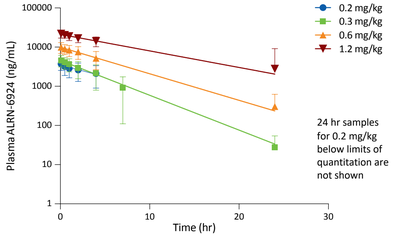
[†]in first treatment cycle

Table 7: Transfusions

	24H SCHEDULE				6H SCHEDULE	TOTAL
	0.2 N=4	0.3 N=16	0.6 N=6	1.2 N=6	0.3 N=7	N=39
RBC TRANSFUSIONS	0	1 (6)	3 (50)	3 (50)	1 (14)	8 (21)
PLATELET TRANSFUSIONS	0	1 (6)	2 (33)	1 (17)	1 (14)	5 (13)

Figure 2: ALRN-6924 Plasma Pharmacokinetics

A



24 hr samples for 0.2 mg/kg below limits of quantitation are not shown

- Mean ± st. dev. following first dose of ALRN-6924

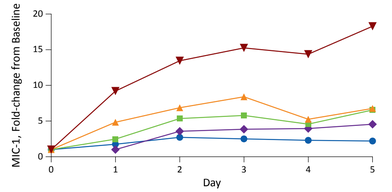
B

	0.2 mg/kg	0.3 mg/kg	0.6 mg/kg	1.2 mg/kg
n of patients	4	22[†]	6	6
$AUC_{0\text{-}24\ hr}$ µg·hr/mL (% CV)	31.8 (53.6)	34.4 (57.0)	83.0 (45.4)	211.9 (26.3)
C_{max} µg/mL (% CV)	3.8 (32.2)	4.9 (31.3)	10.0 (30.9)	22.0 (21.6)
$t_{1/2}$, hr (95% C.I.)	4.9 (2.0 - n.c.)	3.4 (2.5 - 4.7)	4.4 (2.6 - 9.2)	7.1 (3.9 - 12.4)

[†] PK samples unavailable for one 0.3 mg/kg patient

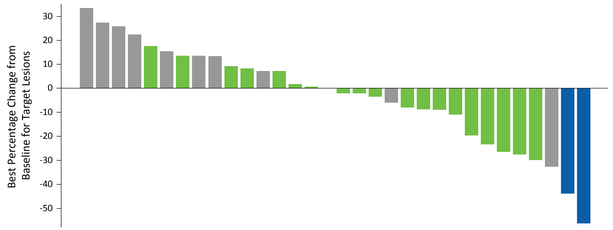
- Slower clearance (longer $t_{1/2}$) at higher ALRN-6924 doses. 3.4 to 7.1 hr half-life yields no accumulation on repeated dosing
- Plasma exposure after a single ALRN-6924 dose: Dose-proportional C_{max}, slightly greater than dose-proportional AUC

Figure 3: Dose-Response Between ALRN-6924 and Serum MIC-1, a Biomarker of p53 Activation



- Macrophage Inhibitory Cytokine-1 (MIC-1, also known as Growth Differentiation Factor-15, or GDF-15) was quantified by a qualified ELISA assay
- Serum samples were collected prior to each of five daily doses of ALRN-6924
- Results are shown as mean change from baseline value prior to first ALRN-6924 dose

Figure 4: Radiological Evaluation of Tumor Response



- The Disease Control Rate (DCR) was 65% for 32 patients with radiological evaluation
- In independent trials of SCLC patients receiving topotecan the DCR was 45% to 63%[2-5]

Conclusions

This is the first clinical study to demonstrate a chemoprotective effect of p53 activation via selective induction of cell cycle arrest in normal cells. This novel strategy has the potential to benefit the >50% of all cancer patients with tumors harboring p53 mutations, which translates to approximately 1 million cancer patients annually in the U.S. alone.

References

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