Prevention of Chemotherapy-induced Myelosuppression in SCLC Patients Treated with the Dual MDMX/MDM2 Inhibitor ALRN-6924

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Abstract

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 increases intracellular p53 levels and initiates its transcriptional activity, leading to cell cycle arrest. This effect is limited to cells with wild-type, functional p53; therefore, for patients with tumors harboring mutated P53, pre-treatment with ALRN-6924 may selectively induce cell cycle arrest in normal cells allowing chemotherapy to selectively target cancer cells that are actively cycling.

Materials and Methods: A Phase 1b study in extensive disease small-cell lung cancer (ED SCLC) patients with ECOG PS 0-2 receiving topotecan was conducted to evaluate the ability of ALRN-6924 to reduce bone marrow toxicity without impacting the efficacy of topotecan. Inclusion criteria included the presence of p53 mutations in tumor tissue as measured by next-generation sequencing. Prophylactic use of growth factors was not permitted in the first treatment cycle. ALRN-6924 was given at three dose levels: 0.3, 0.6 and 1.2 mg/kg on days 0-4 of each treatment cycle. Topotecan was administered 24 hrs after ALRN-6924 on days 1-5 at 1.5 mg/m^2 of each treatment cycle. Hematological laboratory values were coded as AEs based on NCI CTC v5.0. Plasma and serum samples were analyzed for ALRN-6924 pharmacokinetics and pharmacodynamic biomarkers of p53 activation.

Results: As of 31-August-2020, 26 patients were enrolled (6 per dose level and 8 additional patients in the expansion cohort); 25/26 patients were evaluable. Baseline characteristics were typical for this patient population (median age 67 years, 80% males, ECOG PS 0 60%, baseline LDH ≥ULN 40%, chemosensitive population 48%). Median number of completed topotecan treatment cycles was 3. 12% of patients required topotecan dose reduction. Disease control rate was 64%. No patients reported Grade ≥3 events of nausea, vomiting, diarrhea, and 1 patient had fatigue Grade 3. Grade 3/4 anemia, thrombocytopenia and neutropenia were reported in 24%, 36% and 88% of patients and compare favorably to recent historical results of Grade 3/4 anemia, thrombocytopenia and neutropenia of 63%, 70% and 86%.[1]

The 0.3 mg/kg ALRN-6924 dose level showed the most consistent chemoprotection results, with NCI CTC Grade 3/4 anemia, thrombocytopenia and neutropenia limited to 21%, 37% and 79% of patients, respectively, and a 43% rate of neutropenia Grade 4 in the 1st treatment cycle (historical result: 76%); none of the patients treated at this dose level had hematological SAEs nor did they require RBC/platelet transfusions (historical result: 41% and 36%, respectively).

Figure 1: ALRN-6924 Phase 1b Study Schema

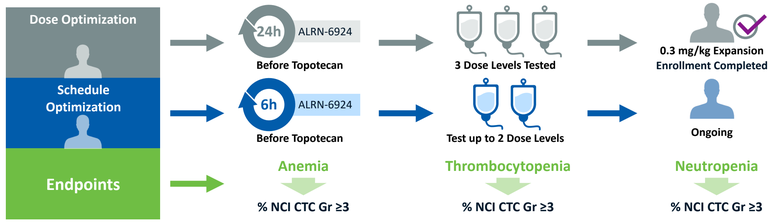


Table 1: Demographics and Key Baseline Characteristics

		0.3 mg/kg N (%) N=14	0.6 mg/kg N (%) N=5	1.2 mg/kg N (%) N=6	Total N (%) N=25
AGE	Median	68.5	67	58	67
GENDER	Male	14 (100)	2 (40)	4 (67)	20 (80)
ECOG PS	0	10 (71)	2 (40)	3 (50)	15 (60)
	1	4 (29)	3 (60)	3 (50)	10 (40)
BASELINE LDH	≥ULN	5 (36)	3 (60)	2 (33)	10 (40)
TIME SINCE PREVIOUS THERAPY	<60 days	7 (50)	1 (20)	5 (83)	13 (52)
STAGE AT INITIAL TUMOR DIAGNOSIS	Extensive Disease	6 (100)	5 (100)	6 (100)	25 (100)
P53 MUTATION STATUS	Mutated	13 (93)	5 (100)	6 (100)	24 (96)

Table 2: Study Drug Exposure

	0.3 mg/kg N=14	0.6 mg/kg N=5	1.2 mg/kg N=6	Total N=25
DURATION OF EXPOSURE (DAYS)				
Mean	62	41	61	57
Median (Min, Max)	59 (6, 204)	27 (6, 90)	42 (27, 157)	55 (6, 204)
NUMBER OF CYCLES COMPLETED				
Mean	3.2	2	3.3	3
Median (Min, Max)	3 (1, 6)	1 (1, 4)	2.5 (1, 8)	3 (1, 8)
TOPOTECAN DOSE REDUCTIONS				
Patients with any dose reductions, N (%)	2 (14)	0	1 (17)	3 (12)
ALRN-6924 DOSE REDUCTIONS				
Patients with any dose reductions, N (%)	0	0	0	0

Table 3: TEAEs Occurring in ≥10% of All Patients

	ALL AEs				ALL AEs GRADE ≥3			
	0.3 mg/kg (N=14) N (%)	0.6 mg/kg (N=5) N (%)	1.2 mg/kg (N=6) N (%)	Total (N=25) N (%)	0.3 mg/kg (N=14) N (%)	0.6 mg/kg (N=5) N (%)	1.2 mg/kg (N=6) N (%)	Total (N=25) N (%)
ALL AEs	14 (100)	5 (100)	6 (100)	25 (100)	13 (93)	5 (100)	6 (100)	24 (96)
NEUTROPENIA	11 (79)	5 (100)	6 (100)	22 (88)	11 (79)	5 (100)	6 (100)	22 (88)
THROMBOCYTOPENIA	9 (64)	4 (80)	5 (83)	18 (72)	5 (36)	2 (40)	2 (33)	9 (36)
LEUKOPENIA	6 (43)	4 (80)	4 (67)	14 (56)	2 (14)	4 (80)	4 (66)	10 (40)
ANEMIA	5 (36)	4 (80)	3 (50)	12 (48)	3 (21)	2 (40)	1 (17)	6 (24)
FATIGUE	3 (21)	2 (40)	2 (33)	7 (28)	0	1 (20)	0	1 (4)
FEVER	2 (14)	1 (20)	0	3 (12)	0	0	0	0

Table 4: Historical Controls

Trial	Phase	N*	Cycles Median	Hematological Toxicity Grade ≥3 (%)				Comments
				Neutropenia	Febrile Neutropenia	Thrombo-cytopenia	Anemia	
Hematological Toxicity Reported by Laboratory Values								
Hart, et al. *JCO*, 2019[1]	2	28	3	86	17	70	63	Chemosensitive population not reported; GCSF not prophylactic in C; Transfusions: Plt 31%, RBC 41%
Hematological Toxicity Reported as AEs								
Pawel, et al. *JCO*, 2014[2]	3	213	5	54	3	54	31	Chemosensitive population 55%; RBC transfusions 53%; Mandatory prophylactic growth factors
Eckardt, et al. *JCO*, 2007[3]	3	151	4	88	5	43	31	Chemosensitive population 100%; RBC transfusions 43%; GCSF 16%
Jotte, et al. *JCO*, 2011[4]	2	26	2	78	9	61	30	Chemosensitive population 100%; Growth factors as necessary; Worst toxicities in cycle #1
Inoue, et al. *JCO*, 2008[5]	2	30	2	87	3	40	30	Chemosensitive population 63%;GCSF not prophylactic

Table 5: Key Toxicities Relative to Recent Historical Control with AE's Graded by Objective Laboratory Values

	Dose Optimization Part of Phase 1b/2 Clinical Trial of ALRN-6924 as a Chemoprotection Agent AEs* NCI CTC GRADE ≥3		Topotecan ± Trilaciclib in SCLC Patients‡ AEs* NCI CTC GRADE ≥3	
	ALRN-6924 0.3 mg/kg+ Topotecan	ALRN-6924 + Topotecan, All Patients	Placebo + Topotecan	Trilaciclib + Topotecan
	N (%) N=14	N (%) N=25	N (%) N=28	N (%) N=32
ALL AEs	13 (93)	24 (96)	27 (96)	28 (88)
NEUTROPENIA	11 (79)	22 (88)	24 (86)	22 (69)
THROMBOCYTOPENIA	5 (37)	9 (36)	20 (70)	22 (68)
ANEMIA	3 (21)	6 (24)	18 (63)	10 (39)
FEBRILE NEUTROPENIA	0	0	5 (17)	2 (6)
FATIGUE	0	0	2 (7)	3 (9)
NAUSEA	0	0	1 (4)	0
NEUTROPENIA NCI CTC GRADE 4**	6 (43)	12 (48)	21 (76)	13 (41)

*AEs based on laboratory values, as applicable
** in the first treatment cycle

‡Hart et al. *ASCO*, 2019 – G1 Therapeutics; Phase 2 Clinical Trial

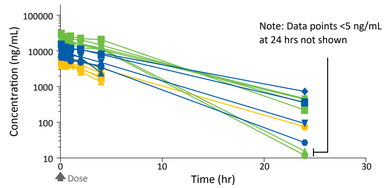
Table 6: Other Results Support Chemoprotection Signal with ALRN-6924 Treatment

SAEs	0.3 mg/kg, N (%), N=14	Total, N (%), N=25
NEUTROPENIA	0	3 (12)
LEUKOPENIA	0	1 (4)
THROMBOCYTOPENIA	0	2 (8)
ANEMIA	0	1 (4)
ANGINA PECTORIS	1 (7)	1 (4)
TRANSFUSIONS	**0.3 mg/kg, N (%), N=14‡**	**Total, N (%), N=25**
RBC TRANSFUSIONS	1 (7)	7 (28)
PLATELET TRANSFUSIONS	1 (7)	4 (16)
PERFORMANCE STATUS	**0.3 mg/kg, N=14**	**Total, N=25**
ECOG PS AT BASELINE (Mean, Median)	0.3, 0	0.4, 0
ECOG FINAL PS (Mean, Median)	0.6, 0	0.8, 0

‡Following abstract submission, one patient was determined to have received one RBC and one platelet transfusion

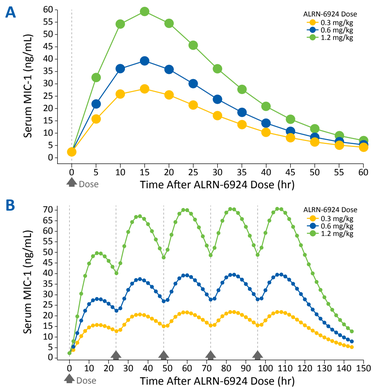
Figure 2: ALRN-6924 Plasma Pharmacokinetics

PARAMETER (AVERAGE)	0.3 mg/kg	0.6 mg/kg	1.2 mg/kg
C_{max} µg/mL	5.0	9.9	21.9
$AUC_{0\text{-}24hr}$ ng·hr/mL	35,862	83,030	250,519
$t_{\frac{1}{2}}$ hr	3.4	4.5	7.1



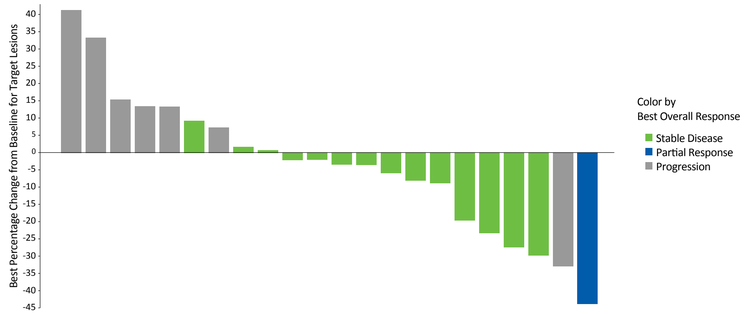
- Monophasic clearance, low patient-to-patient variability
- Slightly less than dose-proportional exposure
- 3.4 to 7.1 hr half-life yields no accumulation on repeated dosing

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



A) Serum MIC-1 following a single ALRN-6924 dose. B) Serum MIC-1 following five daily ALRN-6924 doses. Data modelled from this trial and other ALRN-6924 clinical studies.[6]

Figure 4: Radiological Evaluation of Tumor Response



Disease control rate (DCR) was 64%. In independent trials of SCLC patients receiving second-line topotecan the DCR ranged from 45% to 62%.[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.

References

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