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

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Presented by: Funda Meric-Bernstam

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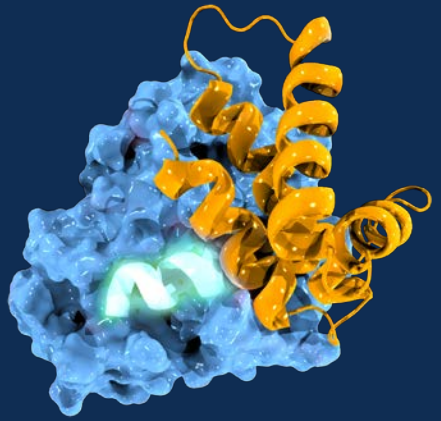
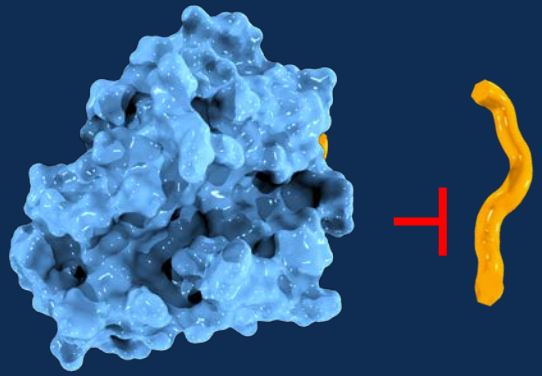
Stapled peptides overcome historical constraints of peptide drugs and limitations of small molecules

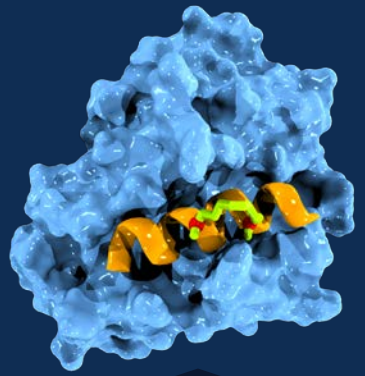
Natural protein-protein helical peptide interface



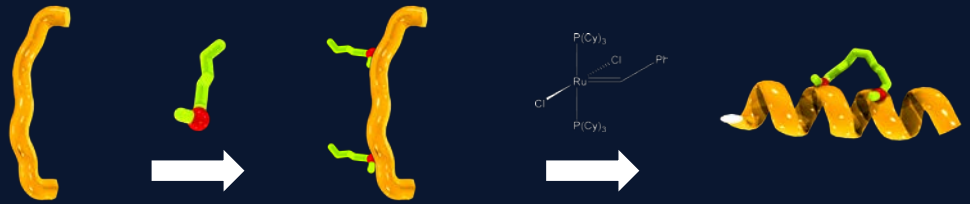
Removal of full protein context destabilizes interface helix



Stapled peptides recapitulate the helical interface and restore functionality



Stapled peptides use a chemical bridge - a “staple” - that resolves the short stability and lack of cell penetrability of peptides



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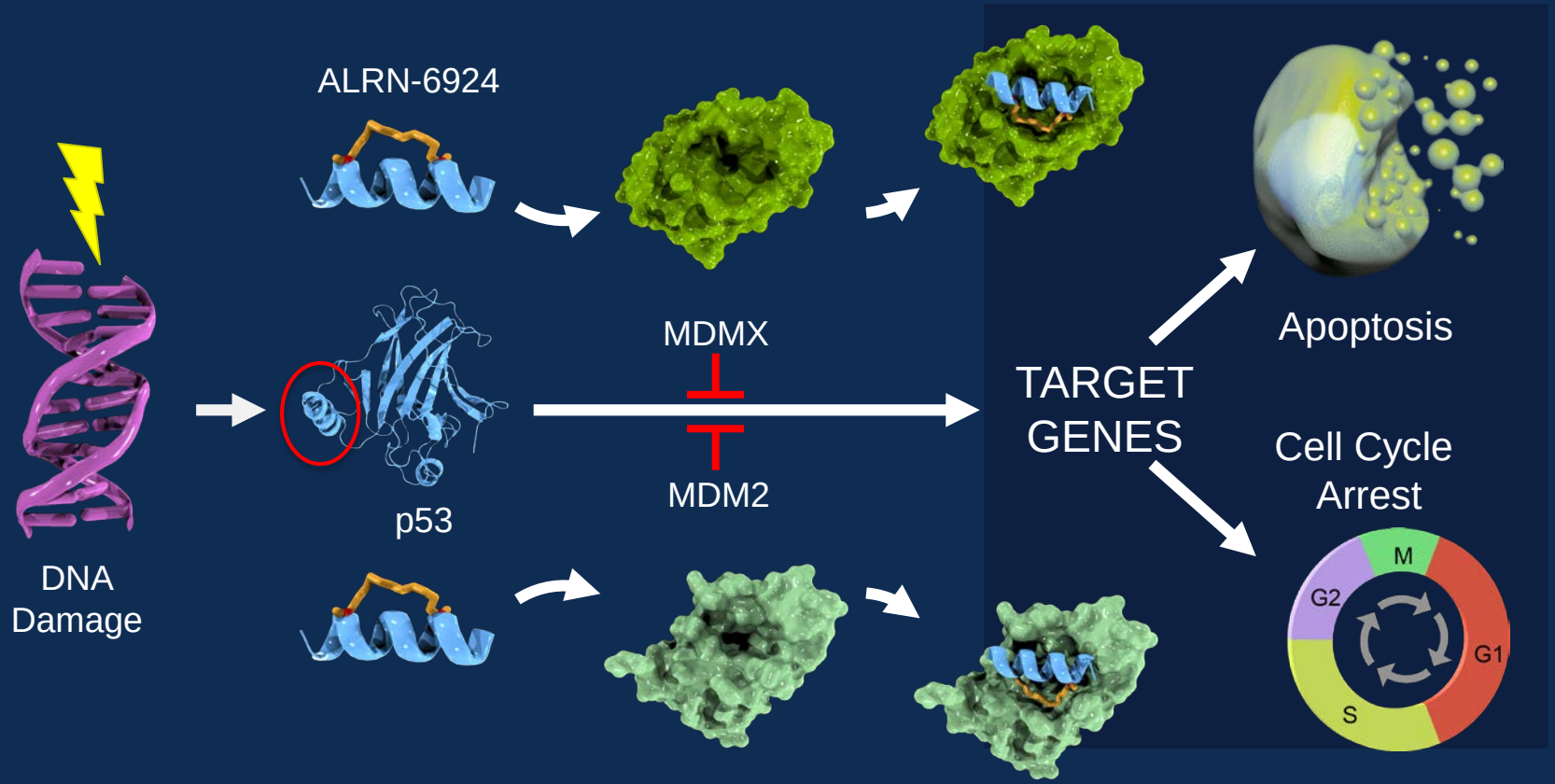
ALRN-6924: First dual inhibitor of MDMX & MDM2



First in human study
Dose escalation with 2 regimens

Objectives

Primary
- Evaluate safety and tolerability
- Determine MTD

Secondary
- Evaluate PK
- Evaluate pharmacodynamic biomarkers (MIC-1, p53, MDM2, MDMX)
- Preliminary evidence of clinical activity
- Determine immunogenicity

Design

- Multicenter, 3+3 cohort design
- Adult patients with advanced solid tumors or lymphoma with WT TP53* who are refractory to or intolerant of standard therapy or for whom no standard therapy exists
- TP53 status determined via NGS-testing of archival or fresh tissue
- Clinical activity assessed via RECIST 1.1 or IWG criteria (Cheson, 2014)
- 2 dosing regimens tested
  - Regimen A: Infusion on Days 1, 8, 15; 28 day cycles
  - Regimen B: Infusion on Days 1, 4, 8, 11; 21 day cycles

* Patients in the first 3 cohorts were not required to have TP53 testing prior to enrollment

Dose escalation

Dose regimen A-2: 2 hour infusion on Days 1, 8, 15, every 28 days

Dose 7A-2 4.4 mg/kg

Modified regimen to improve tolerability of 4.4 mg/kg:
- Added dexamethasone, and fluids in cycles 1 & 2

Dose regimen A: 1 hour infusion on Days 1, 8, 15, every 28 days

Dose 1A 0.16 mg/kg → **Dose 2A 0.32 mg/kg** → **Dose 3A 0.64 mg/kg** → **Dose 4A 1.25 mg/kg** → **Dose 5A 2.1 mg/kg** → **Dose 6A 3.1 mg/kg** → **Dose 7A 4.4 mg/kg**

MTD

Dose Regimen B: 1 hour infusion on Days 1, 4, 8, 11, every 21 days

Dose 3B 0.32 mg/kg → **Dose 4B 0.53 mg/kg** → **Dose 5B 0.8 mg/kg** → **Dose 6B 1.1 mg/kg** → **Dose 7B 1.5 mg/kg** → **Dose 8B 2.0 mg/kg** → **Dose 9B 2.7 mg/kg**

Baseline characteristics

Characteristic	Regimen A (N=41)	Regimen B (N=30)	All patients (N=71)
Age, median (range)	63 (25, 79)	59 (31, 77)	62 (25, 79)
Sex, male (%)	48.8	50.0	49.3
Race, white/black/other (%)	68/22/10	83/13/4	75/18/7
ECOG PS 0/1 (%)	32/68	30/70	31/69
Number of cancer types	20	12	24
TP53 WT confirmed by central or local lab (%)	78.0	96.7	85.9
Prior systemic therapies (%)			
0 - 2	41.5	60.0	49.3
3 - 4	41.5	16.7	31.0
≥5	17.1	23.3	19.7

Related TEAE (≥ 10% or clinically relevant)

N (%)	All Grades	Grade 3	Grade 4
Patients with any AE	68 (95.8)	11 (15.5)	2 (2.8)
Nausea	50 (70.4)	2 (2.8)	0 (0)
Fatigue	38 (53.5)	3 (4.2)	0 (0)
Vomiting	26 (36.6)	1 (1.4)	0 (0)
Anemia	14 (19.7)	1 (1.4)	0 (0)
Decreased appetite	14 (19.7)	0 (0)	0 (0)
Headache	12 (16.9)	0 (0)	0 (0)
Constipation	11 (15.5)	0 (0)	0 (0)
Diarrhea	7 (9.9)	1 (1.4)	0 (0)
Infusion-related reaction	6 (8.5)	1 (1.4)	0 (0)

AEs graded according to CTCAE 4.03

DLT	Dose
Grade 3 Fatigue	3.1 mg/kg
Grade 3 Anemia	4.4 mg/kg
Grade 3 Hypotension	4.4 mg/kg
Grade 4 Neutropenia	4.4 mg/kg
Grade 3 Alk Phos increase	4.4 mg/kg

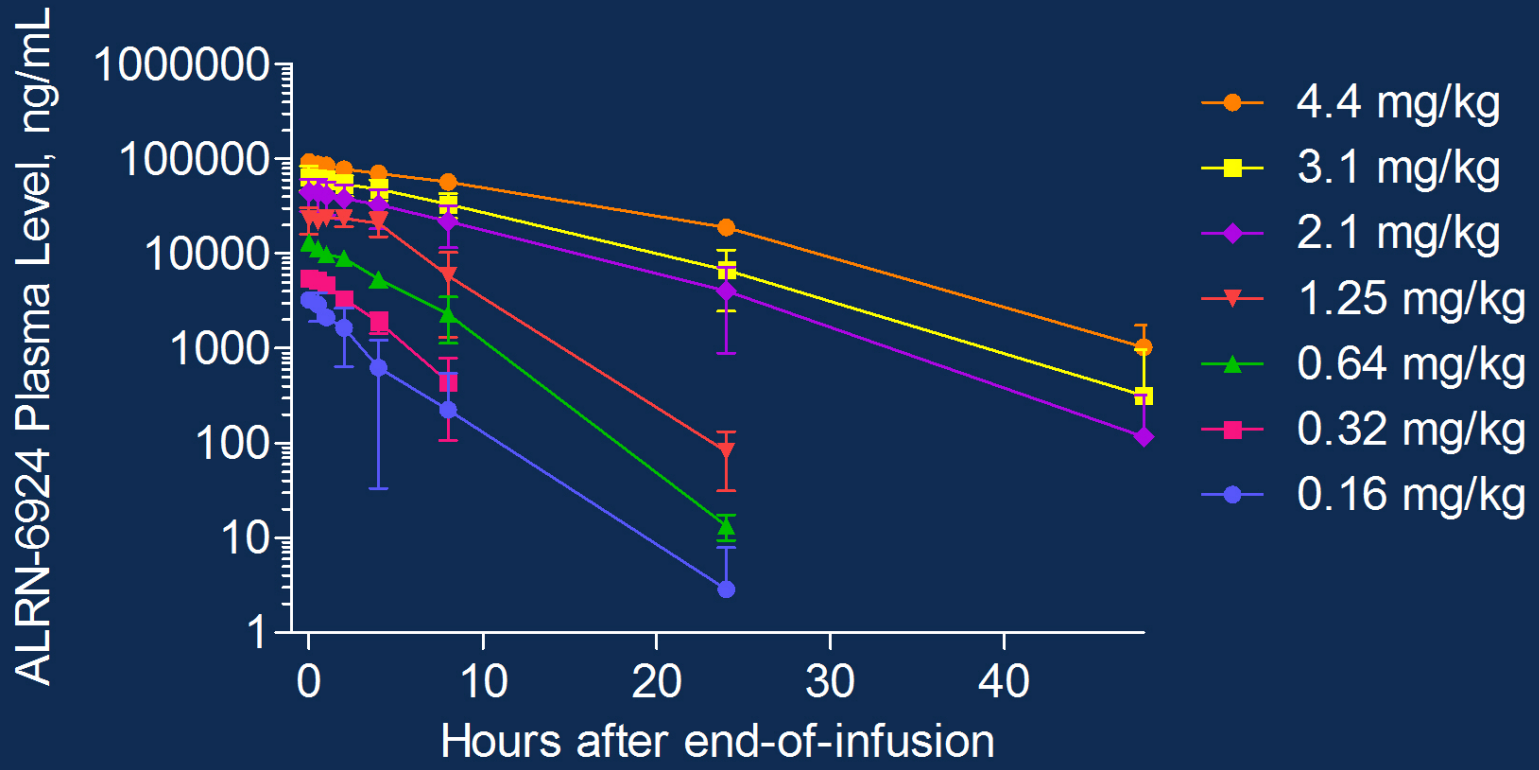
SAE (related)	Dose
Grade 3 Hypotension with SOB potentially due to Drug-Drug Int.	3.1 mg/kg
Grade 3 Hypotension	4.4 mg/kg

Clinically relevant or common (≥20%) laboratory abnormalities

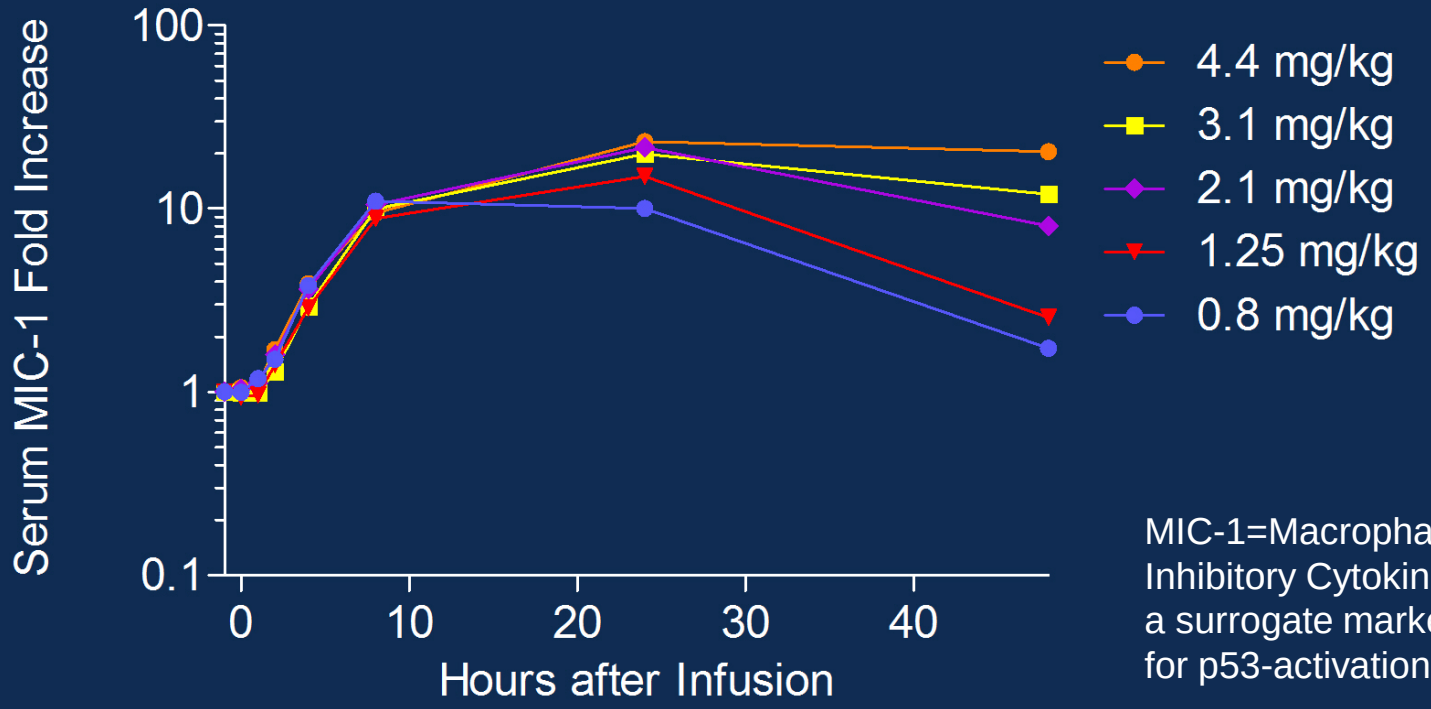
CTCAE Term, N (%)	All Grades	Grade 3	Grade 4
Anemia	58 (81.7)	4 (5.6)	0 (0)
Hypoalbuminemia	32 (45.1)	0 (0)	0 (0)
Lymphocyte count decreased	31 (43.7)	6 (8.5)	1 (1.4)
Hyponatremia	23 (32.4)	5 (7.0)	0 (0)
White blood cell decreased	22 (31.0)	1 (1.4)	0 (0)
aPTT increased	22 (31.0)	1 (1.4)	0 (0)
Platelet count decreased	21 (29.6)	0 (0)	0 (0)
Blood bilirubin increased	19 (26.8)	1 (1.4)	0 (0)
Alkaline phosphatase increased	17 (23.9)	3 (4.2)	0 (0)
Neutrophil count decreased	5 (7.0)	2 (2.8)	1 (1.4)

Graded according to CTCAE 4.03

ALRN-6924 PK shows dose-related exposure increase

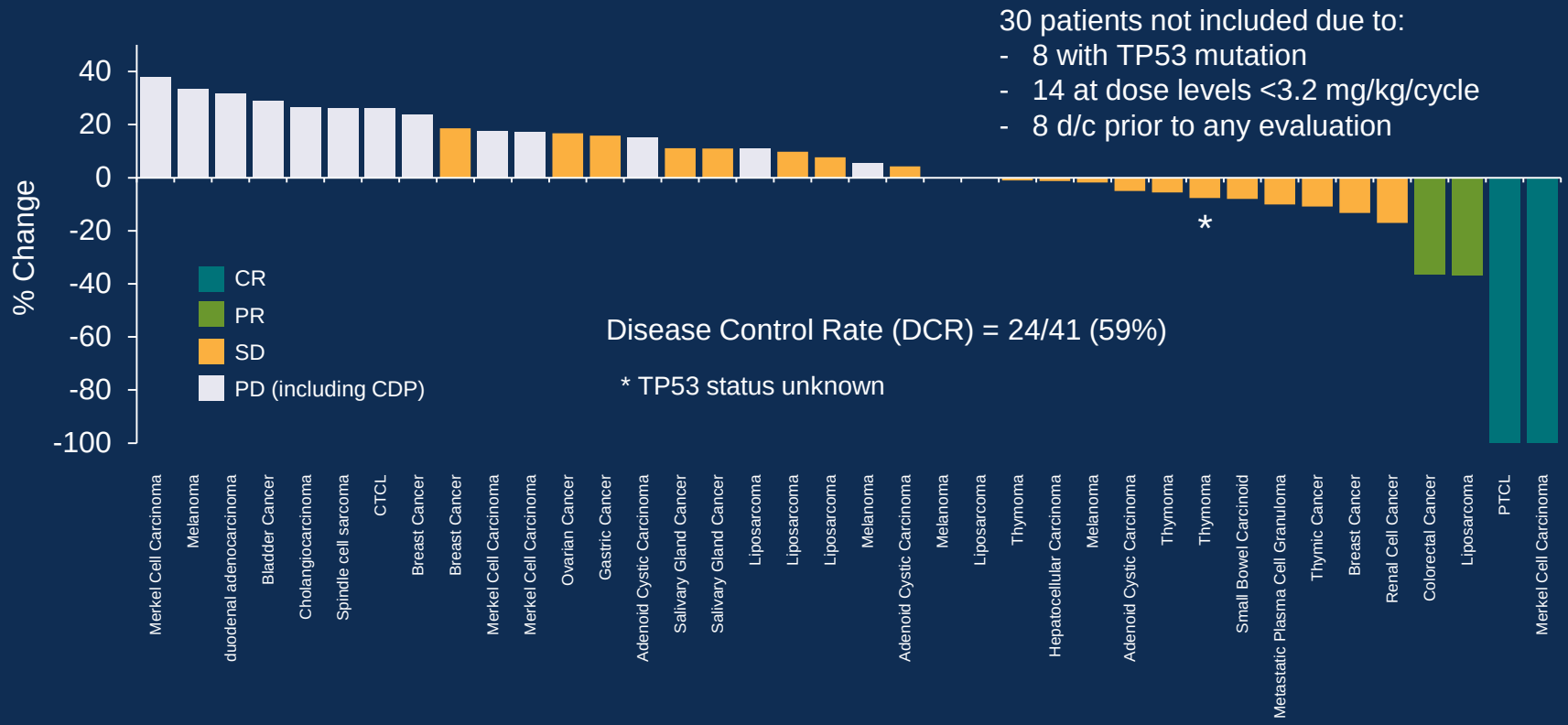


Mean serum MIC-1 increase above baseline following a single dose of ALRN-6924 shows sustained activation of the p53 pathway

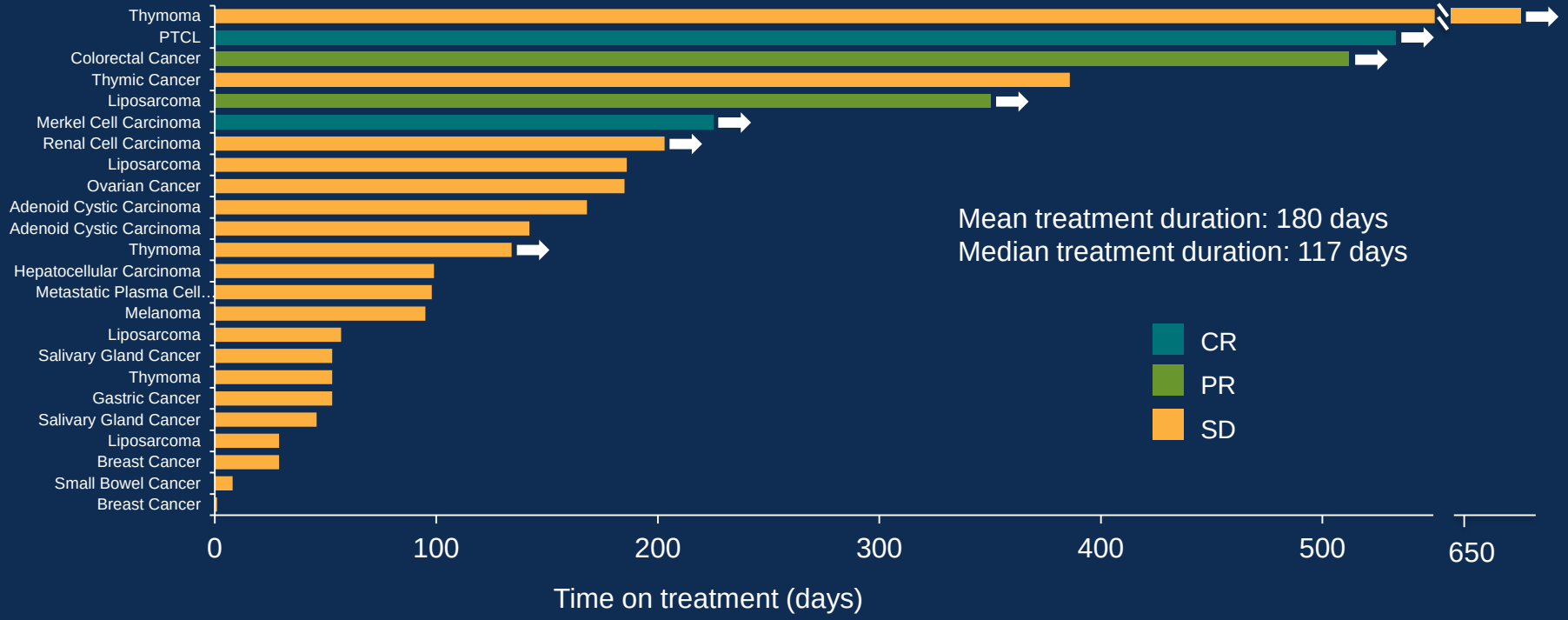


MIC-1=Macrophage Inhibitory Cytokine-1; a surrogate marker for p53-activation

Best overall change in subset of 41/71 patients from dose-escalation treated with ≥3.2 mg/kg per cycle and excluding TP53 mutants

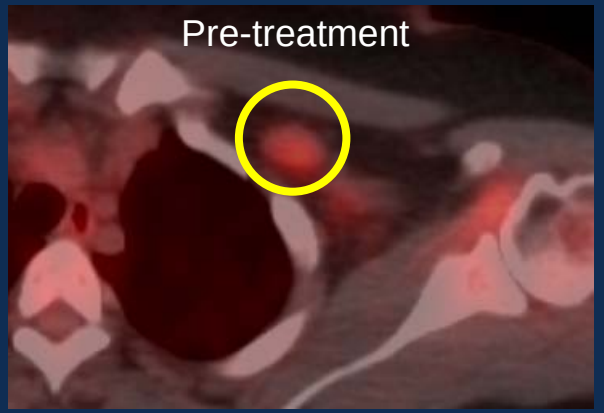


Duration of treatment for patients with disease control from subset of 41 patients in dose-escalation treated with ≥3.2 mg/kg per cycle and excluding TP53 mutants



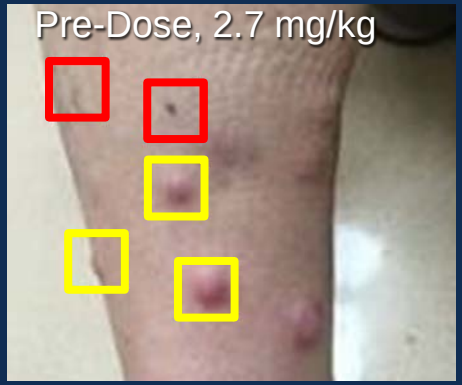
Complete response in peripheral T-cell lymphoma

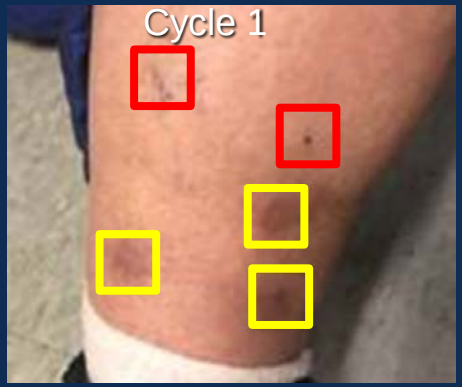
- 51 year old African American female
- CR after 6 cycles of CHOP+E with relapse within 12 months
- Treated with 2.1 mg/kg ALRN-6924 on Days 1, 8, 15 of a 28 day cycle
- Achieved a Complete Response after 6 cycles
- Still on study: 18 months
- Adverse events include fatigue, nausea and vomiting
  - Dose reduced to 1.58 after 6 cycles



Complete response in Merkel cell carcinoma (MCPyV+)

- 73 year old Caucasian female
- Previously treated with radiation followed by an investigational mTOR inhibitor
- Treated with 2.7 mg/kg ALRN-6924 on Days 1, 4, 8, 11 of a 21 day cycle
- Achieved a PR after 3 cycles, pathological CR according to histopathology review of skin biopsy and radiological CR after 6 cycles
- Still on study: 8 months
- Adverse events include anorexia, fatigue, nausea and vomiting
  - Dose reductions: to 2.0 mg/kg after 2 cycles; 1.5 mg/kg after 3 cycles; 1.1 mg/kg after 4 cycles





Conclusions

- ALRN-6924 is well tolerated; most common AEs include GI symptoms, fatigue and headache
  - Patients commonly prophylactically treated with 5-HT3 receptor antagonists
- No Grade 3/4 thrombocytopenia; Grade 3/4 neutropenia seen in <5% of patients
- ALRN-6924 shows dose proportional PK
- Evidence of clinical anti-tumor activity of ALRN-6924 across a variety of tumor types with WT TP53 is encouraging
- Systemic T-cell lymphoma phase 2a open using RP2D of 3.1 mg/kg QWx3 every 28d

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