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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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

Presented by: Funda Meric-Bernstam
ALRN-6924: First dual inhibitor of MDMX & MDM2

DNA Damage

ALRN-6924

p53

MDMX

MDM2

TARGET GENES

Apoptosis

Cell Cycle Arrest

Presented by: Funda Meric-Bernstam
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: 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
- 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

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
## Baseline characteristics

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

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

### 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 |

AEs graded according to CTCAE 4.03
### Clinically relevant or common (≥20%) laboratory abnormalities

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

Graded according to CTCAE 4.03
ALRN-6924 PK shows dose-related exposure increase

ALRN-6924 Plasma Level, ng/mL

Hours after end-of-infusion

- 4.4 mg/kg
- 3.1 mg/kg
- 2.1 mg/kg
- 1.25 mg/kg
- 0.64 mg/kg
- 0.32 mg/kg
- 0.16 mg/kg

Presented by: Funda Meric-Bernstam
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

Disease Control Rate (DCR) = 24/41 (59%)

* TP53 status unknown

30 patients not included due to:
- 8 with TP53 mutation
- 14 at dose levels <3.2 mg/kg/cycle
- 8 d/c prior to any evaluation
Duration of treatment for patients with disease control from subset of 41 patients in dose-escalation treated with \( \geq 3.2 \text{ mg/kg per cycle} \) and excluding TP53 mutants.

Presented by: Funda Meric-Bernstam
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

Presented by: Funda Meric-Bernstam
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
Acknowledgements

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