Safety, Efficacy, and Immune Correlates of Alternative Doses and Schedules of Entinostat Combined With Pembrolizumab in Patients With Advanced Solid Tumors – Results From SNDX-275-0141 Phase I Trial

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I have the following financial relationships to disclose:

- Grant/Research support from Syndax for the conduct of this study
- Employee of: Past Employment at START, now NEXT Oncology

I will discuss the following off label use and/or investigational use in my presentation: Combination of entinostat and pembrolizumab
Entinostat – oral, class I selective histone deacetylase inhibitor

Has demonstrated potent immunomodulatory activity by inhibition of myeloid-derived suppressor cell (MDSC) function

Encouraging preliminary data of the combination of entinostat plus pembrolizumab in PD-1 pretreated patients have been reported:

- Melanoma: 4 of 13 responders (31% ORR)
- NSCLC: 3 of 31 responders (10% ORR)

Overview of Study 0141 Design and Schedule of Blood Samples

Objectives
- Cardiac safety, PK, safety/tolerability (ECG/ 24 hour Holter monitor)
- Immune correlates

Part 1  Double Blind

ARM A
- Entinostat 1mg daily (Days 1-5 every 7 days)
- pembrolizumab 200 mg Q3W
(N=10)

ARM B
- Entinostat 5 mg weekly*
- pembrolizumab 200 mg Q3W
(N=10)

ARM C
- Entinostat 10 mg QoW
- pembrolizumab 200 mg Q3W
(N=10)

Objectives
- Safety/tolerability, PK, efficacy
- Impact on immune correlates

* 5 mg weekly is the dose being used in all ongoing Phase 2 PD-1 combination trials as well as E2112.
## Baseline Demographics of Treatment Arms Are Similar

<table>
<thead>
<tr>
<th></th>
<th>Arm A 1 mg Days 1-5 every 7 (N=8)</th>
<th>Arm B 5 mg weekly (N=9)</th>
<th>Arm C 10 mg QoW (N=9)</th>
<th>Total (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>59.5 (22 - 68)</td>
<td>56.0 (44 - 75)</td>
<td>65.0 (41-70)</td>
<td>60.5 (22-75)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (25.0)</td>
<td>2 (22.2)</td>
<td>3 (33.3)</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (75.0)</td>
<td>7 (77.8)</td>
<td>6 (66.7)</td>
<td>19 (73.1)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (25.0)</td>
<td>3 (33.3)</td>
<td>3 (33.3)</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>1</td>
<td>6 (75.0)</td>
<td>6 (66.7)</td>
<td>6 (66.7)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td><strong>Tumor Type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast (all HR+)</td>
<td>4 (50.0)</td>
<td>4 (44.4)</td>
<td>3 (33.3)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>Prostate</td>
<td>0 (0.0)</td>
<td>2 (22.2)</td>
<td>2 (22.2)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1 (12.5)</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (37.5)</td>
<td>3 (33.3)</td>
<td>3 (33.3)</td>
<td>9 (34.6)</td>
</tr>
</tbody>
</table>
Principal Biomarker Correlates

Hypothesis: Myeloid Derived Suppressor Cells Mediate Resistance to PD1 axis targeting

- Determine the effect on MDSC population in blood after exposure to entinostat or placebo in the lead-in portion of the study.

- Determine the effect of MDSC population in blood after exposure to continuous entinostat amongst three administration schedules.
Immune (MDSC) Biomarkers Were Analyzed at Four Timepoints

**Randomize:**
- 15 mg entinostat
- Placebo

**Randomize:**
- Arm A – 1 mg entinostat, Days 1-5 every 7 days
- Arm B – 5 mg entinostat weekly
- Arm C – 10 mg entinostat every other week

All arms receive pembrolizumab 200 mg Q3W
Lead-in Shows MDSCs Are Significantly Lowered by Entinostat Treatment Compared to Placebo

- After a single entinostat dose, MDSC cell frequency was significantly decreased in patients who received entinostat compared to placebo.

- No statistical difference was observed in frequency of NK, T cell, or B cell populations in patients receiving entinostat relative to the placebo control.

* Unpaired t-test.
Lead-in Shows MDSCs Are Significantly Lowered by Entinostat Treatment Compared to Placebo

** Paired t-test.

** Paired t-test.
In Part 2, Continuous Dosing Maintains Observed Decrease in MDSCs – (141) C1D15

Entinostat Dosing Arms:
- **Arm A**: 1 mg Days 1-5 every 7 days
- **Arm B**: 5 mg once weekly
- **Arm C**: 10 mg once every other week
Entinostat Pharmacokinetics Contribute to Durable Exposure

- Entinostat exposure during the first cycle of treatment increases in a dose dependent manner over the first cycle of treatment by both $C_{\text{max}}$ and AUC.
- Peak exposure generally occurs within 1 hour of dosing, with a residual exposure tail persisting up to 15 days.

### Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Dose Arms</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>AUC$_{\text{(Cycle 1)}}$ (ng*hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg</td>
<td>9</td>
<td>1040</td>
</tr>
<tr>
<td>5 mg</td>
<td>52</td>
<td>1366</td>
</tr>
<tr>
<td>10 mg</td>
<td>118</td>
<td>2432</td>
</tr>
<tr>
<td>15 mg</td>
<td>253</td>
<td>6359</td>
</tr>
</tbody>
</table>

### Chart:

- **$C_{\text{max}}$** and **AUC$_{\text{(Cycle 1)}}$** plotted against time for different dose arms.
- **Entinostat PK** graph showing concentration over time for different dose levels.
A Similar Safety Profile Is Observed As Previously Reported\textsuperscript{1,2} – Grade 3/4 Related Adverse Events

- No notable differences in the safety profile were observed among the 3 arms
- The overall safety profile observed in this study was consistent with previously reported experience of entinostat combined with pembrolizumab\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects With At Least One Grade &gt;= 3 Related Treatment-Emergent Adverse Event</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3.8)</td>
</tr>
</tbody>
</table>

Entinostat + Pembrolizumab Shows Promising Activity In Patients with Heavily Pretreated Cancers

**Encouraging activity:**

- 3 PRs (ORR = 11.5%) in endometrial, HR+ BC, uterine leiomyosarcoma
- 2 SDs > 6 months (HR+ BC)
- 19 (73.1%) and 11 (42.3%) patients on study for 12 and 24 weeks respectively
Conclusions

- Consistent with previous reports, entinostat treatment results in reductions in circulating MDSCs.

- No notable differences in the safety profile were observed among the 3 arms, and the overall safety profile was consistent with previously reported experience of entinostat combined with pembrolizumab.

- The combination of entinostat and pembrolizumab continues to show promising activity in patients with heavily pretreated cancers.

- This trial supports continued study of entinostat 5 mg weekly, the schedule being used in other entinostat/pembrolizumab studies and in the ongoing Phase III E2112 entinostat/exemestane study.
Acknowledgements

- We thank the patients and their families/caregivers
- START study staff

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