Efficacy and Safety of Entinostat (ENT) and Pembrolizumab (PEMBRO) in Patients With Melanoma Previously Treated With Anti-PD-1 Therapy

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- Amgen
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- Syndax
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- Bristol-Myers Squibb

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- Amgen
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Advanced Melanoma Treatment Landscape 2019

- **DTIC**
- **Ipilimumab**
- **Vemurafenib (V)**
- **Dabrafenib (D), Trametinib (T)**
- **Pembrolizumab**
- **Nivolumab**
- **Cobimetinib + V**
- **Binimetinib + Encorafenib**

- High-dose IL-2
- 1980
- 2011
- 2013
- 2015
- 2017
- 2018
A growing minority of melanoma patients are cured with immunotherapy.
And Yet…

Most patients develop resistance

Most patients will still die of metastatic melanoma

IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival.
Most patients are not receiving benefit

What Is The Unmet Need?

We need a better therapeutic approach
1. Improve our understanding of mechanisms of therapeutic resistance

2. Develop more effective therapies (e.g., combinations)
   a. Frontline
   b. Post-PD-1 setting
1. Improve our understanding of mechanisms of therapeutic resistance

2. Develop more effective therapies (eg, combinations)
   a. Frontline
   b. Post-PD-1 setting
Why Does Therapy Fail?

CTLA4, cytotoxic T-lymphocyte-associated protein 4; DAMPS, damage-associated molecular patterns; FASL, FAS ligand; MHC-I, class-I major histocompatibility complex; TCR, T-cell receptor.

Why Does Therapy Fail?

Insufficient TMB/neoantigens

Insufficient priming

Travel to lymph node

Dendritic Cell

Neoantigens

DAMPS

Tumor Cells

Cytotoxic T-Cell Killing

Granzyme-Perforin

Interferon-Gamma

FASL-FAS

MHC-I bound native peptide

Normal Cell

Cytotoxic (Effector) CD8 T-Cell

Activation

Proliferation

Recruitment by cytokine signal (eg, CXCL9/10)

Intra-tumoral regulatory cells (MDSCs, T-Regs)

Recruitment by cytokine signal (eg, CXCL9/10)

Inadequate T-cell recruitment/infiltration

How Do We Address Unmet Need?

1. Improve our understanding of mechanisms of therapeutic resistance

2. Develop more effective therapies (eg, combinations)
   a. Frontline
   b. Post-PD-1 setting
How Do We Address Unmet Need?

1. Improve our understanding of mechanisms of therapeutic resistance

2. Develop more effective therapies (eg, combinations)
   - a. Frontline
   - b. Post-PD-1 setting
Rationale for Entinostat in Combination with anti-PD-(L)1 Therapy

• Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor

• ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment

• Synergy with anti-PD-1 inhibition in preclinical models

† In vivo and in vitro studies were performed using Lewis Lung Carcinoma (LLC) cells. **P<0.001. *P<0.05.

Ab, antibody; Arg1, arginase 1; COX2, cytochrome oxidase subunit 2; iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cells.

In patients with advanced solid tumors, MDSC cell frequency was significantly decreased at Day 14 after a single entinostat dose.

** Paired t-test
**Inclusion Criteria:**

- Recurrent or metastatic melanoma, measurable by RECIST 1.1
- Prior progression on or after anti-PD-(L)1 treatment
- Prior BRAF treatment if indicated
- ECOG Performance Status < 2
- Willingness to participate in baseline and on-treatment biopsy and blood samples

**Primary Endpoint**

- ORR (irRECIST)

**Secondary Endpoints**

- CBR, PFS, OS, safety & tolerability

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**53 patients enrolled, last patient enrolled April 2018**

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CBR, clinical benefit rate; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; ENT, entinostat; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; QW, once a week; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
### Patient Baseline Demographics and PD-1 History

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>32 (60%)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>62.0 (20-86)</td>
</tr>
<tr>
<td>Race, n (%)*</td>
<td></td>
</tr>
<tr>
<td>White/ Other</td>
<td>47 (89%) / 6 (11%)</td>
</tr>
<tr>
<td>ECOG Performance Status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0 / 1</td>
<td>29 (55%) / 24 (45%)</td>
</tr>
<tr>
<td>PD-L1 expression, n (%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>11 (21%)</td>
</tr>
<tr>
<td>Positive</td>
<td>28 (53%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>Visceral metastases, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes / No</td>
<td>34 (64%) / 19 (36%)</td>
</tr>
<tr>
<td>Baseline LDH (%&gt;ULN)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (36%)</td>
</tr>
</tbody>
</table>

### Prior therapy

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>N = 53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment with Ipi &amp; PD-1</td>
<td>37 (70%)</td>
</tr>
<tr>
<td>Prior treatment with BRAF/MEK</td>
<td>12 (23%)</td>
</tr>
</tbody>
</table>

### PD-1 history

<table>
<thead>
<tr>
<th>Best response on prior PD-1 therapy, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>SD</td>
<td>20 (38%)</td>
</tr>
<tr>
<td>PD</td>
<td>22 (42%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (7%)</td>
</tr>
</tbody>
</table>

### Duration of latest PD-1 therapy

Median months (range) 5.2 (0.72-23.1)

### Duration between prior PD-1 therapy and first dose

Median months (range) 2.6 (0.66-37.1)

*Rounding may produce values that do not add up to 100%.

CR, complete response; ECOG, Eastern Cooperative Oncology Group; Ipi, ipilimumab; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease; ULN, upper limit of normal.
10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
- 1 CR, 9 PRs
- Median duration of response: 13 months (range 3-20)
  - 4 responders ongoing
- An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23%-50%)
9 of 10 responses were observed by Week 12

Median PFS: 4.2 months (95% CI: 2.7-7.0) (median follow-up of 10.6 months)
Responses Observed Regardless of Prior Treatment History

Ipi, ipilimumab; Nivo, nivolumab; RT, radiotherapy.
Safety: Treatment-Related Adverse Events Occurring in ≥15% of Patients for All Grade or ≥2 Patients for Grade 3/4

- 6 pts discontinued due to related AEs: increased bilirubin, mucosal inflammation, neutropenia, pneumonitis, constipation and autoimmune hepatitis

<table>
<thead>
<tr>
<th>CTCAE term</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>47.2</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td>Rash</td>
<td>32.0</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>18.9</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>15.1</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>15.1</td>
<td>1 (1.9%)</td>
</tr>
</tbody>
</table>

AE, adverse event; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.
Changes in Peripheral CD8+ T-cell and M-MDSC Levels Associated With Response (n = 49)

Peripheral CD8+ T cells

Peripheral M-MDSCs (CD14+HLA-DR-/lo)

M-MDSCs in responders

M-MDSC, monocytic myeloid-derived suppressor cells; MDSC, myeloid-derived suppressor cell; PBMC, peripheral blood mononuclear cell.
Gene Signatures (RNA seq) Enriched in Responders (n=4) vs Non-Responders (n=4) and Post-treatment vs Pre-Treatment for Responders

**Responders vs non-responders**

<table>
<thead>
<tr>
<th>Hallmark Pathways up</th>
<th>NES</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFA_SIGNALING_VIA_NFKB</td>
<td>2.72</td>
</tr>
<tr>
<td>INFLAMMATORY_RESPONSE</td>
<td>2.34</td>
</tr>
<tr>
<td>EPITHELIAL_MESENCH_TRANS</td>
<td>2.11</td>
</tr>
<tr>
<td>HYPOXIA</td>
<td>2.1</td>
</tr>
<tr>
<td>MYOGENESIS</td>
<td>1.92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hallmark Pathways down</th>
<th>NES</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2F_TARGETS</td>
<td>-1.93</td>
</tr>
<tr>
<td>G2M_CHECKPOINT</td>
<td>-1.68</td>
</tr>
<tr>
<td>OXIDATIVE_PHOSPHORYLATION</td>
<td>-1.55</td>
</tr>
<tr>
<td>FATTY_ACID_METABOLISM</td>
<td>-1.45</td>
</tr>
</tbody>
</table>

**Post vs pre in responders**

<table>
<thead>
<tr>
<th>Hallmark Pathways up</th>
<th>NES</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPITHELIAL_MESENCH_TRANS</td>
<td>2.51</td>
</tr>
<tr>
<td>ALLOGRAFT_REJECTION</td>
<td>2.4</td>
</tr>
<tr>
<td>INTERFERON_GAMMA_RESPONSE</td>
<td>2.36</td>
</tr>
<tr>
<td>IL6_JAK_STAT3_SIGNALING</td>
<td>2.11</td>
</tr>
<tr>
<td>UV_RESPONSE_DN</td>
<td>2.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hallmark Pathways down</th>
<th>NES</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2F_TARGETS</td>
<td>-2.57</td>
</tr>
<tr>
<td>G2M_CHECKPOINT</td>
<td>-2.54</td>
</tr>
<tr>
<td>MYC_TARGETS_V2</td>
<td>-2.13</td>
</tr>
<tr>
<td>OX_PHOSPH</td>
<td>-1.98</td>
</tr>
<tr>
<td>MYC_TARGETS_V1</td>
<td>-1.71</td>
</tr>
</tbody>
</table>

*Top 5 and bottom 5 enriched pathways with adjusted p-value <0.05 (there were only 4 pathways with negative normalized enrichment score and adjusted p value <0.05).

NES (normalized enrichment score)
Individual Gene Changes Post-Treatment vs Pre-treatment in Responders

*Top 10 and bottom 10 gene with adjusted p-value < 0.05.
C, cycle; D, day.
Many Immune Signatures (n=7) Including Those Associated With Increased TIL and IFN Signaling Increase Following Treatment (NanoString)

C, cycle; D, day; IFN, interferon; TIL, tumor infiltrating lymphocyte.
In patients with progressing melanoma on prior PD-1 blockade and both prior PD-1/CTLA-4 blockade, a group with limited treatment options, ENT + PEMBRO demonstrate significant anti tumor activity.

ENT + PEMBRO was safe and tolerable.

Dominant toxicity with ENT + PEMBRO appeared to be related to ENT, with no apparent increase in irAEs with the combination.

Preliminary biomarker analysis demonstrated findings consistent with the mechanism of action of ENT:

- Reduction in circulating MDSCs
- Tumor specific increases in (pre/on) and enriched in (R/NR) inflammatory pathways

ENT, entinostat; PEMBRO, pembrolizumab.
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