Efficacy/safety of entinostat (ENT) and pembrolizumab (PEMBRO) in NSCLC patients previously treated with anti-PD-(L)1 therapy

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DISCLOSURES

M. Hellmann: Consulting for Syndax, Merck, AstraZeneca, BMS, Roche/Genentech, Mirati, Janssen, Shattuck Labs, and Nektar.
Treatment options are limited for patients with NSCLC whose disease has progressed on 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-PD1 inhibition in preclinical models
- Promising activity shown in combination with pembrolizumab in patients with melanoma and lung cancer

NSCLC, non-small cell lung cancer.
ENCORE-601: Open-label study evaluating ENT + PEMBRO in patients with recurrent or metastatic NSCLC and prior progression on anti-PD-1/PD-L1 therapy

**Inclusion Criteria:**
- Recurrent or metastatic NSCLC, measurable by RECIST 1.1
- Prior progression on anti-PD(L1) treatment
- Prior chemotherapy in the advanced/metastatic setting
- Prior ALK or EGFR treatment if indicated
- ECOG Performance Status < 2
- Willingness to baseline and on-Tx biopsy and blood samples

**Phase 2 Primary Endpoint**
- ORR (irRECIST)

**Phase 2 Secondary Endpoints**
- PFS, OS, safety & tolerability

76 patients enrolled (72 efficacy evaluable*), last patient enrolled December 2017
- Sample size was based on single proportion binomial test, assuming a true ORR of 15% & lower threshold of 5%, with 90% power and a 1-sided significance level of 5%.

*4 patients were non-evaluable due to withdrawal of consent or discontinuations for administrative reasons prior to the first tumor assessment.

ALK, anaplastic lymphoma kinase; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ENT, entinostat; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; QW, once a week; Q3W, every 3 weeks.
Patient baseline demographics and PD-(L)1 history

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N=76</th>
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<tbody>
<tr>
<td>Male, %</td>
<td>53%</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>67 yrs (30-85)</td>
</tr>
<tr>
<td>ECOG Performance Status, %</td>
<td></td>
</tr>
<tr>
<td>Grade 0 / Grade 1 / Missing</td>
<td>28% / 71% / 1%</td>
</tr>
<tr>
<td>Current/Former Smoker</td>
<td>88%</td>
</tr>
<tr>
<td>PD-L1 Expression (N=60)</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>15%</td>
</tr>
<tr>
<td>1%-49%</td>
<td>43%</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>42%</td>
</tr>
<tr>
<td>Data not available for 16 patients</td>
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<table>
<thead>
<tr>
<th>PD-(L)1 history</th>
<th>N=76</th>
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<tbody>
<tr>
<td>Best Response on Prior Anti-PD-(L)1, %</td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>1%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>7%</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>45%</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>37%</td>
</tr>
<tr>
<td>Unknown</td>
<td>11%</td>
</tr>
<tr>
<td>Duration on Prior Anti-PD-(L)1</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.3 months</td>
</tr>
<tr>
<td>Time from Prior Anti-PD-(L)1 to Study Therapy</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.2 months</td>
</tr>
<tr>
<td>PD-(L)1 as immediate prior therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>47 (62%)</td>
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ECOG, Eastern Cooperative Oncology Group.
Durable responses were observed in patients who experienced progression on prior anti-PD(L)1 therapy

- **Objective response rate with ENT + PEMBRO was 10% (7 of 72, 95% CI: 4-19%)**
  - Prespecified ORR target not reached; median duration of response was 5.3 months
  - An additional 50% of patients achieved disease stabilization
- **Experience similar in PD1-pretreated melanoma (ORR = 18%)**

CI, confidence interval; ENT, entinostat; PEMBRO, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.

Responses observed regardless of prior treatment history or PD-L1 status

Best Response on Prior PD-(L)1
- Partial Response
- Stable Disease
- Unknown

PD-L1 Status
- (-) <1%
- (+) 1-49%
- (++) ≥50%

Chemo, chemotherapy; ENT, entinostat; Nivo, nivolumab; PEMBRO, pembrolizumab.

ENCORE-601: ENT + PEMBRO in PD-(L)1-Pretreated NSCLC
Treatment-related adverse events occurring in ≥ 10% of patients for All Grade or ≥ 2 patients for Grade 3/4

- 7 patients (9.2%) experienced Grade 3/4 related irAEs
  - pneumonitis, 3; colitis, 3; hyperthyroidism, 1
- 23 patients (30.3%) experienced other Grade 3/4 related AEs
- 11 patients (14%) discontinued a study drug due to a treatment-related AE
- 13 patients (17%) required a dose reduction of study drug, of which 11 remained on study
Biomarkers: Identifying factors that may predict response to ENT + PEMBRO

- No significant association of response with
  - Smoking status
  - PD-L1 expression
  - Prior PD-(L)1 treatment history
  - Other baseline characteristics*
- Peripheral monocyte frequency as a predictor of anti-tumor immune response has been previously shown
  - An association of monocyte levels with response was observed and further explored

*Age, sex, ECOG and visceral involvement.
ECOG, Eastern Cooperative Oncology Group; ENT, entinostat; PEMBRO, pembrolizumab.
Higher baseline levels of peripheral CD14+CD16-HLA-DR^{Hi} classical monocytes are associated with ORR and PFS benefits

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<th>mPFS (95% CI)</th>
<th>ORR (95% CI)</th>
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<tr>
<td>Monocyte^{High}</td>
<td>5.3 months (1.3-NE)</td>
<td>21.1% (6.1-45.6)</td>
</tr>
<tr>
<td>Monocyte^{Low}</td>
<td>2.7 months (1.5-4.1)</td>
<td>6.5% (1.4-17.9)</td>
</tr>
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</table>

- 26% of patients in the monocyte high group (5 of 19) are ongoing and 2% of patients in the monocyte low group (1 of 46) are ongoing.

*High / low defined by midpoint (13.1% of live PBMCs / ml) of range of peripheral monocyte values from available samples.

CI, confidence interval; NE, not estimable; ORR, objective response rate; mPFS, median progression-free survival.
Reduced circulating MDSCs (CD14+HLA-DR$^{\text{neg/low}}$) associated with clinical responses

- Circulating MDSC cell reduction consistent with hypothesized entinostat MOA
- Trend in increased CD8+ T cells observed in responding patients

*% change from baseline was measured at C2D15 (5 wks).

MDSCs, myeloid-derived suppressor cells.

-65.3%, n=6  -10.5%, n=30  25.0%, n=6  -18.3%, n=34

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M-MDSCs

CD8 T cells

*% change from baseline was measured at C2D15 (5 wks). MDSCs, myeloid-derived suppressor cells.
Conclusions: ENT + PEMBRO in PD-(L)1 Pre-treated NSCLC

- ENT + PEMBRO demonstrated anti-tumor activity (ORR 10%) in patients with NSCLC who have progressed on prior PD-(L)1 blockade
  - Prespecified ORR target not reached; may represent clinically meaningful activity
  - An additional 50% of patients achieved disease stabilization
- Most patients tolerated the therapy well
- Responses to ENT + PEMBRO were independent of baseline PD-L1 expression
- Exploratory biomarker analyses identified baseline levels of peripheral classical monocytes as potential predictors of clinical benefit
- Future trial designs prospectively incorporating biomarkers for patient selection are under discussion

ENT, entinostat; ORR, objective response rate; NSCLC, non-small cell lung cancer; PEMBRO, pembrolizumab.
Acknowledgements

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