Phase I study of E7046, a novel PGE$_2$-receptor type 4 inhibitor, in patients with advanced solid tumors: clinical results and effects on myeloid- and T-lymphoid cell-mediated immunosuppression

Presenter Disclosure Information

The following relationships exist related to this presentation:

- *Eisai-travel and research*
E7046 mechanism of action

- E7046 is a potent, highly selective, small-molecule inhibitor of EP₄, the PGE₂-receptor type 4¹
- E7046 represents a first-in-class investigational compound for cancer immunotherapy
- Preclinical data show that E7046 reverses PGE₂-mediated tumor immune suppression²

E7046 promotes:

- Anti-tumor myeloid cell differentiation and function
- Anti-tumor T-cell tumor infiltration and effector function

Preclinical evidence: E7046 combinations

- In animal models, E7046 alone showed mostly an immune-dependent tumor growth inhibitory activity\(^1\)
- E7046 combined with radiation and with immune checkpoint inhibitors showed potent antitumor activity
- Combination treatment represents the best development opportunity

First-in-human phase 1 study of E7046

- In this dose-escalation study, 30 patients were treated with single-agent E7046 in 4 dose cohorts: 125, 250, 500, 750 mg QD

Key eligibility criteria
- Aged ≥ 18 years
- Advanced, nonresectable, or recurrent tumor types with high levels of myeloid infiltrate*
- Measurable disease by irRECIST
- ECOG PS 0 or 1

Primary endpoints
- Safety/tolerability
- MTD and/or RP2D

Selected secondary endpoints
- Pharmacokinetics
- ORR (irRECIST)
- DCR (irRECIST)

Exploratory endpoints
- PD assessments on immune cells in tumor infiltrate and in peripheral blood
- Metabolic response by 18F-FDG-PET

Study demographics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>58.0 (24, 78)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (63.3)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Age Group, years</td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>23 (76.7)</td>
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<tr>
<td>&gt;65</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24 (80.0)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

Tumor type
- Colorectal 13 (43.3)
- Pancreas 6 (20.0)
- SCCHN 4 (13.3)
- Other 7 (23.3)

Prior therapy regimens

<table>
<thead>
<tr>
<th>Prior therapy regimen</th>
<th>Total (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>2</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>3</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>16 (53.3)</td>
</tr>
</tbody>
</table>

Prior immunotherapy 4 (13.3)

*Pancreatic adenocarcinoma; renal clear cell carcinoma; SCCHN, NSCLC; colorectal cancer; hepatocellular carcinoma; serous epithelial ovarian cancer; transitional cell bladder cancer; cervical cancer; TNBC.

DCR, disease control rate; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; 18F-FDG-PET, fluorodeoxyglucose (FDG)-positron emission tomography; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; QD, once daily; RP2D, recommended phase 2 dose; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast cancer.
Safety

- No DLTs were observed and the MTD was not reached

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>Total (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Patients with any TEAEs</td>
<td>28 (93.3)</td>
</tr>
</tbody>
</table>

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; TEAEs: treatment-emergent adverse events.
Duration of treatment

- Preliminary efficacy results showed no objective responses by irRECIST:
  - Stable disease was observed in 7 (23%) of 30 patients
  - 5 Patients had long duration (≥ 18 weeks) of treatment and were clinically stable, with a best response of stable disease
- 10 Patients had duration of E7046 treatment that was longer than their most recent prior therapy

*2 Patients in this group received prior immune checkpoint inhibitor therapy (but not as the most recent prior therapy).
+Patient received at least 1 prior radiotherapy. Data cut-off: August 10, 2017.
Metabolic responses

- Metabolic responses* (¹⁸FDG-PET) were observed in 3 patients

**Metabolic response: Case**
- 74-year-old female
- Metastatic non-small cell lung cancer
- 2 Prior lines of chemotherapy, then failed nivolumab (nonresponder)
- E7046 treatment for 208 days, clinically stable
- Discontinued due to clinical progression

*Metabolic responses were based on EORTC recommendations (Young H, et al. *Eur J Cancer* 1999). Partial metabolic response was defined as a reduction in SUVmax of ≥25% after more than one cycle of drug.
Clinical pharmacokinetics of E7046

- E7046 was rapidly absorbed across all doses and $C_{\text{max}}$ was observed ~2 hours postdose
- Elimination $t_\frac{1}{2}$ was 12 hours
- E7046 exposure was dose proportional up to 500 mg, with no incremental increase at 750 mg
Gene expression changes in blood upon E7046 treatment

- 16 Genes out of a 92-immune-gene panel were modulated (volcano plot)
  - Among the 16 genes, 7 are known to be modulated by EP₄ signaling

- Five EP₄-signaling genes were significantly regulated (paired t-test), implicating target modulation
Cytokine changes in blood upon E7046 treatment

- 14 Cytokines/chemokines out of a panel of 36 were modulated (volcano plot)
- CXCL10 and CCL5, T-cell recruiting chemokines, were significantly upregulated at Cycle 1 Day 15 compared with baseline
Increase in tumor T-cell infiltration after E7046 treatment

IHC Staining

Baseline

Postdose (C2D1)

CD3

CD8

C2D1, Cycle 2, Day 1; IHC, immunohistochemistry.

CD3

CD8

Positive Cells (%) vs. Dose (mg)

Baseline

Postdose

N = 11

P = 0.0145

N = 11

P = 0.0367

*Paired 1-tailed t-test.
Baseline tumor immune characteristics and clinical outcome

- Higher baseline tumor infiltration of T cells (CD3+, CD8+) and of type 2 macrophages are associated with better clinical activity.
Summary

- 30 Patients with advanced malignancies were treated with E7046
- E7046 was well tolerated, with no DLTs

• Modulation of EP4 signaling genes
• Increased levels of T-cell–recruiting chemokines including CXCL10 and CCL5 in the blood

• Increased level of tumor T-cell infiltrate
• 5 Patients with irSD had long duration of treatment and were clinically stable
• 3 Patients achieved metabolic responses

Higher baseline tumor infiltration of T cells and type 2 macrophages was associated with better clinical activity

Dose-proportional exposure up to 500 mg daily