A Phase 1b Study of E7386, a CREB-Binding Protein (CBP)/β-Catenin Inhibitor, in Combination With Lenvatinib in Patients With Advanced Solid Tumors


Introduction

- The canonical Wnt/β-catenin signaling pathway has remarkably diverse roles in cancer; deregulation of this pathway is associated with carcinogenesis, tumor progression, and drug resistance.
- Carcinogenesis is often accelerated by the aberrant activation of component 4.
- Grade ≥ 3 h*ng/mL
- Therefore, the administration schedule of E7386 in Study 102 was changed.
- No significant PK drug–drug interactions between E7386 and lenvatinib were observed.

Pharmacokinetics

- Exposure of E7386 alone (at doses of 100–120 mg BID) at steady state (C0D5) was evaluated using Response Evaluation Criteria in Solid Tumors version 1.1.
- E7386 is the first-in-class, oral, active small molecular protein–protein interaction inhibitor of pericyte-covered vessels and inhibition of the hypoxia-response.
- The canonical Wnt/β-catenin signaling pathway has remarkably diverse roles in cancer; deregulation of this pathway is associated with carcinogenesis, tumor progression, and drug resistance.
- In this subanalysis, part form cycle 1 to day 1, E7386 QD (20 mg) plus lenvatinib 20 mg QD were administered in Schedule B, lenvatinib QD doses were administered in Schedule A,
- Tolerability was evaluated with a 3+3+3 design.
- A patient with biliary tract carcinoma had grade 4 liver disorder that was considered possibly related to lenvatinib.
- Tumor response was assessed by investigators using Response Evaluation Criteria in Solid Tumors version 1.1.
- AEs were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- Dose-limiting toxicities (DLTs) were reported with E7386 160 mg twice daily (BID), and it was judged that QD dosing was not feasible.

Methods

- Previous phase 1 studies in patients with solid tumors (Study 101 in the United Kingdom; ClinicalTrials.gov identifier NCT04013739 and Study 105 in Japan; ClinicalTrials.gov identifier NCT04013740) assessed dose escalation with E7386 alone.
- In a phase I/II trial evaluating pemetrexed plus pembrolizumab, QD doses were administered on days 1 and 8 of each 21-day cycle, and pembrolizumab was administered on days 1 and 8 of each 21-day cycle.
- In the 12-week study, patients were treated with E7386 100 mg BID, 150 mg QD, and 200 mg QD, respectively.
- The optimal therapeutic dose of E7386 was determined to be 300 mg BID based on tumor response rate and maximum tolerated dose.
- Although, the administration schedule of E7386 in Study 101 was changed.

Results

- A total of 147 patients with advanced solid tumors were enrolled.
- No significant PK drug–drug interactions between E7386 and lenvatinib were observed.
- The optimal therapeutic dose of E7386 was determined to be 300 mg BID based on tumor response rate and maximum tolerated dose.
- A total of 147 patients with advanced solid tumors were enrolled.
- No significant PK drug–drug interactions between E7386 and lenvatinib were observed.
- The optimal therapeutic dose of E7386 was determined to be 300 mg BID based on tumor response rate and maximum tolerated dose.

Safety

- There were 2 DLs reported.
- A patient with biliary tract carcinoma had grade 3 peripheral edema that was deemed possibly related to E7386 QD plus lenvatinib 20 mg QD.

Table 2. E7386 PK Parameters for Patients With Solid Tumors Who Received E7386 80 mg QD

<table>
<thead>
<tr>
<th>E7386 80 mg QD Parameters</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>78.3 (23.9)</td>
<td>101 (35.5)</td>
<td>39.2 (12.7)</td>
<td>7.7 (3.4)</td>
<td>51.7 (18.6)</td>
<td>57.8 (20.5)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>7.8 (2.1)</td>
<td>7.9 (2.1)</td>
<td>7.2 (1.9)</td>
<td>7.2 (1.9)</td>
<td>7.8 (2.1)</td>
<td>9.0 (2.5)</td>
</tr>
<tr>
<td>AUC, ng*h/mL</td>
<td>4270 (1350)</td>
<td>4430 (1610)</td>
<td>4200 (1300)</td>
<td>407 (53)</td>
<td>3980 (1280)</td>
<td>395 (101)</td>
</tr>
</tbody>
</table>

Table 3. E7386 PK Parameters for Patients With Solid Tumors Who Received E7386 120 mg BID

<table>
<thead>
<tr>
<th>E7386 120 mg BID Parameters</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>162 (60)</td>
<td>130 (53)</td>
<td>101 (36)</td>
<td>7.7 (3.4)</td>
<td>51.7 (18.6)</td>
<td>57.8 (20.5)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>7.8 (2.1)</td>
<td>7.9 (2.1)</td>
<td>7.2 (1.9)</td>
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<td>395 (101)</td>
</tr>
</tbody>
</table>

Table 4. E7386 PK Parameters for Patients With Solid Tumors Who Received E7386 150 mg QD

<table>
<thead>
<tr>
<th>E7386 150 mg QD Parameters</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
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</tr>
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<tr>
<td>Cmax, ng/mL</td>
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</tr>
<tr>
<td>Tmax, h</td>
<td>7.8 (2.1)</td>
<td>7.9 (2.1)</td>
<td>7.2 (1.9)</td>
<td>7.2 (1.9)</td>
<td>7.8 (2.1)</td>
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ClinicalTrials.gov number: NCT04013740

References

- E7386 in combination with lenvatinib 20 mg QD was deemed biomarker-driven and therefore recommended for evaluation in the phase 2/3 study.
- E7386 was generally well-tolerated at recommended phase 2/3 study dose, with no unexpected safety signals.
- E7386 is the first-in-class, small molecular protein–protein interaction inhibitor of pericyte-covered vessels and inhibition of the hypoxia-response.
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Conclusions

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