Activity of Cabozantinib (XL184) in Advanced Ovarian Cancer Patients: Results From a Phase 2 Randomized Discontinuation Trial (RDT)


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Cabozantinib: A Dual MET/VEGFR2 Inhibitor

- MET is activated in a wide range of malignancies
- MET drives genetic “invasion growth” pathway in tumor cell
- MET and VEGF signaling pathways act synergistically to drive angiogenesis

Proliferation (RAS-MAPK)
Increased invasiveness / EMT (RAS, FAK)
Inhibition of apoptosis (PI3 kinase)

GROWTH-MOTILITY-INVASION

Increased MET
Increased VEGFR2
Decrease TSP-1

ANGIOGENESIS

Anti-metastatic effect in liver

RIP-Tag2 mouse model (pancreatic neuroendocrine tumor)
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Key Study Eligibility Criteria:

- Prior progressive disease and measurable target lesion(s) per mRECIST 1.0
  - Patients with PD per CA125 criteria alone were excluded
- Platinum refractory, resistant or sensitive
- ECOG performance status ≤ 1
Study Endpoints and Assessments

Study Endpoints:

- Efficacy
  - Lead-in Stage: Objective response per mRECIST 1.0
  - Randomized Stage: Progression-free survival
- Safety

Assessments:

- Tumor assessments by CT/MRI/bone scan at baseline and q6 weeks
- Pharmacodynamic assessments
  - Biomarkers, including CA-125
# Baseline Characteristics

<table>
<thead>
<tr>
<th>N = 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years (range)</td>
</tr>
<tr>
<td>Platinum-free Interval(^b), n (%)</td>
</tr>
<tr>
<td>Measurable disease, n (%)</td>
</tr>
<tr>
<td>Refractory/Resistant (≤ 6 months)</td>
</tr>
<tr>
<td>CA125 increased(^a), n (%)</td>
</tr>
<tr>
<td>Sensitive (&gt; 6 months)(^c)</td>
</tr>
<tr>
<td>Primary disease site, n (%)</td>
</tr>
<tr>
<td>Ovary</td>
</tr>
<tr>
<td>Peritoneum</td>
</tr>
<tr>
<td>Metastatic disease, n (%)</td>
</tr>
<tr>
<td>Prior lines of therapy, n (%)</td>
</tr>
<tr>
<td>0-1</td>
</tr>
<tr>
<td>≥ 2</td>
</tr>
<tr>
<td>Histologic subtype, n (%)</td>
</tr>
<tr>
<td>Serous</td>
</tr>
<tr>
<td>Clear Cell</td>
</tr>
<tr>
<td>Endometrioid</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Bone metastases, n (%)</td>
</tr>
<tr>
<td>PLD, pegylated liposomal doxorubicin</td>
</tr>
</tbody>
</table>

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\(^a\) Baseline CA125 ≥ ULN (upper limit of normal)

\(^b\) Platinum-free interval: Progression during treatment with platinum or interval from the time of last dose of platinum to disease progression

\(^c\) Includes 4 patients whose platinum-free interval could not be determined
### Most Frequently Reported Adverse Events During Lead-In Stage Regardless of Causality (N = 70)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades, n (%)</th>
<th>Grade ≥ 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>51 (73)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 (53)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>36 (51)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26 (37)</td>
<td>-</td>
</tr>
<tr>
<td>PPE syndrome&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>25 (36)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (33)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>23 (33)</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>20 (29)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18 (26)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Transaminases increased&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17 (24)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14 (20)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>14 (20)</td>
<td>-</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14 (20)</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (19)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13 (19)</td>
<td>-</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>12 (17)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

**Less frequent but important medical events**

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Thrombosis venous&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Gastrointestinal perforation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

- 37% experiencing ≥ 1 dose reduction
- Two (3%) Related Grade 5 events overall (both after Lead-in Stage):
  - Enterocutaneous fistula
  - Intestinal perforation

<sup>a</sup> CTCAE v.3.0 grading.
<sup>b</sup> Groupings of Preferred Terms related to a particular medical condition
<sup>c</sup> Palmar-Plantar Erythrodysesthesia syndrome.
Hemoglobin Changes Over Time in Patients With Hb <11 g/dL at Baseline (N = 9)

The median maximum rise in Hb was 2.3 g/dL (range 0.3 to 4)
Patient Disposition

Patients Enrolled
N = 70

Open Label Extension
> Week 12
n = 24 (34%)

- Active 16
- Discontinued 8

Randomized at Week 12
n = 13 (19%)

- Active (Blinded) 3
- Discontinued 6

Cross-over to cabozantinib
4

Off-Treatment ≤ Week 12
n = 33 (47%)

- Disease Progression 22 (31%)
- Adverse Event 5 (7%)
- Death 1 (1%)
- Otherb 5 (7%)

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a Includes 7 ovarian cancer patients converted to Open Label Extension of patients with SD in Lead-in Stage after approval of Protocol Amendment 1

b Other includes Patient Request 21 (4%), Lost to F/U 4 (1%), PI Decision 3 (1%) and “Other” 10 (2%)
### Summary of RECIST Response

<table>
<thead>
<tr>
<th>Platinum Free Interval</th>
<th>Number Evaluable</th>
<th>PR N (%)</th>
<th>Week 12 DCR&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month (refractory)</td>
<td>11</td>
<td>2 (18)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>36</td>
</tr>
<tr>
<td>1 – 6 months (resistant)</td>
<td>23</td>
<td>5 (22)</td>
<td>39</td>
</tr>
<tr>
<td>&gt; 6 months (platinum sensitive)</td>
<td>36</td>
<td>10 (28)</td>
<td>67</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>70</strong></td>
<td><strong>17 (24)</strong></td>
<td><strong>53</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> Disease Control Rate (DCR) = (CR + PR + SD) at Week 12 / Response Evaluable

<sup>b</sup> Includes one complete response (CR)
With a median follow-up of 36 weeks, the median duration of response has not been reached
**Effects on Measurable Lesions (N = 64)**

- **Platinum resistant / refractory**
- **Platinum sensitive / undetermined**

% Change vs. Baseline

- **†** Best Radiologic Response in Patients with ≥1 Post-Baseline Tumor Assessment
- **‡** Confirmed PRs
- **‡‡** Clear cell adenocarcinoma subtype
- ***** 0% change from baseline

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a  Best Radiologic Response in Patients with ≥1 Post-Baseline Tumor Assessment

†  Increase > 100% from baseline target lesion sum of longest diameters
Correlation of Response in Measurable Lesions and CA125

Best Radiologic Response (N = 64)\textsuperscript{a}

- Platinum resistant / refractory
- Platinum sensitive / undetermined

% Change vs. Baseline

- Clear cell adenocarcinoma subtype
- Confirmed PRs

Best CA125 Response (N = 52)\textsuperscript{b}

% Change vs. Baseline

+ CA125 responders per GCIG criteria

\textsuperscript{†} Increase in % > upper limit of scale from baseline
\textsuperscript{a} Patients with ≥ 1 Post-Baseline Tumor Assessment
\textsuperscript{b} Only patients with CA125 ≥ 1 x ULN at baseline are shown; Patients with ≥ 1 Post-Baseline CA-125 Assessment

Best response not necessarily from the same time point as the best radiological response.
Re-stabilization of PD after Crossing Over from Placebo to Cabozantinib

a Second PD due to unequivocal progression of nTL (ascites) and new lesion
Summary

- Cabozantinib demonstrates promising activity in both platinum-sensitive and platinum-resistant/refractory ovarian cancer
  - Week 12 overall disease control rate of 53%
  - Response rates of 18% in platinum-refractory, 22% in platinum-resistant and 28% in platinum-sensitive patients
- Cabozantinib shows encouraging duration of response
  - After 36 weeks of follow-up, median duration of response not reached
- Tolerability profile is consistent with that of other tyrosine kinase inhibitors
- Discordant effects observed between CA125 changes and clinical activity
- Simultaneous targeting of MET and VEGFR2 with cabozantinib results in robust effects in patients with advanced ovarian cancer
- Non-randomized expansion cohort is currently accruing in platinum-resistant/refractory ovarian cancer
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