A phase Ib multi-cohort study of xentuzumab and abemaciclib in patients with solid tumors and breast cancer – initial report of four dose-finding cohorts

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Introduction

• The IGF and CDK 4 & 6–Rb pathways are implicated in the pathogenesis and resistance mechanisms of a variety of cancers, including HR+, HER2– breast cancer\(^1\)–\(^4\)

• The cyclin D–CDK 4 & 6 complex phosphorylates Rb, leading to dissociation from E2F transcription factors, which allows target gene transcription and subsequent progression through the G1/S cell-cycle checkpoint\(^5\)

• Abemaciclib is a FDA approved CDK 4 & 6 inhibitor for HR+, HER2– advanced breast cancer therapy in combination with an aromatase inhibitor as initial endocrine-based therapy, with fulvestrant for progression following ET, and as monotherapy for progression following ET and prior chemotherapy in the metastatic setting\(^6\)

• Activation of pIGF-1R/pIR, leads to an increase in cyclin D1; therefore, dual inhibition of IGF and CDK 4 & 6 could lead to decreased cell proliferation through disruption of cell-cycle progression\(^7\), \(^8\)

CDK, cyclin-dependent kinase; ET, endocrine therapy; FDA, Food & Drug Administration; HR+, hormone receptor-positive; HER2–, human epidermal growth factor receptor-2 negative; IGF, insulin-like growth factor; pIGF-1R/pIR, phosphorylated IGF type 1 receptor/insulin receptor; Rb, retinoblastoma protein
• Xentuzumab is a humanized IgG1 mAb that binds with high affinity to IGF-1 and IGF-2 and potently neutralizes proliferative and pro-survival cellular signaling triggered by both proteins\(^8\) (Figure 1). Unlike IGF-IR antibodies, xentuzumab does not elevate growth hormone or induce hyperglycemia.

• We conducted a phase Ib study (NCT03099174) to determine the MTD/RP2D of xentuzumab in combination with abemaciclib, with or without ET (letrozole, anastrozole, fulvestrant). Here, we present an interim analysis of safety and efficacy. At time of writing, 40% of patients are still receiving treatment.
Introduction (cont’d)

Figure 1: Xentuzumab mechanism of action

IR-A/B, insulin receptor isoform A/B
Methods

Prospective, open-label, non-randomized, multiple dose-finding, phase Ib study

- Four dose-finding cohorts evaluated in two parts using a Bayesian Logistic Regression Model with overdose control, fitted to toxicity outcomes

Part 1: Solid tumors

Cohort A
- Women or men aged ≥18 years (≥20 in Japan)
- Advanced/metastatic, measurable or evaluable non-resectable solid tumors
- Received and failed, or been intolerant to, all treatment known to confer benefit, or no therapeutic options deemed appropriate by their treating physician

Cohort A
- Abemaciclib (starting dose 150 mg every 12 h p.o.)
- xentuzumab (starting dose 1000 mg weekly i.v.)

Part 2: Breast cancer

Cohorts B–D

Cohort B
- Abemaciclib† + xentuzumab + letrozole (2.5 mg/day)

Cohort C
- Abemaciclib† + xentuzumab + anastrozole (1 mg/day)

Cohort D
- Abemaciclib† + xentuzumab + fulvestrant (500mg; per label)

*Pre/peri-menopausal patients with postmenopausal status via administration of GnRH agonists were also permitted; †Abemaciclib dose must be ≤150 mg twice daily in these cohorts.

DLT, dose-limiting toxicity; i.v., intravenous; PFS, progression-free survival; p.o, orally
Methods (cont’d)

**Primary endpoints:** MTD for each cohort, and number of patients with DLTs during the MTD evaluation period (first 28-day cycle)

Tumor response and PFS were also assessed

DLT, dose-limiting toxicity; PFS, progression-free survival
Baseline demographics

Data snapshot taken
15 October 2019

N=28
Patients enrolled

*Updated data snapshot from abstract; †Included patients with breast cancer (n=3), lung cancer, sarcoma, and colorectal cancer (n=1 each)
Baseline demographics (cont’d)

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort A n=6</th>
<th>Cohort B n=7</th>
<th>Cohort C n=7</th>
<th>Cohort D n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60.5 (56–66)</td>
<td>56.0 (34–64)</td>
<td>66.0 (35–70)</td>
<td>49.0 (40–70)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5 (83.3)</td>
<td>7 (100)</td>
<td>7 (100)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2 (33.3)</td>
<td>5 (71.4)</td>
<td>5 (71.4)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (33.3)</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (33.3)</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Menopausal status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td></td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td>1 (12.5)</td>
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<tr>
<td>Perimenopausal</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td>6 (85.7)</td>
<td>6 (85.7)</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>Visceral disease, n (%)</td>
<td>6 (100)</td>
<td>5 (71.4)</td>
<td>7 (100)</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (33.3)</td>
<td>6 (85.7)</td>
<td>4 (57.1)</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>1</td>
<td>4 (66.7)</td>
<td>1 (14.3)</td>
<td>3 (42.9)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Prior chemotherapy for advanced disease, n (%)</td>
<td>5 (83.3)</td>
<td>3 (42.8)</td>
<td>5 (71.4)</td>
<td>4 (50.0)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status
Safety

The MTD of xentuzumab in Cohorts A–D was 1000 mg i.v. weekly plus abemaciclib 150 mg p.o. every 12 h

Patients experienced the following cycle 1 DLTs:

- One patient in Cohort A experienced grade 3 neutrophil count decrease (another patient had grade 3 neutrophil count decrease reported on day 29)
- Patients in Cohorts B–D experienced grade 3 neutrophil count decrease (B, n=1), grade 4 thrombocytopenia (C, n=1), and grade 3 neutropenia (D, n=1)
Safety (cont’d)

• No patients experienced a serious AE in Cohort A

• In Cohorts B–D, 11 patients experienced at least one serious AE

• Two patients in Cohort B discontinued xentuzumab due to AEs (blood bilirubin increase and kidney injury; both unrelated to treatment). Two patients in Cohort B discontinued xentuzumab due to AEs (blood bilirubin increase and kidney injury; both unrelated to treatment). Treatment continued for one patient, whereas the other discontinued abemaciclib before xentuzumab, and later discontinued letrozole

• No deaths were reported in any cohort
Table 2. Drug exposure and dose reduction

<table>
<thead>
<tr>
<th></th>
<th>Cohort A n=6</th>
<th>Cohort B n=7</th>
<th>Cohort C n=7</th>
<th>Cohort D n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median treatment duration, months</td>
<td>1.7 (0.9–7.3)</td>
<td>9.3 (1.6–22.0)</td>
<td>6.0 (1.8–13.8)</td>
<td>6.4 (0.5–12.6)</td>
</tr>
<tr>
<td>(range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any dose reduction, n (%)</td>
<td>2 (33.3)</td>
<td>6 (85.7)</td>
<td>5 (71.4)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Xentuzumab dose reduction, n (%)</td>
<td>1 (16.7)</td>
<td>4 (57.1)</td>
<td>1 (14.3)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Abemaciclib dose reduction, n (%)</td>
<td>2 (33.3)</td>
<td>4 (57.1)</td>
<td>5 (71.4)</td>
<td>3 (37.5)</td>
</tr>
</tbody>
</table>
Safety (cont’d)

Drug-related adverse events

• Most DRAEs were reversible

• The most common DRAEs were decreased appetite and diarrhea for Cohort A, and diarrhea for Cohorts B–D (Figure 2)
Safety (cont’d)

Figure 2. Most common drug-related adverse events by cohort

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any related AE</td>
<td>50.0%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>66.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50.0%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>50.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>50.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>50.0%</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>33.3%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33.3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>33.3%</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>33.3%</td>
</tr>
<tr>
<td>WBC count decreased</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

AE, adverse event; WBC, white blood cell
Figure 2. Drug-related adverse events by cohort

Cohorts B–D (n=22)

- Any related AE: 36.4% (Grade 1–2), 63.6% (Grade ≥3)
- Diarrhea: 77.3% (Grade 1–2), 4.5% (Grade ≥3)
- Asthenia: 63.7% (Grade 1–2), 9.1% (Grade ≥3)
- Anemia: 54.5% (Grade 1–2), 4.5% (Grade ≥3)
- Neutropenia: 27.3% (Grade 1–2), 31.8% (Grade ≥3)
- Nausea: 54.5% (Grade 1–2)
- Blood creatinine increased: 45.5% (Grade 1–2)
- Abdominal pain: 40.9% (Grade 1–2)
- Decreased appetite: 40.9% (Grade 1–2)
- Vomiting: 31.8% (Grade 1–2)
- Thrombocytopenia: 22.7% (Grade 1–2), 4.5% (Grade ≥3)
- Platelet count decreased: 18.2% (Grade 1–2), 9.1% (Grade ≥3)

Number of patients
Efficacy

- In Cohort A, one patient had a best overall response of PR, and one had SD; both of these patients had breast cancer
- In Cohorts B–D, four patients had a best overall response of PR; 11 patients had SD, among whom four had SD lasting ≥24 weeks
- Median PFS (95% CI) was 1.7 months (1–7.3) in Cohort A and 9.1 months (3.5–not calculable) in Cohorts B–D (Figure 3)
Efficacy (cont’d)

Figure 4. Progression-free survival by cohort

Cohort A: 1.7 (1.0–7.3)
Cohorts B–D: 9.1 (3.6–NC)

CI, confidence interval; NC, not calculable; PR, partial response; SD, stable disease
Key findings and conclusions

- The MTD and RP2D of xentuzumab was 1000 mg i.v. weekly plus abemaciclib 150 mg p.o. every 12 h, with or without ET
- The safety profile of xentuzumab in combination with abemaciclib alone (cohort A) or with abemaciclib/endocrine therapy (cohorts B–D) was manageable, and in a similar range as published for abemaciclib alone and in combination with endocrine therapy (eg, common occurrence of diarrhea and hematological side effects). Hyperglycemia was not seen.
- Median PFS with xentuzumab in combination with abemaciclib and ET was 9.1 months across pooled breast cancer cohorts, in which 81.8% of patients had visceral metastasis and >50% had received chemotherapy for advanced disease.
- Expansion cohorts to evaluate the efficacy of xentuzumab plus abemaciclib and fulvestrant in HR+, HER2– breast cancer are ongoing.
References

6. Verzenios Film-coated tablets SmPC 2019
Acknowledgments

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