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

Douglas Yee, Mafalda Oliveira, Hiroji Iwata, Anthony Goncalves, Javier García-Corbacho, Marie Paulë Sabin, Alex Prot, Molly Catherine Hardebeck, Marta Pug, Dennis Chin-Lun Huang, Mingchi Hsu, Patricia LoRusso, Molly Catherine Hardebeck, Patricia LoRusso

Introduction

- The IGf and CDK 4/6-RTK pathways are implicated in the proliferation and resistance mechanisms of a variety of cancers, including HR+, PIK3CA-mutant and HER2+ breast cancer.
- The cycle 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.
- Abemaciclib is a FDA-approved CDK 4 & 6 inhibitor for HR+ HER2- breast cancer therapy in combination with an aromatase inhibitor as initial endocrine-based therapy, with fulfillment for progression following ET, and as monotherapy for progression following ET and prior chemotherapy in the metastatic setting.
- Activation of IGf-IR/PDK1 leads to an increase in cycle D1; therefore, dual inhibition of IGf and CDK 4/6 could lead to decreased cell proliferation through disruption of cell-cycle progression.

Xentuzumab is a humanized IgG1 mAb that binds with high affinity to IGf-1 and IGf-2 and potentiates resistance proline and pro-survival cellular signaling triggered by both partners (Figure 1). Unlike IGf-1R antibody, xentuzumab does not elevate growth hormone or induce hyperglycemia.

We conducted a phase Ib study (NCT03097014) to determine the MTD/RP2D of xentuzumab in combination with abemaciclib, or without ET, for patients with advanced or metastatic solid tumors intolerant to all treatment and considered free of disease. Safety of efficacy and safety. At time of writing, 40% of patients are still receiving treatment.

Methods

- Four dose-finding cohorts evaluated in two parts using a Bayesian Logistic Regression Model with control over trend, to lead to toxicities.

Part 1: Solid tumors

- Women or men aged 18 years (≥20% in Japan).
- Advanced/metastatic, measurable or non-measurable solid tumors.
- Received and/or were intolerant to all treatment known to confer benefit or appropriate by their treating physician.

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

Table 1. Baseline characteristics

| Cohort | Patients enrolled | Gender (M/F) | Age (years) | ECOG PS | Baseline demographics | Tumor response and PFS were also assessed
|---------------------------------|----------------|-------------|-----------|----------------------|---------------------------------------------|
| Cohort A | 6 | 4/2 | 56.0 (40–70) | 1.0 | 3 (50.0) | 1 (16.7) | 0.5 (0–3.0) | 1 (16.7) | 2 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 9.1 months (3.6–not calculable) | 11 patients had SD, among whom four had HD lasting >24 weeks. Three patients had a non-CR/PR lasting ≥24 weeks.
| Cohort B | 8 | 7/1 | 56.0 (35–70) | 1.0 | 5 (62.5) | 2 (25.0) | 0.5 (0–3.0) | 1 (12.5) | 4 (50.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 2 (25.0) | 9.1 months (3.6–not calculable) | 11 patients had SD, among whom four had HD lasting >24 weeks. Three patients had a non-CR/PR lasting ≥24 weeks.
| Cohort C | 7 | 6/1 | 54.5 (34–64) | 1.0 | 5 (71.4) | 1 (14.3) | 0.5 (0–3.0) | 0 (0.0) | 4 (57.1) | 0 (0.0) | 1 (14.3) | 0 (0.0) | 2 (28.6) | 9.1 months (3.6–not calculable) | 11 patients had SD, among whom four had HD lasting >24 weeks. Three patients had a non-CR/PR lasting ≥24 weeks.
| Cohort D | 6 | 5/1 | 54.5 (35–70) | 1.0 | 5 (83.3) | 3 (42.9) | 0.5 (0–3.0) | 0 (0.0) | 4 (66.7) | 0 (0.0) | 1 (14.3) | 0 (0.0) | 2 (33.3) | 9.1 months (3.6–not calculable) | 11 patients had SD, among whom four had HD lasting >24 weeks. Three patients had a non-CR/PR lasting ≥24 weeks.

Part 2: Breast cancer

- Women or men aged at least 18 years (≥18 years in Japan).
- Advanced/metastatic, evaluable or non-evaluable solid tumors.
- Received and/or were intolerant to all treatment known to confer benefit or appropriate by their treating physician.

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

Table 2. Drug exposure and dose reduction

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Any related AE</th>
<th>Abemaciclib dose reduction, n (%)</th>
<th>Xentuzumab dose reduction, n (%)</th>
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</thead>
<tbody>
<tr>
<td>Cohort A</td>
<td>5 (83.3)</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Cohort B</td>
<td>6 (75.0)</td>
<td>4 (57.1)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Cohort C</td>
<td>4 (57.1)</td>
<td>5 (71.4)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Cohort D</td>
<td>5 (75.0)</td>
<td>5 (75.0)</td>
<td>3 (42.9)</td>
</tr>
</tbody>
</table>

Table 3. Safety

| Cohort | Overall response rate | Number of patients with DLTs during the MTD evaluation period (first 28-day cycle) |
|---------------------------------|-------------------------------------------------------------|
| Cohort A | 2 (33.3) | 1 (16.7) | 0 (0.0) |
| Cohort B | 4 (57.1) | 4 (57.1) | 4 (57.1) |
| Cohort C | 1 (14.3) | 1 (14.3) | 0 (0.0) |
| Cohort D | 1 (12.5) | 0 (0.0) | 0 (0.0) |

Figure 1: Xentuzumab mechanism of action

Figure 2: Study design

Figure 3: Most common drug-related adverse events by cohort

Figure 4: Progression-free survival by cohort

References


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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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Presented at the San Antonio Breast Cancer Symposium (SABCS), San Antonio, Texas, USA, December 10–14, 2019
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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.)

Cohort A
Abemaciclib + xentuzumab

Part 2: Breast cancer

Cohorts B–D
Women with postmenopausal status
HR+, HER2− breast cancer not amenable to curative resection, or metastatic disease
No prior CDK4 & 6 therapy. Previous (neo)adjuvant chemotherapy permitted. 0–2 prior lines of chemotherapy permitted for metastasis

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

Cohort A
n=6†

Cohort B
n=7

Cohort C
n=7

Cohort D
n=8

*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>
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<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>
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<td>Female, n (%)</td>
<td>5 (83.3)</td>
<td>7 (100)</td>
<td>7 (100)</td>
<td>8 (100)</td>
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<td>Race, n (%)</td>
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<td>Menopausal status, n (%)</td>
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<td>Postmenopausal</td>
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<td>6 (85.7)</td>
<td>6 (85.7)</td>
<td>6 (75.0)</td>
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<td>Visceral disease, n (%)</td>
<td>6 (100)</td>
<td>5 (71.4)</td>
<td>7 (100)</td>
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<td>ECOG PS, n (%)</td>
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<td>0</td>
<td>2 (33.3)</td>
<td>6 (85.7)</td>
<td>4 (57.1)</td>
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<td>4 (66.7)</td>
<td>1 (14.3)</td>
<td>3 (42.9)</td>
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<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
## Safety (cont’d)

### 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><strong>Median treatment duration, months (range)</strong></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>
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<tr>
<td><strong>Any dose reduction, n (%)</strong></td>
<td>2 (33.3)</td>
<td>6 (85.7)</td>
<td>5 (71.4)</td>
<td>3 (37.5)</td>
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<tr>
<td><strong>Xentuzumab dose reduction, n (%)</strong></td>
<td>1 (16.7)</td>
<td>4 (57.1)</td>
<td>1 (14.3)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td><strong>Abemaciclib dose reduction, n (%)</strong></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)

DRAE, drug-related adverse event
Safety (cont’d)

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Patients</th>
</tr>
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<tbody>
<tr>
<td>Any related AE</td>
<td>50.0%</td>
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<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>
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<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), 13.6% (Grade ≥3)
- Asthenia: 63.7% (Grade 1–2), 4.5% (Grade ≥3)
- Anemia: 54.5% (Grade 1–2), 9.1% (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)
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

![Graph showing progression-free survival for different cohorts.]

- **Cohort A**: 1.7 (1.0–7.3) months (95% CI)
- **Cohorts B–D**: 9.1 (3.6–NC) months (95% CI)

**Patients at Risk**

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</table>

Cl, 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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