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

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Abstract #10

Introduction

The TKI and COX 4.6A pathways are implicated in the pathogenesis and resistance mechanisms of a variety of cancers, including HER2+, HER2- breast cancer. The TKI sunitinib, through its potent direct inhibition of PDGF and VEGF signaling, is a novel therapeutic strategy for patients with advanced solid tumors. Sunitinib is a multitargeted TKI that blocks with high affinity to IFG and KIT in breast cancer.

Methods

Four dose-finding cohorts evaluated in two parts using a Bayesian Logistic Regression Model with overdose control, followed to toxicity and efficacy. At the time of data analysis, 45% of patients were still receiving treatment. There was no clinical response in any cohort. At the maximum tolerated dose (MTD), all dose levels were reduced due to adverse events. The safety profile was consistent with previous phase II trials of sunitinib.

Baseline demographics

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
<th>Cohort D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>68 (30-84)</td>
<td>64 (30-82)</td>
<td>68 (30-84)</td>
<td>64 (30-82)</td>
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<td>Sex</td>
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<td>6 (0-20)</td>
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</tr>
</tbody>
</table>

Safety

No patients experienced a serious AE in Cohort A. In Cohort B, 10 patients experienced a serious AE. Two patients in Cohort B discontinued sunitinib due to AEs (dehydration, hypothyroidism). Treatment continued for one patient, whereas the other discontinued incoy to ongoing observation. In Cohort C, 1 patient discontinued treatment due to a serious AE, and another discontinued as a result of AEs. In Cohort D, no deaths were reported in any cohort.

Table 2. Drug exposure and dose reduction

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
<th>Cohort D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration, months</td>
<td>2.3</td>
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<tr>
<td>Dose, percent</td>
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<td>All dose reductions</td>
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<tr>
<td>Abemaciclib dose reduction</td>
<td>0.7</td>
<td>0.7</td>
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</tr>
</tbody>
</table>

Figure 4. Progression-free survival by cohort

Key findings and conclusions

The MTD and RDQ of sunitinib were 1000 mg / week, plus abemaciclib 160 mg / day, with 12% 12% toxicity. The safety profile of sunitinib in combination with abemaciclib was similar to that of sunitinib alone, with the exception of grade 3-4 diarrhea, which was higher in the combination arm. No new safety concerns were identified. The efficacy of sunitinib in combination with abemaciclib was not assessed in this study.

References

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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\(^6\)

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; Rb, retinoblastoma protein
Introduction (cont’d)

• 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}

• 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\textsuperscript{9} (Figure 1). Unlike IGF-1R 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 the time of data analysis, 40\% of patients were still receiving treatment

IGF-1R, IGF type 1 receptor; mAb, monoclonal antibody; MTD, maximum tolerated dose; pIGF-1R/pIR, phosphorylated IGF type 1 receptor/insulin receptor; RP2D, recommended phase 2 dose
Introduction (cont’d)

Figure 1: Xentuzumab mechanism of action

Xentuzumab

IGF-2

Insulin

IGF-1

Tumor cell

Growth/ proliferation/survival

IR-B

Insulin

Glucose homeostasis

Normal cell, e.g. muscle, fat or liver cell

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

**Figure 2. Study design**

**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 were 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**
  - Postmenopausal women*
  - HR+, HER2– breast cancer not amenable to curative resection, or metastatic disease
  - No prior anti-CDK therapy. Previous (neo)adjuvant chemotherapy permitted. Prior chemotherapy (≤2 lines) for advanced disease permitted

- **Cohort B**
  - Abemaciclib† + xentuzumab + letrozole (2.5 mg/day)
  - RP2D₂

- **Cohort C**
  - Abemaciclib† + xentuzumab + anastrozole (1 mg/day)
  - RP2D₃

- **Cohort D**
  - Abemaciclib† + xentuzumab + fulvestrant (500 mg; per label)
  - RP2D₄

**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

*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
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

*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>
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<tbody>
<tr>
<td><strong>Median age, years (range)</strong></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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<tr>
<td><strong>Female, n (%)</strong></td>
<td>5 (83.3)</td>
<td>7 (100)</td>
<td>7 (100)</td>
<td>8 (100)</td>
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<tr>
<td><strong>Race, n (%)</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
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<td>5 (71.4)</td>
<td>5 (71.4)</td>
<td>4 (50.0)</td>
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<tr>
<td>Asian</td>
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<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td>2 (25.0)</td>
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<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td>2 (25.0)</td>
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<td><strong>Menopausal status, n (%)</strong></td>
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<td>1 (14.3)</td>
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<td>1 (12.5)</td>
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<td>Perimenopausal</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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<tr>
<td><strong>Visceral disease, n (%)</strong></td>
<td>6 (100)</td>
<td>5 (71.4)</td>
<td>7 (100)</td>
<td>6 (75.0)</td>
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<td><strong>ECOG PS, n (%)</strong></td>
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<td></td>
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<tr>
<td>0</td>
<td>2 (33.3)</td>
<td>6 (85.7)</td>
<td>4 (57.1)</td>
<td>6 (75.0)</td>
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<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 (42.9)</td>
<td>5 (71.4)</td>
<td>4 (50.0)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status
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). Treatment continued for one patient, whereas the other discontinued abemaciclib before xentuzumab, and later discontinued letrozole
• No deaths were reported in any cohort

AE, adverse event
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>
<td>6.4 (0.5–12.6)</td>
</tr>
<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>
</tr>
<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>

**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 3)

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

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

Cohort A (n=6)

- Any related AE: 50.0%
- Decreased appetite: 66.7%
- Diarrhea: 50.0%
- Asthenia: 50.0%
- Vomiting: 50.0%
- Nausea: 50.0%
- Blood creatinine increased: 33.3%
- Thrombocytopenia: 33.3%
- Anemia: 33.3%
- Neutrophil count decreased: 33.3%
- WBC count decreased: 33.3%

WBC, white blood cell
Safety (cont’d)

Figure 3. Most common drug-related adverse events by cohort (cont’d)

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: 63.6% (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)

Number of patients

Grade 1–2 | 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. Three patients had a non-CR/non-PD lasting ≥24 weeks
• Median PFS (95% CI) was 1.7 months (1.0–7.3) in Cohort A and 9.1 months (3.6–NC) in Cohorts B–D (Figure 4)

CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease
Figure 4. Progression-free survival by cohort

Efficacy (cont’d)

Estimated probability of PFS

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

Patients at risk

Cohort A: 6 5 2 2 1 1 1 1 0
Cohorts B–D: 22 21 16 16 12 12 11 7 7 4 4 4 3 2 2 2 2 2 0

NC, not calculable
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/ET (Cohorts B–D) was manageable, and in a similar range as published for abemaciclib alone and in combination with ET (e.g., 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

1. Ekyalongo RC, Yee D. NPJ Precis Oncol 2017;1:14
6. VERZENIO® (abemaciclib). US Prescribing Information, 2019
Acknowledgments

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• This presentation is the intellectual property of the authors.

• Data were presented previously by Yee D, et al. at SABCS 2019; Poster #P3-11-05.

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