Sapanisertib Plus Exemestane or Fulvestrant in Women with Hormone Receptor–Positive/HER2-Negative Advanced or Metastatic Breast Cancer

Bora Lim1, David A. Potter2, Mohamad A. Salkeni3, Paula Silverman4, Tufia C. Haddad5, Frederic Forget6, Ahmad Awada7, Jean-Luc Canon8, Michael Danso9, Alain Lortholary10, Hugues Bourgeois11, Elizabeth Tan-Chiu12, Sylvie Vincent13, Brittany Bahamon13, Kevin J. Galinsky13, Chirag Patel13, Rachel Neuwirth13, E. Jane Leonard13, and Jennifer R. Diamond14

ABSTRACT

Purpose: This open-label, multicenter, phase IB/II study evaluated sapanisertib, a dual inhibitor of mTOR kinase complexes 1/2, plus exemestane or fulvestrant in postmenopausal women with hormone receptor–positive (HR+)/HER2-negative (HER2–) advanced/metastatic breast cancer.

Patients and Methods: Eligible patients had previously progressed on everolimus with exemestane/fulvestrant and received ≤3 (phase IB) or ≤1 (phase II) prior chemotherapy regimens. Patients received sapanisertib 3 to 5 mg every day (phase IB), or 4 mg every day (phase II) with exemestane 25 mg every day or fulvestrant 500 mg monthly in 28-day cycles. Phase II enrolled parallel cohorts based on prior response to everolimus. The primary objective of phase II was to evaluate antitumor activity by clinical benefit rate at 16 weeks (CBR-16).

Introduction

In women, breast cancer is the leading cause of cancer death and the most commonly diagnosed cancer (1). Hormone receptor–positive (HR+) tumors represent the most common breast cancer subtype with ~75% being estrogen receptor (ER)- or progesterone receptor–positive (HR+). Endocrine therapy is the first-line treatment in both the HR+ adjuvant and metastatic disease settings (4). However, ~30% of patients with metastatic HR+ breast cancer have primary resistance to endocrine therapy, and patients who do respond eventually develop resistance and thus require chemotherapy (5, 6). Of particular interest is the development of new treatment strategies for HR+ breast cancer that has progressed after endocrine therapy with or without a cyclin-dependent kinase (CDK) 4/6 inhibitor.

Results: Overall, 118 patients enrolled in phase IB (n = 24) and II (n = 94). Five patients in phase IB experienced dose-limiting toxicities, at sapanisertib doses of 5 mg every day (n = 4) and 4 mg every day (n = 1); sapanisertib 4 mg every day was the MTD in combination with exemestane or fulvestrant. In phase II, in everolimus-sensitive versus everolimus-resistant cohorts, CBR-16 was 45% versus 23%, and overall response rate was 8% versus 2%, respectively. The most common adverse events were nausea (52%), fatigue (47%), diarrhea (37%), and hyperglycemia (33%); rash occurred in 17% of patients. Molecular analysis suggested positive association between AKT1 mutation status and best treatment response (complete + partial response; P = 0.0262).

Conclusions: Sapanisertib plus exemestane or fulvestrant was well tolerated and exhibited clinical benefit in postmenopausal women with pretreated everolimus-sensitive or everolimus-resistant breast cancer.

Note: Supplementary data for this article is available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Authors: Bora Lim, Breast Oncology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030. E-mail: Bora.Lim@bcm.edu; and Jennifer Diamond, Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO 80045. E-mail: jennifer.diamond@cuanschutz.edu


©2021 American Association for Cancer Research.
Lim et al.

**Translational Relevance**

Sapanisertib (previously TAK-228 or MLN0128) is an investigational, oral, potent, and highly selective ATP-competitive inhibitor of mTOR kinase that exhibits dual specificity against both mTOR complexes (mTORC1 and mTORC2). In this phase IB/II study, we assessed the safety, tolerability, and antitumor activity of sapanisertib in combination with exemestane or fulvestrant in 118 postmenopausal women with hormone receptor–positive (HR+)/HER2–negative (HER2–) advanced breast cancer. Sapanisertib plus exemestane or fulvestrant demonstrated clinical benefit in postmenopausal women with advanced breast cancer, with evidence of renewed sensitivity to mTOR inhibition after progression on everolimus and the same endocrine partner, and a manageable safety profile. AKT1 or APC mutation may correlate with enhanced efficacy. There are few clinical studies reporting data on patients with advanced HR+/HER2– breast cancer with previous everolimus treatment, representing a patient population with a significant unmet medical need, and further evaluation of sapanisertib is warranted.

in turn activates mTORC1. On the basis of this, we hypothesized that sapanisertib in combination with exemestane or fulvestrant could restore endocrine sensitivity in patients with advanced or metastatic ER+/HER2– breast cancer with prior progression on everolimus.

**Patients and Methods**

**Study design and participants**

This multicenter, open-label, phase IB/II study assessed safety, tolerability, and antitumor activity of sapanisertib in combination with exemestane or fulvestrant in postmenopausal women with HR+/HER2– advanced or metastatic breast cancer that had progressed on previous treatment with everolimus plus exemestane or fulvestrant (NCT02049957). Patients were enrolled across approximately 40 centers in the United States, Belgium, and France to receive sapanisertib with either exemestane (any country) or fulvestrant (U.S. only) until disease progression or unacceptable toxicity. The partner drug exemestane or fulvestrant was chosen based on previous combination partner of everolimus, and the patients were assigned to parallel cohorts based on previous responses to everolimus.

Postmenopausal women ≥18 years old with Eastern Cooperative Oncology Group performance status 0 to 2, adequate organ function, and previously treated and progressed on everolimus and either exemestane or fulvestrant in the metastatic setting were eligible. Previous treatment with ≤3 (in phase IB) or ≤1 (in phase II) prior lines of chemotherapy in the metastatic setting were allowed, as were stable brain metastases without requirement for steroids or antiepileptic drugs. Phase II required measurable disease by RECIST version 1.1 or bone lesions. Previous treatment with PI3K, AKT, dual PI3K/mTOR, or TORC1/2 inhibitors (except for everolimus) was not permitted. Two parallel cohorts were enrolled: the everolimus-sensitive cohort was defined as patients who progressed on prior everolimus after achieving complete response (CR) or partial response (PR) of any duration or after stable disease (SD) lasting ≥6 months; all other patients were assigned to the everolimus-resistant cohort.

The primary objective for phase II was to determine the MTD of sapanisertib with exemestane or fulvestrant and secondary objectives included evaluation of the pharmacokinetic (PK) profile of sapanisertib and preliminary antitumor activity. Dose-limiting toxicity (DLT) definitions are in the Supplementary Materials and Methods. In part I of phase IB, patients received unmilled sapanisertib 5 mg every day continuously, and in part II of phase IB, milled sapanisertib 3 and 4 mg every day was administered continuously; the milled formulation allowed improved consistency in drug manufacturing. Oral exemestane (25 mg every day) or intramuscular fulvestrant (500 mg every 28 days, with an extra loading dose on cycle 1 day 15) was administered in 28-day cycles in both parts of phase IB (Supplementary Fig. S1).

The primary objective for phase II was evaluation of antitumor activity of sapanisertib plus exemestane or fulvestrant by clinical benefit rate at 16 weeks (CBR-16). CBR-16 was defined as the proportion of patients who achieved a CR, PR, or SD at 16 weeks. Response was assessed by investigators using RECIST version 1.1 by imaging every two cycles, then every three cycles after cycle 6. Secondary objectives included CBR at 24 weeks (CBR-24), overall response rate (ORR), overall survival (OS), progression-free survival (PFS), and safety and tolerability. Exploratory objectives included assessment of circulating tumor cell (CTC) counts as prognostic markers of response, and characterization of patient tumor genetics in circulating tumor DNA (ctDNA).

Adverse events (AE) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Patients were provided with a glucometer for home glucose monitoring to allow early treatment of hyperglycemia, as needed. All patients signed written informed consent prior to any study-related procedures. The study was conducted in compliance with the protocol, regulatory requirements, and the International Conference on Harmonization Guideline on Good Clinical Practice. The study was approved by Institutional Review Boards/Independent Ethics committees at participating sites.

**PK analysis**

In phase IB, blood samples were collected pre-dose and 0.5, 1, 2, 4, and 8 hours post-dose on day 15 of cycle 1, and on day 1 of cycle 2 (0.5–4 hours). Sapanisertib plasma concentrations were measured using a HPLC/MS-MS validated over the concentration range of 1 to 1,000 ng/mL. Plasma sapanisertib PK parameters were estimated from the concentration–time profiles using noncompartmental methods (Phoenix WinNonlin version 7.0).

**Biomarker assessment**

Whole-blood samples were collected at baseline for enumeration of CTCs of epithelial origin (CD45–EpCAM+, and cytokeratins 8, 18, and/or 19) using the CELLSEARCH® Circulating Tumor Cell Kit. ctDNA from double-spin EDTA-plasma samples collected at baseline and end of treatment were analyzed with a custom PlasmaSelect-R™ Next Generation Sequencing breast cancer gene panel (Personal Genome Diagnostics, Inc.) designed to evaluate 46 genes and seven amplifications (Supplementary Materials and Methods). PTEN expression was determined by IHC on archival tumor tissue and ≥5% tumor cell staining was defined as PTEN positive.

**Statistical analysis**

Phase IB was initially designed as a 6-patient cohort safety run-in. However, after the decision was made to test the improved milled drug formulation, two dose levels were evaluated with 6 patients each to determine the MTD.

For phase II, Bayesian predictive probability design was used to calculate the number of patients for each cohort. In the everolimus-resistant cohort, assuming a baseline CBR-16 rate (null hypothesis) of
10%, to improve to 20% (alternative hypothesis), and 10% \( \alpha \) value and 80% power, 56 response-evaluable patients were required. In the everolimus-sensitive cohort, null hypothesis CBR-16 of 15% to improve to 30%, with a 5% \( \alpha \) and 80% power, 48 response-evaluable patients were required. For biomarker analysis, the mutation status of each gene was associated with response using a logistic regression and Hochberg corrected \( P \) values.

**Results**

**Patients**

Between February 13, 2014 and January 5, 2018, 118 patients were enrolled in phase IB \( (n = 24) \) and phase II \( (n = 94; \text{Fig. } 1) \). Demographics and baseline characteristics were generally similar across both phases and treatment groups \( (\text{Table } 1) \).

**Phase IB: Patients and safety**

In part I of phase IB, patients received unmilled sapanisertib 5 mg every day plus exemestane \( (n = 6) \) or fulvestrant \( (n = 6) \). Three patients receiving unmilled sapanisertib 5 mg every day plus exemestane experienced DLT in cycle 2 (grade 3 fatigue, maculopapular rash, and stomatitis) and 1 patient receiving unmilled sapanisertib 5 mg every day plus fulvestrant experienced DLT in cycle 2 (grade 3 fatigue). Following a protocol amendment to institute use of a new sapanisertib capsule containing milled active pharmaceutical ingredient, 6 patients were treated with milled sapanisertib 3 mg every day with exemestane or fulvestrant with no DLTs. Milled sapanisertib 4 mg every day was evaluated with exemestane or fulvestrant in 6 patients and only 1 patient (exemestane combination) reported DLTs of grade 3 nausea and grade 3 diarrhea. Sapanisertib 4 mg every day (milled formulation) was declared the MTD and recommended phase II dose in combination with exemestane or fulvestrant.

Patients in phase IB received a median of six sapanisertib treatment cycles (range, 1–57). The most common reasons for treatment discontinuation were progressive disease (79%) and AEs (13%; \text{Supplementary Table S1}). All patients in phase IB experienced \( \geq 1 \) AE(s), the most common of which were fatigue (75%), diarrhea and nausea (each 67%), and pruritis (54%; \text{Supplementary Table S2}), and 13 patients (54%) reported drug-related grade \( \geq 3 \) AEs. One patient (5 mg every day sapanisertib/exemestane) died on-study due to disease-related hepatic failure.

**Phase IB: Pharmacokinetics and efficacy**

Sapanisertib exhibited fast oral absorption when administered as unmilled or milled formulations on an empty stomach at doses of 3 to 5 mg with either exemestane or fulvestrant \( (n = 18; \text{Supplementary Table S3); Supplementary Fig. S2}) \. The median time to maximum peak concentration was 0.6 to 2.0 hours for milled drug compared with 3 hours for unmilled. The half-life of sapanisertib was 3.2 to 7.8 hours. Interpatient variability (CV\%) in area under the plasma concentration–time curve from the time 0–8 hours \( (\text{AUC}_{0–8}) \) was lower for the milled sapanisertib plus exemestane combination (CV% range, 14%–18%), with higher variability for the unmilled sapanisertib plus exemestane group (43%), as well as for the milled sapanisertib plus fulvestrant group (69%). Maximum concentration values appeared to be broadly comparable across treatment groups with a dose-related increase \( \text{AUC}_{0–8} \).

All 24 patients in phase IB were response evaluable. One patient (4%) achieved a CR and 3 patients (13%) had a PR, giving an ORR of 17%. Thirteen patients (54%) had SD as best response.

![Figure 1](https://example.com/figure1.png)

Patient disposition flow diagram for phase II of the study.

**Figure 1.**

Patient disposition flow diagram for phase II of the study.
Phase II: Patients and efficacy

Fifty-one everolimus-sensitive and 43 everolimus-resistant patients were enrolled in phase II; baseline characteristics were similar between the groups (Table 1). Seventy-eight patients received exemestane (43 everolimus sensitive; 35 everolimus resistant) and 16 received fulvestrant (8 everolimus sensitive; 8 everolimus resistant; Fig. 1). Patients received a median of three treatment cycles (range, 1–17). The most common reason for treatment discontinuation was progressive disease (79%), followed by AEs (13%; Supplementary Table S4).

All patients were evaluable for efficacy. CBR-16 was 45% (23/51) in the everolimus-sensitive cohort, and 23% (10/43) in the everolimus-resistant cohort (Table 2). CBR-24 was 29% in everolimus-sensitive patients and 23% in everolimus-resistant patients. The best response was PR in 4 patients in the everolimus-sensitive cohort (sapanisertib/exemestane, n = 3; sapanisertib/fulvestrant, n = 1) and 1 in the everolimus-resistant cohort (sapanisertib/fulvestrant). No patients achieved a CR. ORR was 8% and 2% in the everolimus-sensitive and everolimus-resistant cohorts, respectively (Table 2). Median duration of PR was 7.4 months (range, 1.9–12.0) in everolimus-sensitive patients (sapanisertib/exemestane, 9.7 months; sapanisertib/fulvestrant, 5.6 months) and 4.3 months (range, 0–6.5) in everolimus-resistant patients (sapanisertib/exemestane, 2.1 months; sapanisertib/fulvestrant, 6.5 months). A waterfall plot of the best percent change in the sum of the longest diameters of target lesions is presented in Fig. 2. Median PFS was 4.1 months [95% confidence interval (CI), 2.2–5.6] in the everolimus-sensitive cohort and 3.4 months (95% CI, 1.9–3.7) in the everolimus-resistant cohort (Fig. 3A). Median overall survival was 15.9 months (95% CI, 14.1–19.5) and 14.0 months (95% CI, 11.5–16.0) in everolimus-sensitive and everolimus-resistant patients, respectively (Fig. 3B).

Phase II: Safety

All 94 patients experienced ≥1 AE(s); the most common with sapanisertib/exemestane (78 patients) were nausea (49%), fatigue (46%), and hyperglycemia (35%), and the most common with sapanisertib/fulvestrant (16 patients) were nausea (69%), diarrhea (56%), and fatigue (50%; Table 3). Rash, including the preferred terms of rash maculopapular, rash, rash macular, rash papular, and rash erythematous, was reported in 18% of patients in the sapanisertib/exemestane
group and 13% in the sapanisertib/fulvestrant group. Grade ≥3 drug-related AEs were reported in 29% of patients (sapanisertib/exemestane, n = 24; sapanisertib/fulvestrant, n = 3; Supplementary Table S5). The most common drug-related grade ≥3 AEs were fatigue and hyperglycemia (6% each in both combinations). Thirteen percent (sapanisertib/exemestane, n = 9; sapanisertib/fulvestrant, n = 3) received concomitant metformin treatment. Twenty-nine patients (37%) receiving sapanisertib/exemestane and 5 patients (31%) receiving sapanisertib/fulvestrant had AEs resulting in dose holds or reductions. Eleven sapanisertib/exemestane-treated patients and 1 sapanisertib/fulvestrant-treated patient had treatment discontinuation due to AEs, occurring predominantly in the first few cycles. AEs leading to discontinuation included diarrhea, vomiting, asthenia, fatigue, and decreased weight (each 2%). One patient discontinued treatment due to colitis in each combination. There were no on-study deaths during phase II.

### Phase II: Biomarkers

Baseline CTC counts were evaluated in 33 patients (65%) in the everolimus-sensitive cohort, and 29 (67%) in the everolimus-resistant cohort. At baseline, 32 (52%) patients had CTC counts ≥5, including 15 (29%) from the everolimus-sensitive and 17 (40%) from the everolimus-resistant cohort, with the remaining 30 (48%) having CTC counts <5. CBR-16 was higher in patients with a baseline CTC count <5 (13 patients; 43%) compared with ≥5 at baseline (6 patients; 19%). Response rates per CTC count cut-off appeared similar between everolimus-sensitive versus everolimus-resistant cohorts. Of 42 patients in the everolimus-sensitive cohort with PTEN results

### Table 2. Phase II efficacy endpoints (response-evaluable population).

<table>
<thead>
<tr>
<th></th>
<th>Sapanisertib + exemestane (n = 43)</th>
<th>Sapanisertib + fulvestrant (n = 8)</th>
<th>Sapanisertib + exemestane (n = 35)</th>
<th>Sapanisertib + fulvestrant (n = 8)</th>
<th>Resistant total (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best response, n (%)</strong></td>
<td>CR 0 0 0 0 0 0</td>
<td>PR 3 (7) 1 (13) 4 (8) 0 1 (13) 1 (2)</td>
<td>SD 24 (56) 5 (63) 29 (57) 15 (43) 4 (50) 19 (44)</td>
<td>SD at 16 weeks 16 (37) 3 (38) 19 (37) 8 (23) 1 (13) 9 (21)</td>
<td>SD at 24 weeks 9 (21) 2 (25) 1 (11) 2 (23) 5 (63) 9 (21)</td>
</tr>
<tr>
<td><strong>CBR-16, n (%) [95% CI]</strong></td>
<td>19 (44) [29.1–60.1]</td>
<td>4 (50) [15.7–84.3]</td>
<td>23 (45) [31.1–59.7]</td>
<td>8 (23) [10.4–40.1]</td>
<td>2 (25) [3.2–65.1]</td>
</tr>
<tr>
<td><strong>CBR-24, n (%) [95% CI]</strong></td>
<td>12 (28) [15.3–43.7]</td>
<td>3 (38) [8.5–75.5]</td>
<td>15 (29) [17.5–43.8]</td>
<td>8 (23) [10.4–40.1]</td>
<td>2 (25) [3.2–65.1]</td>
</tr>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>3 (7) 1 (13) 4 (8) 0 1 (13) 1 (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*On the basis of confirmed response.*

---

**Figure 2.** Waterfall plots of the best percent change from baseline in the sum of the longest diameter of the target lesions in patients treated with sapanisertib + exemestane or sapanisertib + fulvestrant in phase II (A) everolimus-sensitive cohort and (B) everolimus-resistant cohort.
available, 31 (74%) were PTEN positive at baseline, and of 32 evaluable patients in the everolimus-resistant cohort, 28 (88%) were PTEN-positive. Across both cohorts, the CBR-16 was 42% in PTEN positive patients versus 20% in PTEN-negative patients.

Plasma samples for next-generation sequencing of ctDNA were analyzed from 88 of 94 patients in phase II of the study (48 everolimus sensitive; 40 everolimus resistant). The most frequently mutated genes were KMT2C (55.7% of patients), PIK3CA (46.6%), ESR1 (45.5%), TP53 (42.0%), FAT3 (31.8%), SPEN (23.9%), FAT1 (20.5%), CHD4 (19.3%), MTOR (19.3%), and KTM2D (19.3%). Known resistance mutations to exemestane or fulvestrant, such as ESR1 and PIK3CA mutations (18, 19) were detected in a high proportion of patients at baseline with similar incidence in the sensitive and resistant cohorts as shown in Supplementary Table S6. Although the mutations detected in ctDNA did not change markedly from baseline to end of treatment, some patients showed either new detection or the loss of single gene mutations (Supplementary Table S7). No association with treatment response was observed.

A logistic regression revealed a significant positive association between AKT1 mutation status at baseline and best treatment response [CR + PR; P = 0.0262 (corrected); Supplementary Table S8]. Best response is for 84 response-evaluable patients in phase II who had next-generation sequencing data available at baseline (47 everolimus sensitive; 37 everolimus resistant; Supplementary Fig. S3). Other gene alterations in the panel did not show significant association with best treatment response [CR + PR; e.g., ESR1 or PIK3CA mutations with...
Table 3. Most common all-grade AEs occurring in ≥10% of patients in phase II (safety population).

<table>
<thead>
<tr>
<th></th>
<th>Sapanisertib + exemestane</th>
<th>Everolimus sensitive (n = 43)</th>
<th>Everolimus resistant (n = 35)</th>
<th>Total (n = 78)</th>
<th>Sapanisertib + fulvestrant</th>
<th>Everolimus sensitive (n = 8)</th>
<th>Everolimus resistant (n = 8)</th>
<th>Total (n = 16)</th>
<th>Total phase II (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td>23 (53)</td>
<td>15 (43)</td>
<td>38 (49)</td>
<td>7 (88)</td>
<td>4 (50)</td>
<td>11 (69)</td>
<td>49 (52)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>20 (47)</td>
<td>16 (46)</td>
<td>36 (46)</td>
<td>6 (75)</td>
<td>2 (25)</td>
<td>8 (50)</td>
<td>44 (47)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>17 (40)</td>
<td>9 (26)</td>
<td>26 (33)</td>
<td>3 (38)</td>
<td>6 (75)</td>
<td>9 (56)</td>
<td>35 (37)</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td>11 (26)</td>
<td>16 (46)</td>
<td>27 (35)</td>
<td>0</td>
<td>4 (50)</td>
<td>4 (25)</td>
<td>31 (33)</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td>10 (23)</td>
<td>10 (29)</td>
<td>20 (26)</td>
<td>1 (13)</td>
<td>5 (65)</td>
<td>6 (38)</td>
<td>26 (28)</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td></td>
<td>10 (23)</td>
<td>23 (23)</td>
<td>38 (46)</td>
<td>3 (38)</td>
<td>6 (75)</td>
<td>9 (56)</td>
<td>35 (37)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>6 (14)</td>
<td>5 (14)</td>
<td>11 (14)</td>
<td>1 (13)</td>
<td>2 (25)</td>
<td>3 (19)</td>
<td>28 (30)</td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td></td>
<td>7 (16)</td>
<td>4 (11)</td>
<td>11 (14)</td>
<td>3 (38)</td>
<td>2 (25)</td>
<td>5 (31)</td>
<td>16 (17)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td>7 (16)</td>
<td>3 (9)</td>
<td>10 (13)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10 (11)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>11 (26)</td>
<td>6 (17)</td>
<td>17 (22)</td>
<td>1 (13)</td>
<td>1 (13)</td>
<td>2 (13)</td>
<td>19 (20)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>7 (16)</td>
<td>4 (11)</td>
<td>11 (14)</td>
<td>3 (38)</td>
<td>2 (25)</td>
<td>5 (31)</td>
<td>16 (17)</td>
<td></td>
</tr>
<tr>
<td>UTI increased</td>
<td></td>
<td>6 (14)</td>
<td>5 (14)</td>
<td>12 (15)</td>
<td>3 (38)</td>
<td>1 (13)</td>
<td>4 (25)</td>
<td>16 (17)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>6 (14)</td>
<td>6 (17)</td>
<td>12 (15)</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (13)</td>
<td>14 (15)</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td>8 (19)</td>
<td>4 (11)</td>
<td>12 (15)</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (13)</td>
<td>14 (15)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>6 (14)</td>
<td>5 (14)</td>
<td>11 (14)</td>
<td>1 (13)</td>
<td>2 (25)</td>
<td>3 (19)</td>
<td>14 (15)</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td>7 (16)</td>
<td>3 (9)</td>
<td>10 (13)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10 (11)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td>3 (7)</td>
<td>4 (11)</td>
<td>7 (9)</td>
<td>1 (13)</td>
<td>2 (25)</td>
<td>3 (19)</td>
<td>10 (11)</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
<td>7 (16)</td>
<td>1 (3)</td>
<td>8 (10)</td>
<td>1 (13)</td>
<td>1 (13)</td>
<td>2 (13)</td>
<td>10 (11)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AST, aspartate aminotransferase; UTI, urinary tract infection.

The phase II portion of the trial confirmed clinical benefit at 16 weeks with sapanisertib and endocrine therapy. CBR-16 was 45% in patients who progressed on prior everolimus after achieving CR or PR of any duration or after SD lasting ≥6 months (everolimus sensitive) and 23% in patients who progressed on prior everolimus after achieving SD <6 months or progressive disease as best response (everolimus resistant). Although target accrual for the everolimus-resistant cohort was not reached despite extension of enrollment (enrolled, 43; planned sample size, 56), CBR-16 in both everolimus-sensitive and -resistant groups exceeded our hypothesized effective rates of 30% and 20%, respectively. The efficacy of the combination was especially promising as the endocrine therapy partners (exemestane or fulvestrant) administered in this trial were the same agents on which the patients previously progressed in combination with everolimus. In patients with prior sensitivity to everolimus, CBR-16 of 45% compares favorably with other agents evaluated in similar heavily pretreated patient populations after prior everolimus treatment, for instance the CDR4/6 inhibitor palbociclib (CBR-24, 17.4%; ref. 23), and the pan-PI3K inhibitor buparlisib (CBR-14, 33%; CBR-24, 25%; ref. 24). In addition to our observations in patients with breast cancer, sapanisertib has demonstrated a manageable safety profile and broader activity in a phase I study in patients with other advanced solid tumors (25), which supports further clinical development. Furthermore, evidence of sapanisertib activity has been reported in a patient-derived xenograft model of everolimus-resistant pancreatic neuroendocrine tumors (26), suggesting that further development of sapanisertib for everolimus-resistant cancers is warranted.

Of note, 2 patients in our study achieved exceptional responses to treatment: 1 patient in phase IB who received 5 mg every day sapanisertib plus fulvestrant was treated within the main study from...
February 2014 to July 2018, then continued treatment on a single-patient investigational new drug (IND) application until September 2019, so her total duration of therapy was approximately 5 years and 7 months: 1 patient in the everolimus-sensitive cohort in phase II received sapanisertib 4 mg every day in combination with fulvestrant from March 2017 to June 2018 within the main study, then continued treatment on a single-patient IND until February 2019, with a total duration of therapy of 23 months.

On the basis of sapanisertib’s known mechanism of action, it is plausible to hypothesize that sensitivity to the combination may result from dual inhibition of mTORC1 and mTORC2 (16), versus inhibition of mTORC1 only with everolimus, especially in AKT1-activated breast cancers (27). mTORC2 is associated with breast tumor invasion (28), and the inhibition of invasion- and metastasis-associated genes by sapanisertib has been described (17). Supporting our hypothesis (28), and the inhibition of invasion- and metastasis-associated genes by sapanisertib has been described (17). Supporting our hypothesis (28), we observed a positive association between exploratory biomarkers and treatment response. Despite these limitations, our efficacy results as demonstrated by CBR-16, as well as safety data, support future development of sapanisertib combinations with endocrine therapy, with potential stratification for AKT1 mutation status.

In summary, sapanisertib in combination with exemestane or fulvestrant in postmenopausal women with advanced/metastatic breast cancer demonstrated clinical benefit and evidence of renewed sensitivity to mTOR inhibition after progression on everolimus and the same endocrine partner, with a manageable safety profile. Molecular analysis suggested a positive association between AKT1 mutation status and best response. On the basis of these results, a randomized phase II study of sapanisertib in combination with fulvestrant in postmenopausal women with HR+/HER2 advanced or metastatic breast cancer following progression on aromatase inhibitor therapy was conducted, and results will be published soon (33).

Authors’ Disclosures
B. Lim reports grants from Takeda Oncology during the conduct of the study, as well as grants from Merck, Puma Biotechnology, and Genentech outside the submitted work. D.A. Potter reports grants from Takeda during the conduct of the study, grants from ImmunoMedi Therapeutics outside the submitted work, and has a patent for Therapeutic Compounds and Methods issued and a patent for BIGUA-NIDE COMPOUNDS pending. M.A. Salkeni reports grants from Takeda/Millennium during the conduct of the study, grants from Pfizer outside the submitted work, and research funding paid to WVU Research Corp. for the conduct of clinical trials. T.C. Haddad reports reports from Takeda Oncology during the conduct of the study, as well as grants from Takeda Oncology outside the submitted work. A. Awada reports grants from Roche and BMS, as well as personal fees from Lilly, Amgen, ESAI, Pfizer, Novartis, Genomic Health, Ipsen, Bayer, Leo Pharma, Merck, Daichii, and Seattle Genetics outside the submitted work. J.-L. Canon has received personal fees from Millennium Pharmaceuticals Inc. during the conduct of the study. E.J. Leonard reports other from Takeda Pharmaceuticals outside the submitted work. J.R. Diamond reports other from Takeda during the conduct of the study, as well as grants and other from Takeda outside the submitted work. B. Bahamon reports personal fees from Millennium Pharmaceuticals Inc. during the conduct of the study, grants from Takeda Oncology during the conduct of the study, as well as grants and other from Takeda outside the submitted work. No disclosures were reported by the other authors.

Data Availability Statement
The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Authors’ Contributions
B. Lim: Conceptualization, resources, data curation, supervision, validation, investigation, methodology, writing—original draft, writing—review and editing. M.A. Salkeni: Data curation, investigation, visualization, writing—review and editing. P. Silverman: Supervision, investigation, writing—review and editing. T.C. Haddad: Formal analysis, investigation, project administration, writing—review and editing, site PI for Mayo Clinic, aided in interpretation of the formal analysis. F. Forget: Resources, data curation, formal analysis, investigation, writing—original draft, writing—review and editing. A. Awada: Data curation, formal analysis, investigation, writing—review and editing. J.-L. Canon: Validation, investigation, writing—review and editing. M. Danso: Data curation, writing—review and editing. A. Lortholary: Resources, data curation, supervision, validation, visualization. H. Bourgeois: Validation, investigation, writing—original draft, writing—review and editing. E. Tan-Chiu: Writing—review and editing. S. Vincent: Formal analysis, methodology, writing—review and editing.
B. Bahamon: Data curation, writing-review and editing. K.J. Galinsky: Formal analysis, visualization, writing-review and editing. C. Patel: Conceptualization, formal analysis, investigation, writing-review and editing. R. Neuwirth: Conceptualization, formal analysis, methodology, writing-review and editing. E.J. Leonard: Resources, data curation, formal analysis, supervision, methodology, writing-original draft, project administration, writing-review and editing. J.R. Diamond: Conceptualization, resources, data curation, formal analysis, supervision, investigation, visualization, methodology, writing-original draft, writing-review and editing.

Acknowledgments
The authors thank all patients included in this study and their families, as well as all physicians, nurses, study coordinators, and study center staff participating in the study. The authors would like to thank the Personal Genome Diagnostic group for ctDNA sequencing, particularly Donna Nichol, PhD, and Eric Kong, PhD. They also acknowledge writing support from Helen Wilkinson and Helen Kitchen (FireKite, an Ashfield company, part of UDG Healthcare plc), which was funded by Millennium Pharmaceuticals, Inc., and compiled with Good Publication Practice 3 ethical guidelines (Battisti et al., Ann Intern Med 2015;163:461–4), and editorial support from Marcel Kuttab, PharmD (Millennium Pharmaceuticals, Inc.). This work was supported by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The sponsor was involved in study design, in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 30, 2020; revised February 9, 2021; accepted March 31, 2021; published first April 5, 2021.

References
6. Pritchard KE. Endocrine therapy: is the original draft, writing-review and editing.
Sapanisertib Plus Exemestane or Fulvestrant in Women with Hormone Receptor–Positive/HER2-Negative Advanced or Metastatic Breast Cancer

Bora Lim, David A. Potter, Mohamad A. Salkeni, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-20-4131

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2021/04/02/1078-0432.CCR-20-4131.DC1

Cited articles
This article cites 32 articles, 7 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/27/12/3329.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link
http://clincancerres.aacrjournals.org/content/27/12/3329.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.