A First-in-Human Study of the New Oral Selective Estrogen Receptor Degrader AZD9496 for ER+/HER2- Advanced Breast Cancer

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Abstract

Purpose: AZD9496 is an oral nonsteroidal, small-molecule inhibitor of estrogen receptor alpha (ERα) and a potent and selective antagonist and degrader of ERs. This first-in-human phase I study determined the safety and tolerability of ascending doses of oral AZD9496 in women with estrogen receptor (ER)+/HER2- advanced breast cancer, characterized its pharmacokinetic (PK) profile, and made preliminary assessment of antitumor activity.

Patients and Methods: Forty-five patients received AZD9496 [20 mg once daily (QD) to 600 mg twice daily (BID)] in a dose-escalation, dose-expansion ‘rolling 6’ design. Safety, tolerability, and PK activity in each cohort were reviewed before escalating to the next dose. PK was determined by mass spectrometry. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Objective tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Results: Most common causally related AEs were diarrhea (35.6%), fatigue (31.1%), and nausea (22.2%), and seven patients had grade ≥3 AEs. Three patients experienced a dose-limiting toxicity: one each at 150 mg BID (abnormal hepatic function), 400 mg BID (diarrhea and elevated liver function tests), and 600 mg BID (diarrhea), and all were reversible. The maximum tolerated dose was not reached. Partial response was confirmed in one patient, who also had decreased tumor marker Ca15.3. Four patients had stable disease at 12 months follow-up.

Conclusions: AZD9496 is well tolerated with an acceptable safety profile, showing evidence of prolonged disease stabilization in heavily pretreated patients with ER+/HER2- advanced breast cancer. Clin Cancer Res; 24(15); 3510-8. ©2018 AACR.

See related commentary by Jordan, p. 3480

Introduction

Approximately 70% of breast cancers are estrogen receptor (ER) positive, and inhibiting ER signaling is a mainstay of treatment (1). Three classes of endocrine agents are used: aromatase inhibitors, selective estrogen receptor modulators (SERMs), and selective estrogen receptor degraders (SERDs), each with unique modes of action. Aromatase inhibitors prevent the conversion of androgens to estrogens (2). SERMS bind to the ER and act as mixed antagonists/agonists (3), and SERDs bind to, antagonize, and degrade the ER (4).

Current endocrine therapies can be effective, but many patients develop primary or secondary resistance, ultimately leading to disease progression and death. Therefore, drug resistance is a major clinical challenge (1). Only around 30% of patients with metastatic breast cancer achieve objective tumor regression with initial endocrine treatment, and another 20% experience prolonged stable disease (5). Resistance mechanisms include deregulation of the ER pathway itself, alterations in cell-cycle and cell survival signaling molecules, development of escape pathways, and acquisition of activating mutations in the ER gene (ESR1) that allow tumors to survive and proliferate without depending on estrogen (5). Although the benefit of SERMs and aromatase inhibitors declines after resistance develops, it is well known that the ER itself remains involved in the pathogenesis and progression of advanced disease and, therefore, remains an important therapeutic target (6–9).

Fulvestrant is the only SERD approved for treating advanced ER+/HER2- metastatic breast cancer and is effective in both endocrine treatment-naïve patients and in patients whose disease has progressed while on other endocrine therapies (10–12). Indeed, although ESR1 mutations appear to predict resistance to aromatase inhibitor therapy, such mutations do not appear to influence outcomes in patients treated with fulvestrant (13). Fulvestrant is a standard-of-care medication for patients with advanced ER+/HER2- metastatic breast cancer, but it has some limitations: intramuscular injection restricts the maximum...
Translational Relevance

Endocrine resistance is a challenge for patients with estrogen receptor (ER)–positive breast cancer. Fulvestrant, a selective estrogen receptor degrader (SERD), is a standard-of-care medication for advanced ER+/HER2− metastatic breast cancer, but its intramuscular administration restricts the maximum feasible dose. Orally bioavailable SERDs may achieve greater clinical anti-ER activity than fulvestrant, which may translate into improved clinical outcomes. This phase I study reports safety, tolerability, pharmacokinetics, and preliminary antitumor activity of the oral SERD AZD9496, which shows prolonged disease stabilization in some heavily pretreated patients with ER+/HER2− metastatic breast cancer, including those previously treated with fulvestrant. These results support the further clinical development of AZD9496. Oral SERDs could be the next generation of endocrine therapy and are a priority for clinical investigation.

Phase I Study of Oral SERD AZD9496

The primary objective was to investigate the safety and tolerability of ascending doses of oral AZD9496 in patients with metastatic or locoregionally recurrent ER+/HER2+ advanced breast cancer. Secondary objectives were to characterize the PK of AZD9496 and its metabolites after a single oral dose and at steady-state after multiple doses and to obtain a preliminary assessment of antitumor efficacy. Exploratory analyses included investigating potential determinants of response or resistance to AZD9496 in plasma (such as ESR1 mutation status in circulating tumor DNA) and pharmacodynamic biomarker changes in tumor tissue and circulating tumor cells will be reported separately (manuscript in preparation, Daniel Hayes, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI).

Patient selection and screening

Patients were recruited from hospitals in the United States, the United Kingdom, and Korea. The protocol was approved by the respective regulatory authorities and the research ethics committee of each participating site and was subject to Ethics Committee and Institutional Review Board approvals. All patients provided their written informed consent at study enrollment. Patients were screened within 28 days prior to study admission to gather demographic data and standard medical and surgical history.

Patient eligibility

Key inclusion criteria included female patients of any menopausal status, age at least 18 years, and with a diagnosis of ER+/HER2− adenocarcinoma of the breast, metastatic, or locoregionally recurrent, and not amenable to treatment with curative intent. Pre- or perimenopausal women must have started luteinizing hormone-releasing hormone (LHRH) agonist treatment at least 4 weeks before study treatment and must have continued this treatment throughout the study. Disease must have progressed after at least 6 months of endocrine therapy for ER+ breast cancer. (Before protocol amendment of 21 August 2015, patients must have spent ≥6 months on a line of endocrine therapy in the advanced setting). Radiological or objective evidence of progression on or after the last systemic therapy was needed before starting study treatment.

Key exclusion criteria included receipt of more than two lines of chemotherapy for advanced disease, or systemic anticancer therapy within 14 days of the first dose of study treatment. Radiotherapy for palliation was permitted if received more than 1 week before the first dose of study treatment. Patients were excluded if they were receiving any medications known to induce or inhibit cytochrome P450 CYP3A4/5 or CYP2C8 or had life-threatening visceral, central nervous system, or pulmonary lymphangitic metastases, inadequate bone marrow reserve or organ function, unexplained symptomatic endometrial disorders, uncontrolled symptomatic thyroid dysfunction, or an Eastern Cooperative Oncology Group (ECOG) performance status of ≥2.

Dose escalation and dose expansion

A “rolling 6” design was used, in which each cohort of at least three and up to six patients received AZD9496 at an escalating dose (18). Dosing began at 20 mg once daily (QD). Patients were dosed in cycles: cycles 1 to 6 each were 4 weeks long, and further cycles each were 6 weeks long. Dose-limiting toxicities (DLTs) were assessed for the first 28 days of treatment (cycle 1), and the dose was escalated in the next cohort if no DLTs were observed in the previous cohort. If two or more patients in any cohort
experienced a DLT, the dose was considered nontolerated. If only one patient experienced a DLT, the cohort was expanded to include six evaluable patients, and if no further DLTs occurred, dose escalation could continue. Dose interruptions and reductions were permitted if patients experienced adverse events (AEs). Tolerability assessments were planned to continue until the maximum tolerated dose (MTD; the last dose below the nontolerated dose) or MFD (a reasonable number of acceptably sized tablets given, or evidence of saturation of absorption observed) was reached. Patients were dosed until confirmed disease progression or unacceptable toxicity.

At selected doses, escalation cohorts were expanded to include six evaluable patients in order to further investigate safety, tolerability, PK, and biological activity of AZD9496.

Safety and tolerability assessments

Safety was assessed in terms of AEs (including treatment emergent AEs (TEAEs; any event not present prior to receipt of the first dose of study drug or a worsening of an existing event), serious AEs (SAEs), causally related AEs (any event deemed related to the study drug in the investigator's opinion), AEs leading to discontinuation, and AEs leading to death), laboratory data, vital signs, electrocardiogram changes, and ECOG assessment. AE severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. An independent safety review committee reviewed the safety, tolerability, and preliminary PK data (if available) from patients in each escalation cohort before escalating to the next dose.

PK assessments

Plasma PK parameters (including AUC, maximum plasma concentration \(C_{\text{max}}\), and time to maximum plasma concentration \(t_{\text{max}}\)) were determined for AZD9496 and its metabolites M3 and M5 (30- and threefold lower potency than parent, respectively, and both formed by oxidation of the parent) after a single dose, and at steady-state after multiple dosing (i.e., 13 days of dosing in the dose-escalation cohorts and 11 days in the dose-expansion cohort). AZD9496 concentration was also determined in urine for patients in the dose-escalation cohorts. 4β-Hydroxy-cholesterol:cholesterol ratios were determined as a marker of hepatic CYP3A4 induction potential by AZD9496.

AZD9496 and metabolites were determined in plasma using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. The validated range was 1.00 to 5,000 ng/mL for AZD9496, 1.00 to 2,000 ng/mL for M3, and 0.1 to 200 ng/mL for M5. AZD9496 concentrations were also determined in urine using a validated LC-MS/MS method with a validated range of 50.0 to 50,000 ng/mL. For patients in the dose-escalation cohorts, in cycle 1 venous blood samples were taken predose and at regular intervals on day 1 (over 24 hours) and day 15 (over 10 hours), and predose on days 2 and 16. In cycles 2 to 4, samples were taken predose on day 1. For patients in the dose-expansion cohorts, in cycle 1 blood samples were taken on day 1 (over 72 hours) and day 15 (over 10 hours), and predose on day 8. In cycles 2 to 4, samples were taken predose on day 1. For patients participating in PK profiling (those in the dose-expansion cohort), two additional blood samples were taken predose on days 1 and 15 of cycle 1, and day 1 of cycles 2 to 4, to determine 4β-hydroxy-cholesterol:cholesterol ratios. Urine samples were collected predose, and 0 to 4, 4 to 8, 8 to 10, and 10 to 24 hours postdose on days 1 and 15 (cycle 1 only) from patients in the dose-escalation cohorts.

Antitumor efficacy assessment

Objective tumor response assessment was based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines for response (19). Computed tomography/magnetic resonance imaging (CT/MRI) was performed of the chest, abdomen, and pelvis (and any other sites at which new disease was suspected) of all patients at baseline (within 28 days of study start), at 8, 16, and 24 weeks after the start of treatment, and every 12 weeks thereafter until objective disease progression was confirmed. Patients underwent a bone scan or skeletal survey at baseline and at follow-up visits if clinically indicated.

Data derivation and analysis

The number of patients was chosen based on the desire to obtain adequate data while exposing as few patients as possible to the investigational product and procedures. The safety analysis set was all patients who received at least one dose of AZD9496. The PK analysis set was all patients who received at least one dose of AZD9496 and who have at least one measured concentration of AZD9496 at a scheduled postdose PK time point.

PK parameters were derived by standard noncompartmental methods using Phoenix WinNonlin (Certara), version 6.4. No formal statistical analysis was done for this study; data were summarized using standard summary statistics (SAS version 9.2).

Results

The study commenced in October 2014, and recruitment was completed on February 26, 2016, ahead of the final data cutoff on January 31, 2017. Forty-five patients were enrolled: all met the inclusion criteria and received AZD9496 at various doses (from 20 mg QD to 600 mg twice daily (BID); Supplementary Fig. S1). Patients were allocated to cohorts containing between four and six patients, and each cohort received AZD9496 at an escalating dose. Six further patients were selected for an expansion cohort after the 400 mg BID dose escalation and received AZD9496 at 250 mg BID at the same time as the 600 mg BID cohort.

Baseline characteristics

Baseline patient demographics are shown in Table 1. Patients were mostly white (n = 31; 68.9%) with a median age of 62 years (range, 41–83 years). All patients had metastatic disease on study entry. Most patients had measurable disease (n = 39; 86.7%), and many had visceral disease (n = 36; 80.0%). Twenty-five patients (55.6%) had received prior treatment with fulvestrant before enrolling in the study. Of these, 10 received fulvestrant as the immediate therapy prior to enrollment; five as a monotherapy, and five as part of combination treatment.

Safety and tolerability

Forty-four patients (97.8%) experienced at least one AE, and most were CTCAE grade 1 or 2. The most common AEs of any grade were fatigue (n = 19; 42.2%), nausea (n = 18; 40.0%), and diarrhea (n = 17; 37.8%). Forty patients (88.9%) experienced AEs that were considered by the investigator, using his/her clinical judgment, to be related to the study drug. The most common causally related AEs of any
grade were diarrhea (n = 16; 35.6%), fatigue (n = 14; 31.1%), nausea (n = 10; 22.2%), and upper abdominal pain (n = 6; 13.3%), grading of these AEs are shown in Table 2. Causally related SAEs occurred in two patients (4.4%; diarrhea, abnormal hepatic function) and causally related AEs of CTCAE grade ≥3 or higher occurred in seven patients (15.6%). These were diarrhea (n = 3; 6.7%), increased alanine aminotransferase (ALT) (n = 2; 4.4%), and fatigue, vomiting, and increased aspartate aminotransferase (AST) (each n = 1; 2.2%).

Three patients experienced DLTs, which were reversible in all patients. One patient in the 150 mg BID cohort experienced abnormal hepatic functions [elevated AST, ALT, gamma-glutamyl transferase (GGT; grade 3), bilirubin, and alkaline phosphatase (ALP; grade 2)]. AZD9496 was withdrawn, and the abnormal hepatic functions returned to baseline. One patient in the 400 mg BID cohort experienced grade 3 diarrhea and grade 3 elevated AST, ALT, and GGT and was managed with dose interruption and reduction. A further patient, in the 600 mg BID cohort, experienced grade 3 diarrhea, which was managed with dose interruption. Dose escalation was stopped at 600 mg BID. All other causally related grade ≥3 events resolved, and no AEs leading to death were reported.

### Table 1. Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Race</th>
<th>Median age, years (range)</th>
<th>Number of prior endocrine regimens, median (range)</th>
<th>Number of prior chemotherapy regimens, median (range)</th>
<th>Abnormal hepatic function</th>
<th>Abnormal hepatic function</th>
<th>Abnormal hepatic function</th>
<th>Abnormal hepatic function</th>
<th>Abnormal hepatic function</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>70.0 (63–82)</td>
<td>(n = 4)</td>
<td>(n = 6)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>70.0 (63–82)</td>
<td>(n = 4)</td>
<td>(n = 6)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>70.0 (63–82)</td>
<td>(n = 4)</td>
<td>(n = 6)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 2. Causally related AEs occurring in more than three patients (≥5%) treated with AZD9496

<table>
<thead>
<tr>
<th>Causally related AEs by preferred term, n (%)</th>
<th>20 mg QD (n = 4)</th>
<th>40 mg BID (n = 6)</th>
<th>80 mg BID (n = 5)</th>
<th>150 mg BID (n = 12)</th>
<th>250 mg BID (n = 6)</th>
<th>400 mg BID (n = 6)</th>
<th>600 mg BID (n = 6)</th>
<th>CTCAE grade (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>2 (33.3)</td>
<td>2 (40.0)</td>
<td>0</td>
<td>5 (41.7)</td>
<td>4 (66.7)</td>
<td>3 (50.0)</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (75.0)</td>
<td>2 (33.3)</td>
<td>1 (20.0)</td>
<td>1 (16.7)</td>
<td>4 (33.3)</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>8 (17.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>3 (50.0)</td>
<td>2 (33.3)</td>
<td>3 (50.0)</td>
<td>2 (33.3)</td>
<td>9 (20.0)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Abdominal pain (upper)</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (20.0)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>6 (13.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hot flush</td>
<td>1 (25.0)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3)</td>
<td>3 (50.0)</td>
<td>0</td>
<td>5 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8.3)</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>1 (2.2)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>2 (4.4)</td>
<td>0</td>
</tr>
<tr>
<td>Myelalgia</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (20.0)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (8.3)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>3 (6.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; QD, once daily.

*aCausally related to the study drug in the investigator’s opinion.

*bPooled data from dose escalation and expansion groups.
Pharmacokinetics

Single-dose pharmacokinetics of AZD9496. Following a single dose on day 1, AZD9496 was rapidly absorbed at all dose levels, with median $T_{\text{max}}$ 1.55 to 3.0 hours (Fig. 1A; Table 3). Plasma concentrations underwent a rapid and biphasic decline following the peak, with a mean alpha half-life of 0.99 to 1.99 hours and a mean terminal half-life of 1.4 to 5.7 hours (Table 3).

Following a single AZD9496 dose of 20 up to 400 mg (day 1), the area under the concentration–time curve (AUC) increased in reasonable proportion to the increasing dose. At 600 mg, a more than dose-proportional increase in AUC and $C_{\text{max}}$ was observed.

Multiple-dose pharmacokinetics of AZD9496

Multiple-dose AUC and $C_{\text{max}}$ were consistently and dose-dependently lower than those for single dose for 40 mg up to 600 mg. Based on the temporal change parameter, which compares $AUC_{\text{tau}}$ on day 15 with $AUC_{\text{inf}}$ on day 1, a time-dependent reduction in AZD9496 exposure was observed across the BID dose range, with more marked reductions at higher doses (mean reduction of 24% and 77% for the 40 and 600 mg BID dose level, respectively). No reduction in exposure was observed for the 20 mg QD dose group (Fig. 1B and Table 3). These data correlated with the dose-dependent increase in the marker for hepatic CYP induction (4β-hydroxycholesterol:cholesterol ratio). The median (min, max) percentage change from baseline (day 1) in 4β-hydroxy-cholesterol:cholesterol ratio to day 15 was between −5.7% (−16.4, 8.00) for the 20 mg QD dose and 247% (106, 298) for the 600 mg BID dose.

Pharmacokinetics of metabolites

Following single doses and at steady-state, the plasma concentration–time profiles of metabolites M3 (around 30-fold lower in potency on ERα degradation than AZD9496; ref. 20) and M5 (around threefold lower potency on ERα degradation than AZD9496; ref. 20) closely followed that of AZD9496 but at lower concentrations (Supplementary Fig. S2; Supplementary Tables S1 and S2): around 9% to 20% was detected for M3 and around 2% was detected for M5, relative to AZD9496 exposure. AZD9496 was not detected in urine.

Preliminary antitumor efficacy

Duration on treatment. The median duration on treatment with AZD9496 was 2.1 months (range, 0.7–21.1 months, across the range of doses examined). Twelve patients (26.6%) received AZD9496 for 6 months or longer, and 10 patients (22.2%) and four patients (8.9%) exhibited stable disease at 6 and 12 months’ follow-up, respectively. Treatment was ongoing in six patients (13.3%) up to the data cutoff of January 31, 2017 (Fig. 2).

Tumor responses. One patient in the 250 mg BID cohort was observed to have had a partial response at cycle 9 (day 251), which was confirmed by a subsequent scan 4 weeks later (Fig. 3). This patient had metastatic breast cancer at study entry and had received eight prior chemotherapy regimens, she was fulvestrant naïve, and had not received prior cyclin-dependent kinase 4/6 or mTOR inhibitor therapy (Fig. 2). In this patient, the serum tumor marker Ca15.3 (raised at baseline: 60 U/mL) started to decrease early (2 months after starting AZD9496) and steadily, to reach normal levels after cycle 8 (23 U/mL). This biochemical response was maintained at the time of RECIST partial response (15 U/mL) and at the last assessment before data cutoff, 2 months later (10 U/mL).

Discussion

Resistance to endocrine therapies is an important clinical challenge and continues to drive the search for more effective agents (1). Fulvestrant is effective in patients with metastatic breast cancer, including those who experience progression after endocrine treatment, but is associated with administration and PK limitations at its approved 500 mg once-monthly intramuscular dose. An orally bioavailable SERD, without the bioavailability and PK limitations of fulvestrant, is clearly an unmet medical need.

This first-in-human study investigated the safety and tolerability of AZD9496: a new, nonsteroidal small-molecule inhibitor.
of ERα, which has shown promise in preclinical models of ER+ advanced breast cancer (17). To our knowledge, this is the first published study reporting results of a completed first-in-human study with an oral SERD.

AZD9496 was shown to have a tolerable safety profile, with most AEs of CTCAE grade 1 or 2. The most common causally related AEs were diarrhea, fatigue, nausea, and upper abdominal pain, but these were largely mild (grade 1 or 2) and manageable without dose reduction or interruption. Two patients (4.4%) experienced a causally related SAE (diarrhea and abnormal hepatic function tests), and seven patients (15.6%) experienced a causally related grade 3 AE. DLTs were observed in three patients, and all were reversible. One patient (150 mg BID) experienced abnormal hepatic functions, another (400 mg BID) developed grade 3 diarrhea and abnormal hepatic functions, and another (600 mg BID) developed grade 3 diarrhea. However, only one of these patients (receiving 150 mg BID) permanently discontinued AZD9496, following which the abnormal hepatic functions returned to baseline. The other two DLTs (in patients receiving 400 and 600 mg BID) were resolved with dose reduction and/or interruption, and the patients remained on-study. Because no two patients in any cohort experienced a DLT, the MTD was not required to see significant tumor growth inhibition in this Table 3. PK parameters for AZD9496 following single doses (day 1) and multiple doses (day 15)

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (ng/mL)</td>
<td>AUCinf (ng·h/mL)</td>
<td>t1/2 (h)</td>
</tr>
<tr>
<td>150 mg BID</td>
<td>1.2 (0.23)</td>
<td>1.50 (1.00, 4.05)</td>
<td>1.37 (0.42)</td>
</tr>
<tr>
<td>300 mg BID</td>
<td>1.2 (0.23)</td>
<td>2.00 (1.50, 3.00)</td>
<td>2.33 (1.94)</td>
</tr>
<tr>
<td>400 mg BID</td>
<td>1.2 (0.23)</td>
<td>2.00 (1.50, 3.00)</td>
<td>2.33 (1.94)</td>
</tr>
<tr>
<td>600 mg BID</td>
<td>1.2 (0.23)</td>
<td>2.00 (1.50, 3.00)</td>
<td>2.33 (1.94)</td>
</tr>
</tbody>
</table>

NOTE: Temporal change for AUC calculated as follows: AUCtau/AUCinf. Data are geometric mean (CV%) for Cmax and the AUC variables, arithmetic mean (SD) for other parameters. 

Table 3. PK parameters for AZD9496 following single doses (day 1) and multiple doses (day 15)
Figure 2.
Duration on AZD9496 treatment by dose (cohort) and prior fulvestrant. Data cutoff: January 31, 2017. Patients are ordered on the y-axis by the cohort. When a patient received fulvestrant in several lines, the duration of most the most recently received is shown. BID, twice daily; EXP, dose-expansion group; PR, partial response; QD, once daily.
I studies. The pharmacodynamic biopsy data will be presented separately (manuscript in preparation).

We note some limitations to this study. First, cohorts were small, containing between four and six patients only, and this may have been insufficient to detect the less frequent effects of AZD9496 treatment. Second, the minimum washout period between previous anticancer regimens and starting AZD9496 treatment was 14 days. Because fulvestrant has a half-life of 50 days, the possibility that these results include synergistic effects of AZD9496 and fulvestrant cannot be ruled out. Third, this study was a nonrandomized, noncomparator trial, so assessment of both efficacy and safety may be difficult in this heavily pretreated, heterogeneous population.

This phase I study suggests that AZD9496 has an acceptable safety and tolerability profile and shows preliminary evidence of prolonged stabilization of disease in some women with heavily pretreated, advanced breast cancer, including in those previously treated with fulvestrant. A presurgical window of opportunity study (NCT03236974) will now compare the pharmacodynamic effects of AZD9496 (expression of ER, PR, and Ki67 in tumor tissue) with those of fulvestrant in women with hormone receptor positive early breast cancer awaiting surgery with curative intent.

Disclosure of Potential Conflicts of Interest
A.C. Armstrong holds ownership interest (including patents) in AstraZeneca. K. Jhaveri is a consultant/advisory board member for ADCT Therapeutics, AstraZeneca, Bristol Myers- Squibb, Novartis, Pfizer, and Spectrum Pharmaceuticals. T. Klinowska holds ownership interest (including patents) in AstraZeneca. S.-A. Im is a consultant/advisory board member for AstraZeneca, Hanmi, Novartis, Pfizer, and Roche. No potential conflicts of interest were disclosed by the other authors.

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Writing, review, and/or revision of the manuscript: E.P. Hamilton, M.R. Patel, A.C. Armstrong, R.D. Baird, K. Jhaveri, M. Hoch, T. Klinowska, J.P.O. Lindemann, S.R. Morgan, G. Schiavon

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