# A Phase I Study Investigating AZD8186, a Potent and Selective Inhibitor of PI3Kβ/δ, in Patients with Advanced Solid Tumors

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## ABSTRACT

**Purpose:** To characterize safety and tolerability of the selective PI3Kβ inhibitor AZD8186, identify a recommended phase II dose (RP2D), and assess preliminary efficacy in combination with abiraterone acetate or vistusertib.

**Patients and Methods:** This phase I open-label study included patients with advanced solid tumors, particularly prostate cancer, triple-negative breast cancer, and squamous non–small cell lung cancer. The study comprised four arms: (i) AZD8186 monotherapy dose finding; (ii) monotherapy dose expansion; (iii) AZD8186/abiraterone acetate (with prednisone); and (iv) AZD8186/vistusertib. The primary endpoints were safety, tolerability, and identification of the RP2D of AZD8186 monotherapy and in combination. Secondary endpoints included pharmacokinetics (PK), pharmacodynamics, and tumor and prostate-specific antigen (PSA) responses.

**Results:** In total, 161 patients were enrolled. AZD8186 was well tolerated across all study arms, the most common adverse events being gastrointestinal symptoms. In the monotherapy dose-finding arm, four patients experienced dose-limiting toxicities (mainly rash). AZD8186 doses of 60-mg twice daily [BID; 5 days on, 2 days off (5:2)] and 120-mg BID (continuous and 5:2 dosing) were taken into subsequent arms. The PKs of AZD8186 were dose proportional, without interactions with abiraterone acetate or vistusertib, and target inhibition was observed in plasma and tumor tissue. Monotherapy and combination therapy showed preliminary evidence of limited antitumor activity by imaging and, in prostate cancer, PSA reduction.

**Conclusions:** AZD8186 monotherapy had an acceptable safety and tolerability profile, and combination with abiraterone acetate/prednisone or vistusertib was also tolerated. There was preliminary evidence of antitumor activity, meriting further exploration of AZD8186 in subsequent studies in PI3Kβ pathway–dependent cancers.

## Introduction

The PI3K signaling pathway plays an important role in many tumor types, controlling cell growth, proliferation, survival, metabolism, migration, and angiogenesis (1–3). PI3K enzyme complexes comprise a heterodimer between a p110 catalytic subunit and a p85 regulatory subunit. The p110 catalytic subunit is further subdivided into four isoforms: PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ (4). Although the PI3Kγ and δ isoforms are largely associated with regulation of immune cells (5, 6), PI3Kβ has a broader tissue distribution and plays a key role in driving tumor progression, particularly in scenarios of inactivation or loss of the tumor-suppressor gene PTEN (7, 8). Increased PI3K signaling driven by PTEN loss is implicated in the development of solid tumors, including breast, colon, lung, and prostate (9).

Development of PI3K inhibitors is challenging because of toxicity risks associated with inhibiting multiple isoforms, so one way to optimize efficacy while minimizing potential toxicity is to develop isoform-specific drugs. AZD8186 is a potent, selective inhibitor of

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## Translational Relevance

The PI3K signaling pathway plays an important role in many tumor types, but development of PI3K inhibitors is challenging because of toxicity risks associated with inhibiting multiple PI3K isoforms. AZD8186 is a potent, selective inhibitor of PI3Kβ. In this phase I open-label study, we evaluated the safety, tolerability, and recommended phase II dose of AZD8186 monotherapy and in combination with abiraterone acetate or vistusertib. Eligible patients had advanced prostate cancer, triple-negative breast cancer, or squamous non–small cell lung cancer, and patients with other solid tumor types were eligible if they were PTEN deficient/mutated or PIK3CB mutated/amplified. As monotherapy and in combination, AZD8186 was well tolerated, with few dose-limiting toxicities reported. Both monotherapy and combination therapy showed preliminary evidence of antitumor activity, which merits further assessment in subsequent studies.

PI3Kβ ($IC_{50}$, 4 nmol/L), with minimal activity against PI3Kδ and selectivity over PI3Kα and γ (10, 11). Preclinically, AZD8186 has single-agent activity across cell lines and tumor models enriched for PTEN loss. In PTEN-null tumor models, AZD8186 combines in an additive manner with antiandrogens (e.g., abiraterone acetate), docetaxel, PI3K pathway inhibitors (e.g., PI3Kα inhibitors AZD8835 and BYL719), and the mTORC 1/2 inhibitor vistusertib, to deliver increased antitumor activity (10, 12, 13). The vistusertib combination was initiated to determine its potential to achieve comprehensive targeting of PI3K pathway. This was in response to a number of preclinical studies that demonstrated PI3K pathway reactivation attributed to vistusertib's intrinsic mechanisms of resistance (12, 14).

We present data from a first-in-human, phase I, open-label, multicenter study of AZD8186 in patients with solid tumors. The aims were to: characterize safety and tolerability; identify a recommended phase II dose (RP2D) for different schedules of AZD8186 monotherapy and in combination with abiraterone acetate (with prednisone) or vistusertib; and assess the preliminary efficacy of AZD8186 combined with abiraterone acetate or vistusertib in PTEN-mutated/deficient or *PIK3CB*-mutated/amplified triple-negative breast cancer (TNBC) or metastatic castration-resistant prostate cancer (mCRPC), respectively.

## Patients and Methods

### Study design

This phase I, open-label, multicenter trial (ClinicalTrials.gov: NCT01884285) was conducted at 13 centers in Canada, the United States, Spain, and the UK between July 2013 and February 2020. The study had a multi-arm design (Supplementary Fig. S1) and included patients with mCRPC, TNBC, and squamous non–small cell lung cancer (sqNSCLC). Patients with other advanced solid tumors with known PTEN deficiency/mutation or mutation/amplification of *PIK3CB* were included if the tumors were resistant to standard therapies, or no standard therapies were available.

The study comprised four arms (Supplementary Fig. S1). In an AZD8186 monotherapy dose-finding arm, patients received escalating doses and different schedules of AZD8186 monotherapy [5 days on, 2 days off (5:2); 2 days on, 5 days off (2:5); or continuous daily dosing]. Intermittent dosing schedules were investigated initially in preclinical studies and the 5:2 schedule was found to be as efficacious as continuous dosing. Hence, the intermittent schedules were taken forward into the combination arms.

All AZD8186 doses were given twice daily (BID) on an empty stomach (at least 2 hours before and 1 hour after dosing) with two doses taken at least 12 hours apart. From a starting dose of 30-mg BID (based on non-clinical efficacy and toxicity studies), escalations to higher dose levels (60, 120, 180, 240, and 360-mg BID) were permitted if no dose-limiting toxicity (DLT) was observed in a cohort of three to six evaluable patients after review of safety data from three or more evaluable patients. The cohort was expanded to include six evaluable patients if one patient experienced a DLT, but recruitment ceased if two or more patients experienced a DLT.

In an AZD8186 monotherapy dose-expansion arm, patients with PTEN-deficient/mutated mCRPC or TNBC willing to undergo paired tumor biopsies (pre-dose and on-treatment) received AZD8186 at dose(s) and schedule(s) defined from the dose-finding arm.

In an AZD8186/abiraterone acetate dose-finding arm, patients with mCRPC received AZD8186 (60 or 120-mg BID; 5:2 schedule), plus abiraterone acetate 1,000 mg and prednisone 10 mg once daily in a fasted state (water only for at least 2 hours prior and 1 hour after each dose). In a dose-expansion cohort, patients with PTEN-deficient/mutated or *PIK3CB*-mutated/amplified mCRPC received AZD8186 plus abiraterone acetate and prednisone at the doses and schedule established in the dose-finding arm.

In an AZD8186/vistusertib dose-finding arm, patients with mCRPC, TNBC, sqNSCLC, or other solid tumors received AZD8186 [30, 60, or 120-mg BID (5:2)] plus vistusertib 100 mg or 125-mg BID (2:5). A dose-expansion cohort (AZD8186 plus vistusertib in patients with PTEN-deficient/mutated or *PIK3CB*-mutated/amplified TNBC) was planned but not conducted as clinical development of vistusertib was stopped.

PTEN deficiency (centrally determined by IHC using the CST138G6 PTEN antibody assay and defined by an H-score ≤10; ref. 15) and deleterious alterations in PTEN and/or activating alterations in *PIK3CB* [determined by local testing using Clinical Laboratory Improvement Amendments (CLIA)-certified next-generation sequencing (NGS)] were prospectively examined in the dose-expansion cohorts. In the other study arms, testing was not mandatory, but PTEN IHC assessments were performed retrospectively when tissue was available.

The study was designed, conducted, and reported in accordance with the ethical principles of the Declaration of Helsinki (16). The protocol was approved by independent ethics committees and institutional review boards at each study site. All patients provided written informed consent.

### Study population

Eligible patients were adults (≥18 years old) with an Eastern Cooperative Oncology Group performance status of 0 or 1. All patients had histologically or cytologically proven advanced cancer: mCRPC, sqNSCLC, TNBC, or confirmed PTEN-deficient/mutated or *PIK3CB*-mutated/amplified solid malignancy that had progressed after standard-of-care treatment. Patients with mCRPC were required to have a baseline prostate-specific antigen (PSA) level ≥2 ng/mL. In the AZD8186/abiraterone acetate arms, patients could have received treatment with abiraterone acetate, enzalutamide, and/or docetaxel. The key exclusion criteria included: prior exposure to AZD8186 or any inhibitor of PI3K, AKT or mTOR; any cytotoxic chemotherapy, investigational agents, or other anticancer drugs within 14 days before study enrollment; and inadequate bone marrow reserve or organ function. Full inclusion/exclusion criteria are provided in Supplementary Table S1.

### Endpoints

The primary endpoints of the study were safety and tolerability, and identification of the RP2D of AZD8186 monotherapy and in combination with abiraterone/prednisone or vistusertib. Secondary endpoints included the pharmacokinetic (PK) and pharmacodynamic (PD) properties of AZD8186, tumor response, and, in patients with mCRPC, PSA response.

### Assessments

#### Safety and tolerability

All adverse events (AE) and serious AEs (SAE), including DLTs, were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4) and classified according to the Medical Dictionary for Regulatory Activities (version 20.0). A DLT was defined as any hematological or non-hematological severe treatment-related toxicity (i.e., not attributable to the disease or disease-related processes under investigation) during the first 21 days of multiple dosing (see the Supplementary Appendix for further details).

#### PK

PK sampling was performed to evaluate single-dose and steady-state PK of AZD8186 and its active metabolite (AZ13472080; M1) during monotherapy and combination therapy. Details of schedules for collection of blood samples for PK analyses are described in Supplementary Table S2. The concentrations of AZD8186 in plasma were determined using a validated bioanalytical method (see the Supplementary Appendix for details). PK analyses were performed by non-compartmental analyses using Phoenix WinNonlin software (version 6.3).

#### Tumor response

Tumor assessments were performed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; ref. 17) at baseline and every 6 weeks (every 12 weeks for mCRPC) until treatment discontinuation or withdrawal of consent. For patients with measurable disease, tumor response was defined as complete response, partial response, stable disease, or progressive disease.

#### PWGC2 response

For patients with mCRPC, bone lesions were assessed according to the Prostate Cancer Clinical Trials Working Group (PCWG2) guidelines at baseline and every 12 weeks until treatment discontinuation or withdrawal of consent (18, 19). PCWG2 progression was defined as two or more new metastatic bone lesions confirmed on bone scan, compared with the prior scan.

#### PSA response

For patients with mCRPC, PSA assessments were performed at baseline and at least once every cycle. PSA response was defined as decline of >50% versus baseline, confirmed at the next measurement at least 4 weeks later (20). PSA progression was defined as an increase of ≥25% and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later (19).

#### PD

Blood samples were collected at scheduled timepoints during AZD8186 monotherapy. As PI3Kβ controls pathway activation and regulates platelet function, changes in biomarkers of PI3Kβ inhibition were assessed in platelet-rich plasma. The ratios of phosphorylated (p) AKT1, including pAKT (T308) and pAKT (S473):total AKT, and pGSK3β:total GSKβ were assessed using solid-phase enzyme-linked immunosorbent Mesoscale Discovery multiplex assays.

Paired fresh tumor biopsies were collected during the AZD8186 monotherapy arms at screening and after ≥3 consecutive days of dosing during Week 2 (preferably 2–4 hours post-AZD8186 dosing). pAKT (S473) and PRAS40 were assessed by IHC in three non-consecutive sections as previously described (21). Digital image analysis by HALO (Indica Laboratories) was used to quantify pAKT (S473) staining intensity specifically at the cellular membrane as a measure of active AKT (22, 23). pPRAS40 staining intensity was assessed in the cytosolic location.

### Statistical analyses

The number of patients enrolled was that required to obtain adequate tolerability, safety, and PK data while exposing as few patients as possible to the investigational product and procedures. In the dose-finding arms, three to six evaluable patients were allocated for each cohort. In the dose-expansion arms, ≥12 evaluable patients were required. Definitions of the analysis sets used in this study, including the safety, PK, PD, and efficacy sets, are presented in the Supplementary Appendix.

Statistical evaluation was performed using SAS software (version 9.4). Descriptive statistics were used to measure safety, PK, and antitumor response. Waterfall plots, indicating the percentage of change from baseline, were generated for RECIST and PSA response.

In the combination therapy arms, PK interaction was evaluated by comparing the $C_{max}$ value and area under the concentration–time curve (AUC) of AZD8186 observed in the monotherapy dose-finding arm to those observed with combination therapy. A mixed effects model with treatment as a fixed effect and patient as a random effect was used to compare log-transformed $AUC_{0-t}$ and $C_{max}$ values of these treatments. Geometric least squares means and confidence limits were calculated by exponentiation and the drug effect was exponentially back-transformed onto the original scale. For the AZD8186/abiraterone acetate combination, a pooled analysis of 120-mg dose groups from the dose-finding and dose-escalation cohorts was also conducted.

### Data availability

Data underlying the findings described previously in this article may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

## Results

### Baseline characteristics and study attrition

In total, 161 patients were enrolled, including 67, 25, 35, and 34 in the monotherapy dose-finding, monotherapy dose-expansion, AZD8186/abiraterone acetate, and AZD8186/vistusertib arms, respectively. Of these, 147 patients [$n = 63$ (94.0%), 20 (80.0%), 34 (97.1%), and 30 (88.2%), respectively] received at least one dose of study medication (Supplementary Fig. S2). Of 14 patients who were enrolled but did not receive study treatment, the most common reason was failure to fulfill eligibility criteria ($n = 10$). The most common reason for AZD8186 discontinuation in each study arm was disease progression [monotherapy dose-finding arm, 71.4% ($n = 45$); monotherapy dose-expansion arm, 90.0% ($n = 18$); AZD8186/abiraterone acetate arm, 64.7% ($n = 22$); AZD8186/vistusertib arm, 53.3% ($n = 16$); Supplementary Fig. S2]. Across the four study arms, median age was 60–70 years (**Table 1**). Most patients were male (60%–100%) and had

**Table 1.** Baseline characteristics (safety analysis set).

| | AZD8186 monotherapy (dose finding) $n = 63$[a] | AZD8186 monotherapy (dose expansion) $n = 20$[a] | AZD8186 + AAP $n = 34$[a] | AZD8186 + vistusertib $n = 30$[a] |
|---|---|---|---|---|
| Median age, years (range) | 64.0 (18–92) | 60.0 (41–76) | 70.0 (42–83) | 65.0 (45–89) |
| Sex, *n* (%) | | | | |
| Male | 49 (77.8) | 12 (60.0) | 34 (100) | 25 (83.3) |
| Female | 14 (22.2) | 8 (40.0) | 0 | 5 (16.7) |
| ECOG performance status, *n* (%) | | | | |
| 0 | 19 (30.2) | 4 (20.0) | 27 (79.4) | 10 (33.3) |
| 1 | 44 (69.8) | 16 (80.0) | 7 (20.6) | 20 (66.7) |
| PTEN IHC status | | | | |
| Deficient | 20 (31.7) | 17 (85.0) | 22 (64.7) | 6 (20.0) |
| Proficient | 7 (11.1) | 1 (5.0) | 4 (11.8) | 10 (33.3) |
| Unknown/not determined | 36 (57.1) | 2 (10.0) | 8 (23.5) | 14 (46.7) |
| Primary tumor location, *n* (%) | | | | |
| Prostate | 41 (65.1) | 13 (65.0) | 34 (100) | 20 (66.7) |
| Breast | 10 (15.9) | 2 (10.0) | 0 | 2 (6.7) |
| Lung | 6 (9.5) | 0 | 0 | 2 (6.7) |
| Other[b] | 6 (9.5) | 5 (25.0) | 0 | 5 (16.7) |
| Unknown | 0 | 0 | 0 | 1 (3.3) |
| Extent of disease, *n* (%) | | | | |
| Metastatic | 53 (84.1) | 20 (100) | 34 (100) | 29 (96.7) |
| Locally advanced | 10 (15.9) | 0 | 0 | 1 (3.3) |
| Recurrence of earlier cancer, *n* (%) | | | | |
| No | 40 (63.5) | 16 (80.0) | 21 (61.8) | 26 (86.7) |
| Yes | 23 (36.5) | 4 (20.0) | 13 (38.2) | 4 (13.3) |
| Prior anticancer therapy received | | | | |
| 1 line | 7 (11.1) | 3 (15.0) | 8 (23.5) | 3 (10.0) |
| 2 lines | 2 (3.2) | 3 (15.0) | 9 (26.5) | 4 (13.3) |
| 3 lines | 13 (20.6) | 6 (30.0) | 8 (23.5) | 5 (16.7) |
| 4 lines | 7 (11.1) | 1 (5.0) | 5 (14.7) | 4 (13.3) |
| 5+ lines | 33 (52.4) | 7 (35.0) | 4 (11.8) | 14 (46.7) |
| Unspecified | 1 (1.6) | 0 | 0 | 0 |
| Median time from diagnosis to first dose, days (range) | 1,890 (406–9,050) | 1,384 (346–7,311) | 1,992 (142–7,416) | 2,553 (459–7,516) |

Abbreviations: AAP, abiraterone acetate and prednisone; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; PTEN, phosphatase and tensin homolog.

[a]All patients received at least one dose of AZD8186.

[b]Including biliary tract, colon, colorectal, head and neck, rectal, skin/soft tissue, and uterus.

metastatic disease (84%–100%), and the most common primary tumor location was prostate (65%–100%). The distribution of patients across the different doses and schedules is shown in **Table 2**.

## AZD8186 monotherapy

### Monotherapy dose-finding arm

The median (range) total treatment duration for AZD8186 in the monotherapy dose-finding arm was 47 (5–597) days (**Table 2**).

*DLTs and definition of RP2D:* Of 63 patients in the safety analysis set, 53 were evaluable for DLTs. Four patients (7.5%) experienced a DLT [one patient in each of the 120-mg BID (5:2) and 300-mg BID (5:2) cohorts and two patients in the 360-mg BID (5:2) cohort]. In all four patients, the DLT was a grade 3 rash (macular, maculo–papular, or unspecified). One patient in the 360-mg BID (5:2) cohort, in addition to grade 3 macular rash, experienced grade 2 abdominal pain and nausea, and grade 1 diarrhea and vomiting, which were considered as AEs of special interest and counted as DLTs.

The RP2D of AZD8186 monotherapy was formally declared as 60-mg BID (5:2) by the safety review committee at the end of dose-escalation period and was, therefore, further investigated in the expansion arm. However, on the basis of subsequent evaluation of the overall safety profile observed at the different monotherapy schedules and doses evaluated in the monotherapy dose escalation, doses of 120-mg BID (continuous and 5:2) were later considered to be tolerated and further evaluated in subsequent arms of the study.

*Safety and tolerability:* All 63 patients experienced at least one AE, with 55 patients (87.3%) experiencing an AE considered causally related to AZD8186 (**Table 3**). Grade ≥3 events causally related to AZD8186 were reported in 20 patients (31.7%) and SAEs causally related to AZD8186 were reported in 10 patients (15.9%; Supplementary Table S4). The most common causally related AEs were diarrhea (41.3%; $n = 26$), nausea (27.0%; $n = 17$), vomiting (23.8%; $n = 15$), and fatigue (22.2%; $n = 14$; **Fig. 1A**). The most common grade ≥3 causally related AEs were anemia, aspartate aminotransferase increase, colitis, hypophosphatemia, and maculo-papular rash (all 4.8%; $n = 3$), which were reversible with dose interruption and/or supportive care. Single cases of grade 4 AEs were observed, of which one event each of hypokalemia (120-mg BID; 5:2) and platelet count decreased (180-mg BID; 5:2) were considered related to AZD8186 treatment. Eleven patients (17.5%) had AEs leading to discontinuation of study treatment (Supplementary Table S5). No deaths were reported in the AZD8186 monotherapy dose-finding arm.

**Table 2.** Summary of AZD8186 exposure (safety analysis set).

| Study arm | AZD8186 dosing regimen | *N* | Relative dose intensity (mean %; SD) | Treatment cycles received (median; IQR) | Total treatment duration (days; median; range) | |
|---|---|---|---|---|---|---|
| AZD8186 monotherapy dose finding | 30 mg BID (5:2) | 7 | 96.5 (6.1) | 1.0 (1.0–2.0) | 26.0 (8–82) | 47.0 (5–597)[a] |
| | 60 mg BID (5:2) | 6 | 98.5 (2.6) | 3.0 (2.0–4.0) | 75.0 (26–113) | |
| | 120 mg BID (5:2) | 13 | 89.1 (18.7) | 2.0 (1.0–3.0) | 40.0 (12–194) | |
| | 240 mg BID (5:2) | 6 | 99.2 (1.4) | 1.5 (1.0–2.0) | 26.0 (5–166) | |
| | 360 mg BID (5:2) | 6 | 84.7 (25.9) | 2.0 (1.0–2.0) | 40.0 (10–83) | |
| | 300 mg BID (5:2) | 2 | 37.8 (2.2) | 1.0 (1.0–1.0) | 20.5 (19–22) | |
| | 180 mg BID (5:2) | 4 | 75.2 (15.9) | 2.0 (1.5–2.5) | 41.5 (19–69) | |
| | 30 mg BID (continuous) | 4 | 89.1 (10.9) | 5.0 (4.5–6.0) | 136.5 (105–184) | |
| | 60 mg BID (continuous) | 3 | 96.2 (6.1) | 2.0 (2.0–3.0) | 37.0 (33–85) | |
| | 120 mg BID (continuous) | 5 | 83.1 (18.5) | 2.0 (2.0–3.0) | 61.0 (56–70) | |
| | 120 mg BID (2:5) | 3 | 86.6 (7.6) | 4.0 (2.0–21.0) | 104.0 (36–597) | |
| | 240 mg BID (2:5) | 4 | 94.6 (14.2) | 4.5 (2.5–9.5) | 119.0 (44–359) | |
| AZD8186 monotherapy dose expansion | 60 mg BID (5:2) | 12 | 97.8 (3.8) | 2.0 (1.0–3.5) | 42.0 (8–145) | 59.0 (8–364)[a] |
| | 120 mg BID (continuous) | 8 | 96.6 (9.1) | 3.0 (2.0–9.0) | 72.0 (28–364) | |
| AZD8186 + AAP | Dose finding: 60 mg BID (5:2) | 5 | 96.9 (5.1) | 7.0 (4.0–9.0) | 186.0 (82–278) | 99.5 (5–534)[a] |
| | Dose finding: 120 mg BID (5:2) | 11 | 86.7 (22.7) | 3.0 (2.0–6.0) | 79.0 (15–534) | |
| | Dose expansion: 120 mg BID (5:2) | 18 | 86.8 (17.7) | 4.5 (3.0–8.0) | 112.0 (5–337) | |
| AZD8186 + vistusertib | 30 mg BID (5:2) + 100 mg vistusertib | 7 | 90.5 (8.5) | 2.0 (1.0–3.0) | 40.0 (7–390) | 42.5 (3–390)[a] |
| | 60 mg BID (5:2) + 100 mg vistusertib | 4 | 78.4 (17.5) | 3.0 (2.5–3.5) | 78.5 (41–105) | |
| | 60 mg BID (5:2) + 125 mg vistusertib | 4 | 79.8 (14.2) | 2.0 (1.0–3.5) | 59.0 (3–110) | |
| | 120 mg BID (5:2) + 125 mg vistusertib | 10 | 77.9 (38.8) | 2.5 (1.0–4.0) | 71.5 (12–208) | |
| | 120 mg BID (5:2) + 100 mg vistusertib | 5 | 96.6 (4.5) | 2.0 (1.0–2.0) | 35.0 (16–44) | |

Note: Dosing of AZD8186 was 5 days on, 2 days off (5:2); 2 days on, 5 days off (2:5), or continuous.
Abbreviations: AAP, abiraterone acetate plus prednisone; BID, twice daily; IQR, interquartile range; SD, standard deviation.
[a]Overall treatment duration.

Dose interruption or reduction was reported in 31 (49.2%) and 11 (17.5%) patients, respectively (Supplementary Table S3). At least one dose interruption was reported in each dose cohort, and most interruptions were related to AEs ($n = 24$; 38.1%). Of the 11 patients with dose reductions, 10 had reductions related to AEs; in the remaining patient the reduction was due to "other" (unspecified) reasons (Supplementary Table S3).

*PK:* AZD8186 was absorbed rapidly in plasma with a median $T_{max}$ value of 1.2–4.1 hours for a single dose, and 1.5–3.0 hours for multiple dosing (Supplementary Fig. S3). A similar profile was seen for the equipotent metabolite M1, with median $T_{max}$ value of 2.0–6.0 hours and 2.2–6.0 hours for single and multiple AZD8186 dosing, respectively (Supplementary Fig. S4). A summary of PK parameters for AZD8186 and M1 is presented in Supplementary Tables S6 and S7, respectively. After single- and multiple-dose administration, $C_{max}$ and AUC values increased with dose for both AZD8186 and M1. Geometric mean terminal elimination half-life for AZD8186 after a single dose ranged from 2.1 to 6.2 hours, with an overall range of 1.4–13.8 hours, and for M1 ranged from 4.2 to 8.6 hours, with a range of 3.2–13.0 hours.

*Efficacy:* In total, 34 patients were evaluable by RECIST 1.1. Of 18 patients with non-prostate cancer, a confirmed partial response (duration, 372 days) was reported in one patient (5.6%; 120-mg BID; 2:5), who had PTEN-deficient colorectal carcinoma. The tumor was classified as microsatellite instability-high by local testing, and central NGS analyses revealed many clinically relevant mutations, including *KRAS* G13D and deleterious mutations in *PTEN*, *PIK3R2,* and *SETD2*. The remaining patients had a best objective response of stable disease ($n = 7$; 38.9%) or disease progression ($n = 10$; 55.6%). Of 16 patients with prostate cancer, 6 (37.5%) had a best objective response of stable disease and 10 (62.5%) had disease progression.

Of 40 patients with prostate cancer that were PSA evaluable at baseline, one patient (2.5%; 240-mg BID; 2:5) experienced a partial PSA response (PTEN status unknown) and one patient (2.5%) experienced PSA progression. Of the remaining 38 patients, 34 (85.0%) did not meet the criteria for response or progression, and 4 (10.0%) were not evaluable at follow-up.

**Monotherapy dose-expansion cohort**

Patients in the monotherapy dose-expansion arm received either AZD8186 60-mg BID (5:2) or 120-mg BID (continuous; **Table 2**). Median (range) total treatment duration for AZD8186 was 59.0 (8–364) days (**Table 2**).

*Safety and tolerability:* Both AZD8186 doses were well tolerated. Of 20 patients in the safety analysis set, 19 (95.0%) experienced at least one AE. Eleven patients (55.0%) experienced an AE considered to be causally related to AZD8186 (**Table 3**). Grade ≥3 events causally related to AZD8186 were reported in three patients (15.0%) and SAEs causally related to AZD8186 were reported in two patients (10.0%; Supplementary Table S4). As in the monotherapy dose-finding arm, the most common treatment-related AEs were gastrointestinal symptoms (**Fig. 1B**). One patient had an AE leading to discontinuation of study treatment (Supplementary Table S5). No grade ≥3 treatment-related AEs were reported in more than one patient and no grade 4 AEs or deaths were reported.

Dose interruption was reported in seven patients (35.0%), six of whom were in the 60-mg BID (5:2) cohort (Supplementary Table S3). The most common reasons for dose interruption were forgetting to take the dose ($n = 3$) and AEs ($n = 2$). No dose reductions were reported.

**Table 3.** AEs reported with AZD8186 therapy (safety analysis set).

| Event, *n* (%) | AZD8186 monotherapy (dose finding) *n* = 63 | AZD8186 monotherapy (dose expansion) *n* = 20 | AZD8186 + AAP (dose finding) *n* = 16 | AZD8186 + AAP (dose expansion) *n* = 18 | AZD8186 + vistusertib *n* = 30 |
|---|---|---|---|---|---|
| **Any AE** | 63 (100.0) | 19 (95.0) | 16 (100) | 18 (100) | 29 (96.7) |
| Any AE causally related to AZD8186 only | 55 (87.3) | 11 (55.0) | 12 (75.0) | 15 (83.3) | 27 (90.0) |
| Any AE causally related to abiraterone acetate only | — | — | 10 (62.5) | 15 (83.3) | — |
| Any AE causally related to vistusertib only | — | — | — | — | 26 (86.7) |
| **Any grade ≥3 AE** | 39 (61.9) | 8 (40.0) | 9 (56.3) | 14 (77.8) | 23 (76.7) |
| Any grade ≥3 AE causally related to AZD8186 only | 20 (31.7) | 3 (15.0) | 5 (31.3) | 8 (44.4) | 17 (56.7) |
| Any grade ≥3 AE causally related to abiraterone acetate only | — | — | 4 (25.0) | 7 (38.9) | — |
| Any grade ≥3 AE causally related to vistusertib only | — | — | — | — | 17 (56.7) |
| **Death** | 0 | 0 | 1 (6.3) | 1 (5.6) | 2 (6.7) |
| Death causally related to AZD8186 only | 0 | 0 | 0 | 0 | 0 |
| Death causally related to abiraterone acetate only | — | — | 0 | 0 | — |
| Death causally related to vistusertib only | — | — | — | — | 0 |
| **Any SAE (including deaths)** | 23 (36.5) | 4 (20.0) | 9 (56.3) | 10 (55.6) | 15 (50.0) |
| Any SAE (including deaths), causally related to AZD8186 only | 10 (15.9) | 2 (10.0) | 3 (18.8) | 3 (16.7) | 11 (36.7) |
| Any SAE (including deaths), causally related to abiraterone acetate only | — | — | 0 | 3 (16.7) | — |
| Any SAE (including deaths), causally related to vistusertib only | — | — | — | — | 11 (36.7) |
| **Any SAE causing discontinuation of AZD8186** | 6 (9.5) | 0 | 3 (18.8) | 2 (11.1) | 3 (10.0) |
| Any SAE causing discontinuation of AZD8186, causally related to AZD8186 only | 5 (7.9) | 0 | 2 (12.5) | 0 | 1 (3.3) |
| Any SAE causing discontinuation of AZD8186, causally related to abiraterone acetate only | — | — | 0 | 1 (5.6) | — |
| Any SAE causing discontinuation of AZD8186, causally related to vistusertib only | — | — | — | — | 1 (3.3) |
| **Any AE leading to discontinuation of AZD8186** | 11 (17.5) | 1 (5.0) | 5 (31.3) | 4 (22.2) | 6 (20.0) |
| **Any AE leading to discontinuation of abiraterone acetate** | — | — | 3 (18.8) | 5 (27.8) | — |
| **Any AE leading to discontinuation of vistusertib** | — | — | — | — | 6 (20.0) |
| **Any AE leading to dose modification of AZD8186** | 10 (15.9) | 0 | 2 (12.5) | 3 (16.7) | 5 (16.7) |
| **Any AE leading to dose modification of abiraterone acetate** | — | — | 2 (12.5) | 7 (38.9) | — |
| **Any AE leading to dose modification of vistusertib** | — | — | — | — | 4 (13.3) |
| **Dose-limiting toxicities** | 4 (7.7)[a] | — | 0[b] | — | 1 (5.0)[c] |

Abbreviations: AAP, abiraterone acetate plus prednisone; AE, adverse event; SAE, serious adverse event.
[a]*n* = 53 evaluable patients.
[b]14 evaluable patients.
[c]*n* = 20 evaluable patients

*Efficacy:* Of seven patients with non-prostate cancer with RECIST 1.1 measurable disease, 1 (14.3%) had a best objective response of stable disease and 6 (85.7%) had disease progression. Of eight patients with prostate cancer with RECIST 1.1 measurable disease, 6 (75.0%) had a best objective response of stable disease and 2 (25.0%) had disease progression.

Of 13 patients with prostate cancer that were PSA evaluable at baseline, one patient (7.7%; 120-mg BID) had a partial PSA response (PTEN deficiency confirmed) and 1 (7.7%) had PSA progression. Of the remaining 11 patients, 9 (69.2%) did not meet the criteria for response or progression, and two patients (15.4%) were not evaluable at follow-up.

### PD (monotherapy dose-finding and dose-expansion arms)

Substantial reductions were seen in the platelet-rich plasma analyses of proximal markers of PI3Kβ inhibition [pAKT (S473), pAKT (T308), and pGSK3β], with slightly deeper and longer reduction in the pooled 120-mg BID monotherapy cohort compared with the pooled 60-mg BID cohort (**Fig. 2A–C**). Data for all doses and cohorts in the monotherapy dose-finding arm for pAKT (S473):tAKT (S473) and pGSK3β:tGSK3β are shown in Supplementary Fig. S5. In an exploratory analysis investigating free plasma exposure of the active moiety (AZD8186 and M1), a good correlation with the peripheral PD markers pAKT (S473), pAKT (T308), and pGSK3b was observed.

IHC staining of paired biopsies from six patients in the 120-mg BID cohort of the monotherapy dose-expansion arm showed a substantial reduction in the PI3Kβ downstream marker pAKT (S473) membrane fraction in all six patients and the AKT downstream marker pPRAS40 in five of the six patients (**Fig. 2D** and **E**; Supplementary Table S8). Representative IHC staining of tumor biopsies is shown in **Fig. 2F** and **G**).

## AZD8186 + abiraterone acetate

### Dose-finding arm

AZD8186 dosing in the AZD8186/abiraterone acetate dose-finding arm ($n$ = 16) was based on safety and efficacy findings in the monotherapy dose-finding arm, with patients receiving 60 or 120-mg AZD8186 BID (5:2; **Table 2**). Median (range) treatment duration was 186.0 (82–278) days for AZD8186 60-mg BID (5:2) and 79.0 (15–534) days for AZD8186 120-mg BID (5:2). Median (range) duration of abiraterone acetate treatment was 186.0 (83–280) days and 67.0 (18–252) days, respectively.

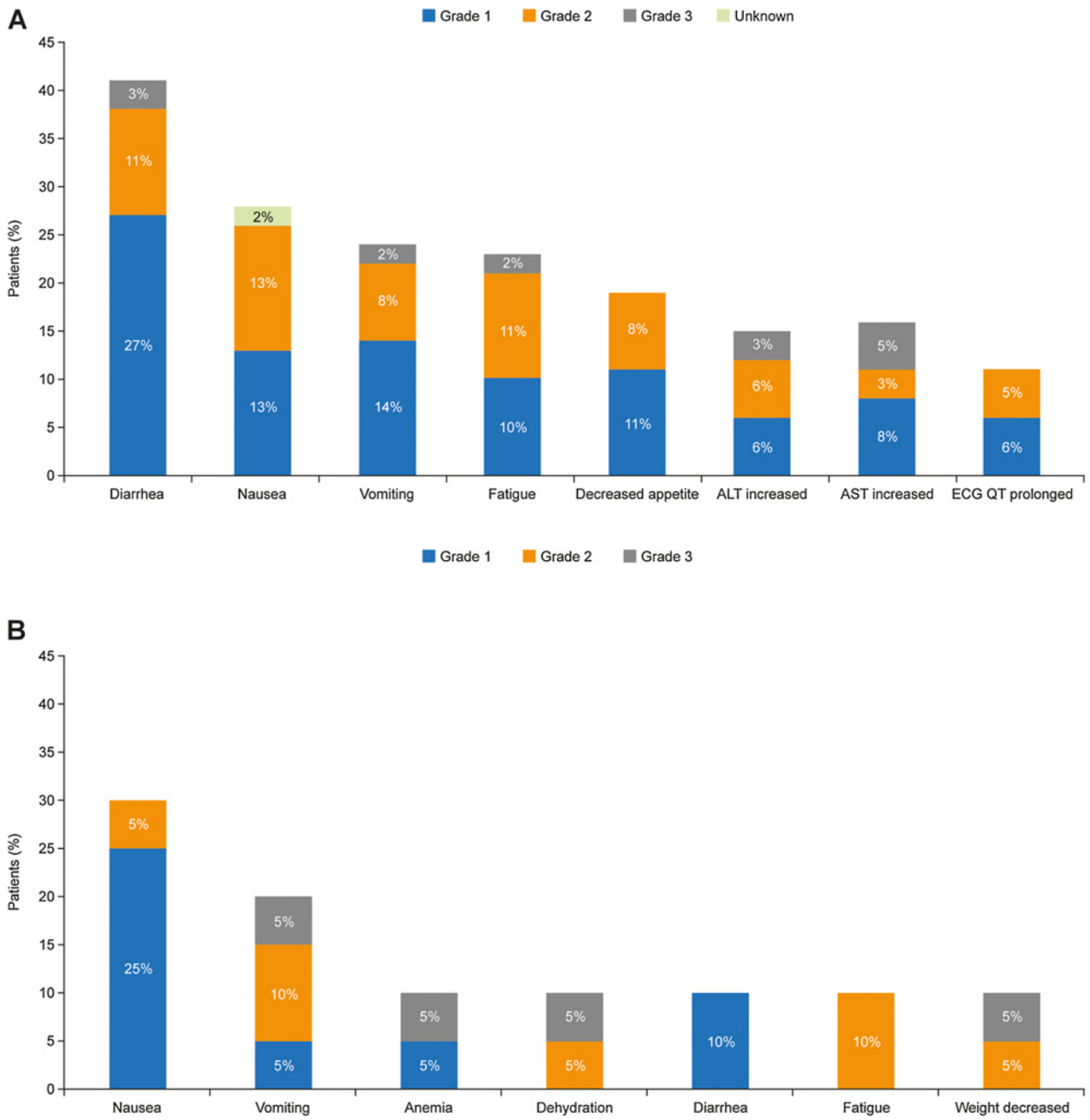


**Figure 1.**
Summary of treatment-related AEs* by maximum reported CTCAE grade in the monotherapy (**A**) dose-finding and (**B**) dose-expansion arms (safety analysis set). *, AEs considered by the investigator to be related to AZD8186 treatment occurring in ≥10% of patients in the dose-finding or dose-expansion arms, respectively. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; ECG QT, electrocardiogram QT interval

*DLTs and definition of RP2D:* In 14 patients evaluable for DLT, no DLTs were observed when AZD8186 was combined with abiraterone acetate. AZD8186 120-mg BID (5:2) was, therefore, considered to be the RP2D in combination with the clinically approved abiraterone/prednisone dose, and was further evaluated in the expansion cohort.

*Safety and tolerability:* AEs were reported in all 16 patients in the safety analysis population. Grade ≥3 AEs causally related to AZD8186 only or abiraterone acetate only were reported in five patients (31.3%) and four patients (25.0%), respectively (**Table 3**). SAEs causally related to AZD8186 only were reported in three patients (18.8%; Supplementary Table S4). No SAEs were considered causally related to abiraterone acetate only. One death (6.3%; respiratory failure) was reported in a patient receiving AZD8186 120-mg BID (5:2) in the context of SAEs of sepsis, double pneumonia, and alcohol withdrawal syndrome. Neither the death nor the associated SAEs were considered to be

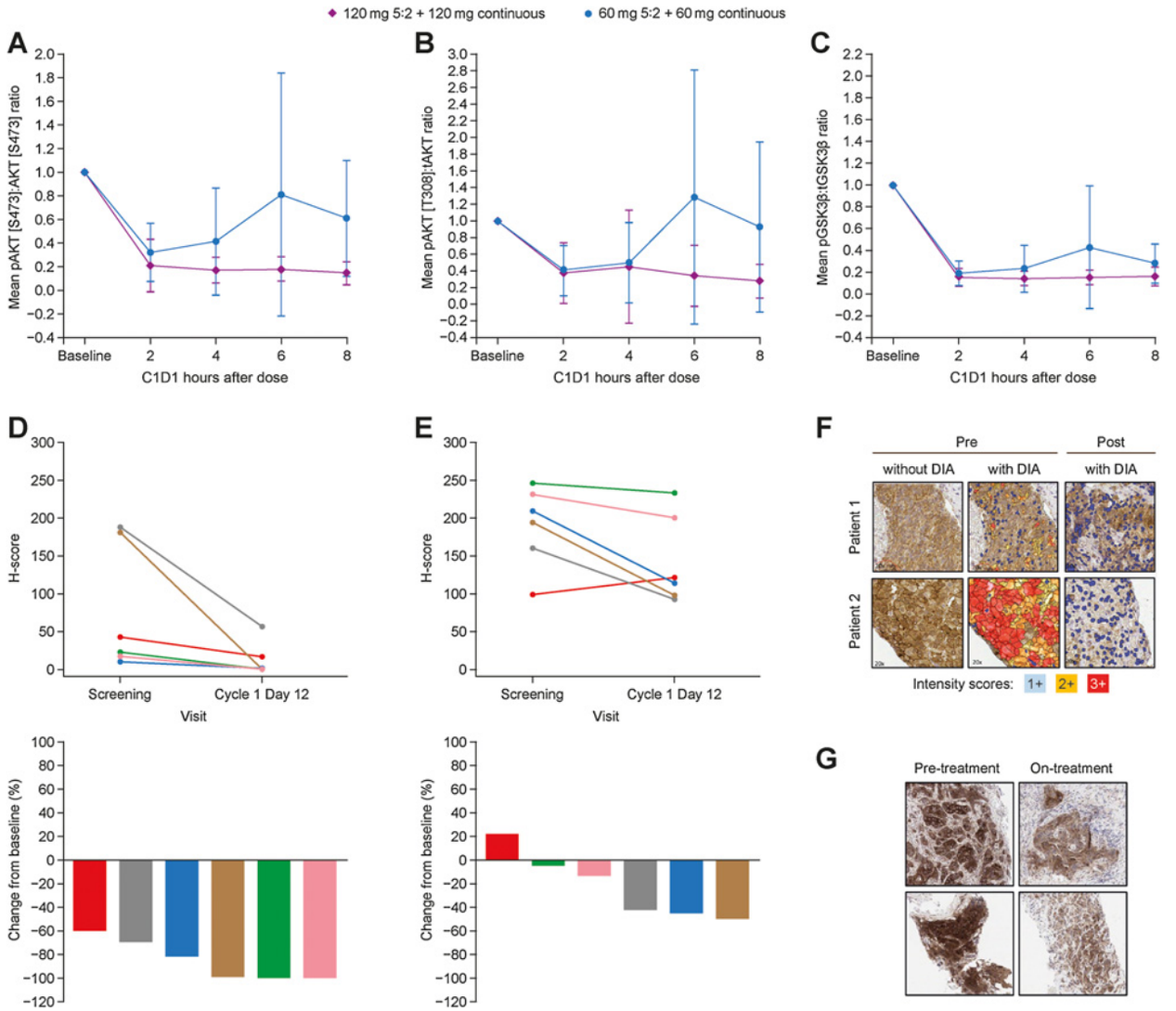


**Figure 2.**

Assessment of PD biomarkers after treatment with AZD8186 (PD analysis set; pooled data for 60-mg and 120-mg BID cohorts). Mean ratio of (**A**) pAKT (S473):tAKT(S473); (**B**) pAKT (T308):tAKT (T308); and (**C**) pGSK3β:tGSK3β over time in platelet-rich plasma (AZD8186 monotherapy arms). Total H-scores (top) and the percentage of change from baseline (bottom) are shown for (**D**) membranous pAKT (S473) and (**E**) pPRAS40 in individual patients*. Examples of membrane (**F**) pAKT scoring by DIA and (**G**) pPRAS40 scoring pre-treatment and 4 hours after dose at C1W2† (PD analysis set). C1D1, cycle 1 day 1; C1W2, cycle 1 week 2; DIA, digital image analysis; p, phosphorylated; t, total. *, Data for individual patients shown as different colors; †, On-treatment tumor biopsies were collected in week 2, after dose on days 11 or 12 for 5 days on/2 days off schedule or after dose on days 11–14 for continuous schedule.

causally related to AZD8186 or abiraterone acetate. The most common AEs causally related to AZD8186 were diarrhea (37.5%; $n = 6$) and nausea (37.5%%; $n = 6$); diarrhea was the only AZD8186-related grade ≥3 treatment-related AE reported in more than one patient (12.5%; $n = 2$). Grade 4 AEs were reported in one patient in each of the two dose groups but were not considered to be causally related to AZD8186. Five patients (31.3%), all receiving AZD8186 120-mg BID (5:2), discontinued AZD8186 because of an AE (Supplementary Table S5).

Dose interruption or reduction of AZD8186 was reported in 9 (56.3%) and 2 (12.5%) patients, respectively (Supplementary Table S3). AEs were the most common reason for both dose interruption ($n = 8$) and reduction ($n = 2$). Dose interruption or reduction of abiraterone acetate was reported in 9 (56.3%) and 3 (18.8%) patients, respectively, with AEs again the most common reason for dose interruption ($n = 9$) and reduction ($n = 2$). Dose interruption or reduction of prednisone was reported in 9 (56.3%) and 3 patients (18.8%), respectively. Despite these dose interruptions and reductions, the median relative dose intensities for AZD8186, abiraterone acetate, and prednisone were all >90% (Supplementary Table S9).

*PK:* The drug–drug interaction analysis comparing $C_{max}$ and $AUC_{\tau}$ values of AZD8186 monotherapy with abiraterone acetate + AZD8186 suggests that abiraterone acetate has little or no effect on the PK profile of AZD8186 (Supplementary Fig. S6;

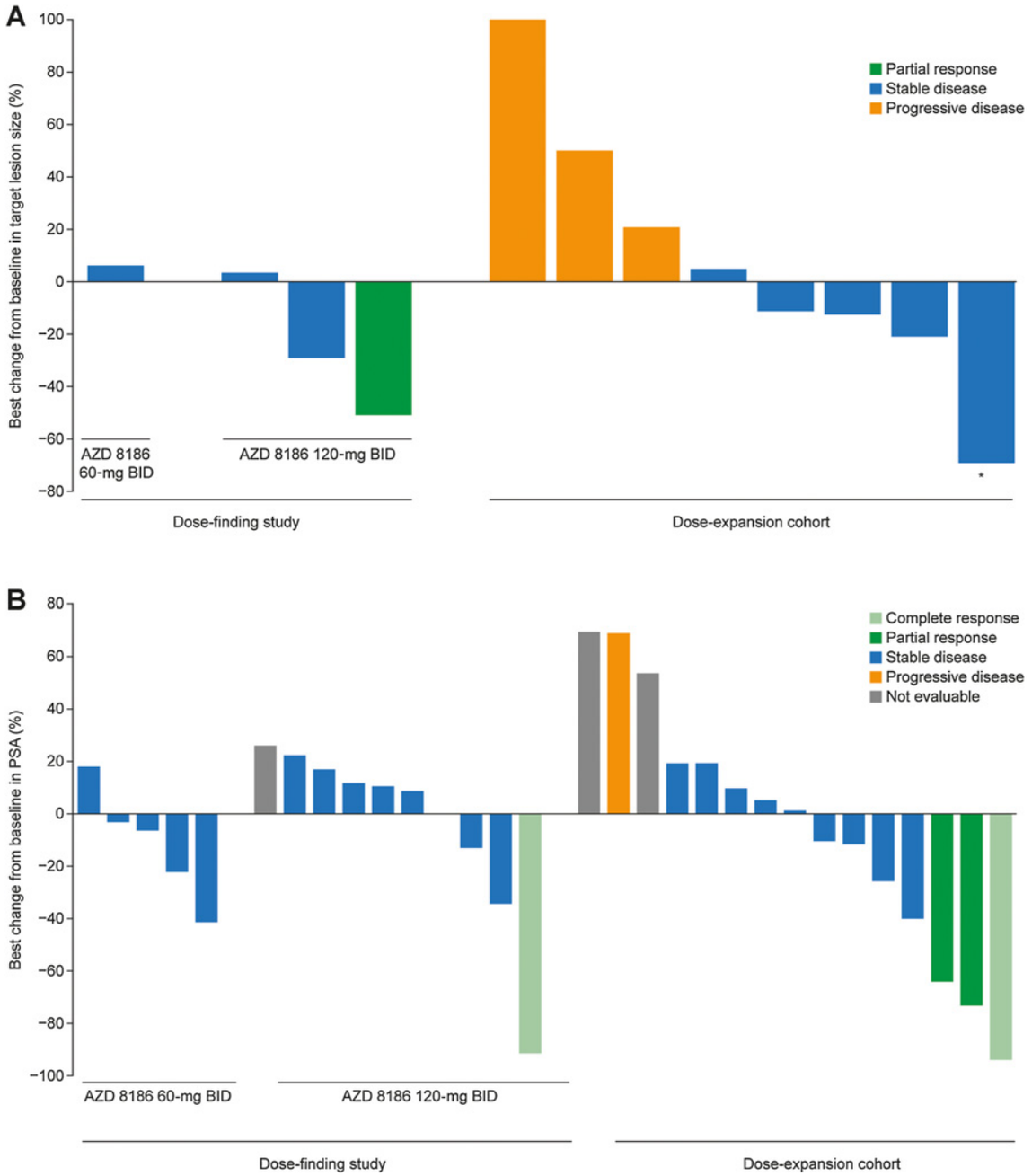


**Figure 3.**

Best response for (**A**) target lesions, based on RECIST ($n = 12$ with measurable disease), and (**B**) PSA concentration ($n = 30$ evaluable for response) by patient and dose in the efficacy-evaluable analysis set (AZD8186/abiraterone acetate combination arm). *, Response was not confirmed at follow-up scan.

Supplementary Table S10). Similarly, there was little effect of AZD8186 on the PK of abiraterone acetate (Supplementary Fig. S7; Supplementary Table S10).

*Efficacy*: Among patients with RECIST 1.1 measurable disease ($n = 4$), three had stable disease and one (120-mg BID; 5:2) had a partial response (duration, 172 days; **Fig. 3**). This patient was not PTEN-deficient (PTEN mutation status not evaluated). Of note, the patient with the partial response had not previously received abiraterone acetate, enzalutamide, or docetaxel, making it difficult to determine the relative contributions of AZD8186/abiraterone to this response.

Of 15 patients that were PSA evaluable at baseline, one patient (6.7%) receiving AZD8186 120-mg BID (5:2) had a complete response (duration, 197 days) in addition to the RECIST 1.1 partial response noted above. Of the remaining 14 patients, 13 (86.7%) had stable disease and one was not evaluable (6.7%; **Fig. 3**). Among patients

evaluable for PCWG2 bone–lesion response ($n = 10$), 6 (60.0%) had non-progressive disease and 4 (40.0%) had progressive disease (Supplementary Table S11).

**Dose-expansion cohort**

In the expansion cohort, 18 patients with CRPC received AZD8186 120-mg BID (5:2) in combination with abiraterone, with a median (range) duration of 112.0 (5–337) days (**Table 2**). Median duration of abiraterone acetate treatment was 86.0 (5–337) days. Of the 18 patients, 14 (77.8%) had previously received abiraterone and/or enzalutamide.

*Safety and tolerability:* AEs were reported in all 18 patients, with AEs causally related to AZD8186 only or abiraterone acetate only each reported in 15 patients (83.3%; **Table 3**). SAEs causally related to AZD8186 only or abiraterone acetate only, were each reported in three patients (16.7%). One death (5.6%; metastatic prostate cancer) was reported during the safety follow-up period and was not considered to be causally related to study drug. The most common AEs causally related to AZD8186 treatment were diarrhea (50.0%; $n = 9$), nausea (44.4%; $n = 8$), and vomiting (38.9%, $n = 7$). The most common grade ≥3 AEs causally related to AZD8186 treatment were alanine aminotransferase increased (16.7%; $n = 3$) and aspartate aminotransferase increased (16.7%; $n = 3$). One patient reported a grade 4 AE considered to be related to study treatment (alanine aminotransferase increased). Four patients (22.2%) discontinued AZD8186 because of an AE (Supplementary Table S5).

Dose interruption or reduction of AZD8186 was reported in 13 patients (72.2%) and four patients (22.2%), respectively, with AEs the most common reason for both interruption ($n = 10$; 55.6%) and reduction ($n = 4$; 22.2%; Supplementary Table S3). Dose interruption of abiraterone acetate and prednisone was reported in 13 patients (72.2%) and 14 patients (77.8%), respectively, with dose reductions in six patients (33.3%) and four patients (22.2%), primarily for AEs (reductions and interruptions) or forgetting to take the dose (reductions only).

*Efficacy:* Five of eight patients (62.5%) with RECIST 1.1-measurable disease had a best objective response of stable disease and 3 (37.5%) had progressive disease (**Fig. 3**). Of 15 patients that were PSA evaluable at baseline, one had a complete response (6.7%). This PTEN-deficient patient had not previously received treatment with abiraterone acetate, enzalutamide, or docetaxel. In addition, two patients (13.3%) had partial responses, both of whom had previously received enzalutamide and docetaxel (one PTEN deficient and one with a PTEN mutation). Of the remaining patients, 9 (60.0%) had stable disease, 1 (6.7%) had progressive disease, and 2 (13.3%) were not evaluable (**Fig. 3**). Of 14 patients evaluable for PCWG2 bone–lesion response, 9 (64.3%) had non-progressive disease, 4 (28.6%) had progressive disease, and one patient (7.1%) was not evaluable at follow-up (Supplementary Table S11).

### AZD8186 + vistusertib

Seven patients received AZD8186 30-mg BID (5:2) + vistusertib 100 mg, four patients each received AZD8186 60-mg BID (5:2) + vistusertib 100 mg and AZD8186 60-mg BID (5:2) + vistusertib 125 mg, 10 patients received AZD8186 120-mg BID (5:2) + vistusertib 125 mg, and five received AZD8186 120 mg BID (5:2) + vistusertib 100 mg (**Table 2**). The median (range) duration of treatment was 42.5 (3–390) days for AZD8186 and 41.0 (2–387) days for vistusertib.

**DLTs and definition of RP2D**

Of 20 evaluable patients, one [AZD8186 120-mg BID (5:2) + vistusertib 125 mg] experienced three concurrent grade 3 DLTs (mucosal inflammation, maculo–papular rash, and blood phosphorus decreased). An RP2D of AZD8186 in combination with vistusertib was not formally declared, as enrollment in the AZD8186/vistusertib dose-finding arm was halted due to discontinuation of vistusertib development. The dose-expansion arm was not initiated.

*Safety and tolerability:* AEs were experienced by 29 patients (96.7%) in the safety analysis set, with grade ≥3 AEs causally related to AZD8186 only or vistusertib only each reported in 17 patients (56.7%; **Table 3**). SAEs causally related to AZD8186 only (Supplementary Table S4) or vistusertib only were each reported in 11 patients (36.7%). The most common AEs causally related to AZD8186 were diarrhea (56.7%; $n = 17$), nausea (53.3%; $n = 16$), and fatigue (36.7%; $n = 11$). The most common grade ≥3 causally related AEs were increased alanine aminotransferase and diarrhea (16.7%; $n = 5$ and 13.3%; $n = 4$, respectively). Six patients (20.0%) had an AE leading to discontinuation of AZD8186 (Supplementary Table S5). Two AEs leading to death (6.7%) were reported during safety follow-up (subarachnoid hemorrhage, $n = 1$; pulmonary embolism, $n = 1$); neither was considered to be causally related to study medication.

Overall, 20 patients (66.7%) and five patients (16.7%) had dose interruptions or reductions, respectively (Supplementary Table S3). The most common reasons for interruptions and reductions of AZD8186 were AEs (56.7% and 16.7%, respectively). Dose interruption or reduction of vistusertib occurred in 18 patients (60.0%) and seven patients (23.3%), respectively. No significant effects on cholesterol or glucose levels and blood pressure were observed following treatment with AZD8186 + vistusertib.

*PK:* The estimate of geometric mean ratio percentage for AZD8186 $AUC_{0-12}$ and $C_{max}$ values was not affected by the presence of vistusertib (Supplementary Table S12). As no data on vistusertib monotherapy were collected during the study, effects of AZD8186 on the PK of vistusertib could not be determined.

*Efficacy:* Of eight patients with non-prostate cancer with RECIST 1.1-measurable disease, 3 (37.5%) had a best objective response of stable disease and 5 (62.5%) had disease progression. Of nine patients with prostate cancer with RECIST 1.1-measurable disease, 1 (11.1%) had a best objective response of partial response (PTEN deficiency and mutation status unknown), 2 (22.2%) had stable disease, and 6 (66.7%) had disease progression.

## Discussion

This was the first-in-human study of AZD8186, in which the optimal dosing and schedule were identified and supported by safety and PK data. AZD8186 had an acceptable safety and tolerability profile, both as monotherapy and in combination with abiraterone acetate (and prednisone) or vistusertib, when compared against other PI3K inhibitors such as copanlisib and idelalisib (24, 25). Dose-dependent effects of target inhibition were observed in plasma (60-mg and 120-mg BID AZD8186) and tumor tissue (120-mg BID AZD8186). The PKs of AZD8186 were dose proportional, without interactions with abiraterone acetate or vistusertib. AZD8186 (as monotherapy and in combination) also showed preliminary evidence of anti-tumor activity by both radiography and PSA reduction.

Dose discontinuations and reductions were consistent with rates described for licensed PI3K inhibitors, idelalisib and copanlisib (26, 27). Dose interruptions were slightly higher in the AAP and vistusertib combinations, mainly to allow patients to recover and restart therapy to derive further benefit from study medication.

Gastrointestinal AEs (constipation, diarrhea, nausea, and vomiting) and fatigue were the most frequently reported treatment-related AEs during AZD8186 treatment, and most were grade 1 or 2 in severity. In general, treatment-emergent AEs, including colitis, diarrhea, and rash, were easily manageable by best supportive care and short treatment interruptions at recommended doses but were dose limiting at the highest doses tested. This safety profile could be the consequence of PI3Kδ inhibition at highest doses tested but not at the recommended doses where PI3Kβ inhibition prevails.

There was no clear pattern regarding the efficacy of AZD8186 in patients with PTEN alterations: of two patients with RECIST 1.1 partial responses, one had PTEN-deficient disease and one did not (mutation status unknown). Of five patients with prostate cancer with PSA responses, three were in PTEN-deficient disease, one was in PTEN-mutant disease, and one had no PTEN deficiency (mutation status unknown). It should be noted, however, that patient numbers were small, most patients with mCRPC were heavily pre-treated, and PTEN testing was mandatory only in the dose-expansion cohorts and was performed by IHC without assessment of genetic loss. AZD8186 remains to be tested in a different patient population and/or with a different combination partner other than abiraterone or vistusertib. Analogous data have been reported in similar studies, in which PTEN/PI3K mutation status was again evaluated only in a subset of study participants (28). Further studies with AZD8186 or other PI3K inhibitors will be needed to establish the predictive potential of PTEN as a biomarker. In addition, PTEN deficiency/inactivation is only one of several mechanisms leading to activation of the PI3K/AKT pathway (29). Several potential mechanisms of resistance to PI3K inhibitor treatment have been identified, including signaling through the RAS–MEK–ERK pathway via HRAS, compensatory increases in HER2/3 expression activating ERK signaling, and activation of the NOTCH–MYC pathway (30, 31).

A second PI3Kβ inhibitor, GSK2636771, is currently in development for solid tumors. As with AZD8186, first-in-human results confirmed clinically relevant target inhibition with the RP2D (400 mg) and a manageable safety profile (32), further demonstrating the proof of mechanism of this PI3Kβ inhibitor. A preliminary association between *PIK3CB* genomic aberrations and clinical benefit was also reported (32). As in the present study, the most common treatment-related AEs were gastrointestinal symptoms (diarrhea, nausea, and vomiting) and fatigue. A dual PI3Kβ/δ inhibitor, KA2237, has been investigated in patients with lymphoma, with preliminary results from a first-in-human study showing a manageable toxicity profile and promising single-agent clinical activity in heavily pretreated relapsed/refractory B-cell lymphoma (33).

The multi-arm trial design, allowing several different regimens, schedules, and combinations to be evaluated, is an important strength of the present study. However, the small numbers of patients in each treatment cohort mean that conclusions, particularly related to efficacy, should be drawn with care. In the future, trials with larger cohorts will be needed to further explore the efficacy and tolerability of AZD8186. Additional trials will also be needed to help understand whether PTEN deficiency or mutation status is predictive of response with PI3Kß inhibitors. One avenue for future development is the combination of PI3K inhibitors with immunotherapy, such as T-cell vaccines and checkpoint inhibitors (34). Other possible combinations for PI3Kß inhibitors include docetaxel and paclitaxel, as well as other novel therapies such as PI3Kα inhibitors in patients with hormone receptor–positive breast cancer who progress after alpelisib treatment, where PTEN deficiency is a known resistance mechanism (35). The efficacy and safety of AZD8186 are currently being evaluated in studies in combination with docetaxel in solid tumors (phase I; ClinicalTrials.gov: NCT03218826), and with weekly paclitaxel in gastric cancer (phase I/II; NCT04001569).

## Conclusion

In this phase I study, optimal dosing for AZD8186 was identified and supported by PK and PD data. AZD8186 monotherapy at the selected RP2D had an acceptable safety and tolerability profile, and combination with abiraterone acetate (and prednisone) or vistusertib was also tolerated. Target inhibition was observed in plasma and tumor tissue at the RP2D selected for further development, and there was some preliminary evidence of antitumor activity. This merits further exploration of the potential of AZD8186 to affect PI3Kβ-driven disease in larger clinical studies, in a more precisely defined population and in combination with other agents targeting this pathway.

## Authors' Disclosures

A.D. Choudhury reports grants from AstraZeneca during the conduct of the study; A.D. Choudhury also reports grants from Bayer, as well as personal fees from Clovis, Dendreon, Bayer, AstraZeneca, Astellas, and Blue Earth outside the submitted work. C.S. Higano reports grants from AstraZeneca, personal fees from AstraZeneca, and other support from AstraZeneca during the conduct of the study. C.S. Higano also reports personal fees from Advanced Accelerator Applications, Blue Earth, Dendreon, Janssen, Merck, Tolmar, Vaccitech, Menarini, Astellas, Bayer, Ferring, Pfizer, and Clovis; grants from Aptevo, Astellas, Bayer, Emergent, F. Hoffmann-La Roche, Ferring, Genentech, Medivation, Pfizer, and Clovis; and other support from Exelixis, Candel, Advanced Accelerator, Astellas, Bayer, Blue Earth, Ferring, Janssen, Merck, Pfizer outside the submitted work. J.S. de Bono reports grants and personal fees from AstraZeneca during the conduct of the study; J.S. de Bono also reports grants and personal fees from Amgen, Astellas, Bayer, Bioxcel Therapeutics, Boehringer Ingelheim, Cellcentric, Daiichi, Eisai, Genentech/Roche, Genmab, GSK, Harpoon, ImCheck Therapeutics, Janssen, Merck Serono, Merck Sharp & Dohme, Menarini/Silicon Biosystems, Orion, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Terumo, and Vertex Pharmaceuticals outside the submitted work. In addition, J.S. de Bono reports a patent for DNA repair defects PARP (ICR owned patent) and does not receive royalties issued, and a patent for Abiraterone acetate (ICR owned patent) but does not receive any royalties issued. N. Cook reports grants from Cancer Research UK, other support from AstraZeneca, and grants from NIHR during the conduct of the study. N. Cook also reports non-financial support and other support from Roche; other support from Tarveda, Taiho, Pfizer, Bayer, Orion, Avacta, Eisai, UCB, Merck, Boehringer, Stemline, Starpharma, and Ergomed; and personal fees and other support from RedX outside the submitted work. D.E. Rathkopf reports other support from AstraZeneca during the conduct of the study, as well as other support from Janssen, Celgene/BMS, Genentech/Roche, Phosplatin, Myovant, AstraZeneca, Bayer, and Taiho outside the submitted work. K.B. Wisinski reports other support from AstraZeneca during the conduct of the study. K.B. Wisinski also reports grants and personal fees from Pfizer; personal fees from Sanofi, AstraZeneca, and Eisai; personal fees and other support from Novartis; and other support from Context Therapeutics outside the submitted work. J. Martin-Liberal reports personal fees from Astellas and Highlight Therapeutics; grants and personal fees from Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer, Roche, and Sanofi; and grants from Ipsen outside the submitted work. E.I. Heath reports other support from Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Caris Life Sciences, Celgene, Celldex, Corcept Therapeutcs, Curemeta, Dendreon, eFFECTOR Therapeutics, Esanik, Fortis Therapeutics, Genentech/Roche, GlaxoSmithKline, Ignyta, Inovio Pharmaceuticals, Medivation, Merck Sharp & Dohme, Merck, Millennium, Oncolys BioPharma, Plexxicon, Sanofi, Seattle Genetics, Synta, Tokai Pharmaceuticals, and Zenith Epigenetics outside the submitted work. R.D. Baird reports grants and personal fees from AstraZeneca and Genentech/Roche, as well as personal fees from Novartis during the conduct of the study. R.D. Baird also reports grants and personal fees from Boehringer Ingelheim, as well as personal fees from Shionogi, Daiichi-Sankyo, and Molecular Partners outside the submitted work. M. Quintela-Fandino reports grants from AstraZeneca during the conduct of the study; M. Quintela-Fandino also reports

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## Note

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