Clinical Trials: Targeted Therapy

Clinical Cancer Research

Randomized Phase II Study Evaluating Akt Blockade with Ipatasertib, in Combination with Abiraterone, in Patients with Metastatic Prostate Cancer with and without PTEN Loss

Johann S. de Bono[1], Ugo De Giorgi[2], Daniel Nava Rodrigues[1], Christophe Massard[3], Sergio Bracarda[4], Albert Font[5], Jose Angel Arranz Arija[6], Kent C. Shih[7], George Daniel Radavoi[8], Na Xu[9], Wai Y. Chan[9], Han Ma[9], Steven Gendreau[9], Ruth Riisnaes[1], Premal H. Patel[9], Daniel J. Maslyar[9], and Viorel Jinga[8]

Abstract

Purpose: PI3K–Akt–mTOR and androgen receptor (AR) signaling are commonly aberrantly activated in metastatic castration-resistant prostate cancer (mCRPC), with PTEN loss associating with poor prognosis. We therefore conducted a phase Ib/II study of the combination of ipatasertib, an Akt inhibitor, with the CYP17 inhibitor abiraterone in patients with mCRPC.

Patients and Methods: Patients were randomized 1:1:1 to ipatasertib 400 mg, ipatasertib 200 mg, or placebo, with abiraterone 1,000 mg orally. Coprimary efficacy endpoints were radiographic progression-free survival (rPFS) in the intent-to-treat population and in patients with PTEN-loss tumors.

Results: rPFS was prolonged in the ipatasertib cohort versus placebo, with similar trends in overall survival and time-to-PSA progression. A larger rPFS prolongation for the combination was demonstrated in PTEN-loss tumors versus those without. The combination was well tolerated, with no treatment-related deaths.

Conclusions: In mCRPC, combined blockade with abiraterone and ipatasertib showed superior antitumor activity to abiraterone alone, especially in patients with PTEN-loss tumors.

See related commentary by Zhang et al., p. 901

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous disease, characterized by activation of the PI3K–Akt–mTOR and androgen receptor (AR) signaling pathways (1, 2). Of interest, approximately 40% to 60% of mCRPCs have a functional loss of PTEN, an important tumor suppressor phosphatase, which results in hyperactivation of the PI3K–Akt–mTOR pathway (3, 4).

The PI3K–Akt–mTOR and AR pathways exhibit cross-talk regulation (5). In mCRPC, the PI3K–Akt–mTOR pathway can be activated with treatments reducing AR signaling, such as the antiandrogen abiraterone acetate (1, 2). Abiraterone acetate, by blocking androgen production in the testes, adrenal glands, and tumor cells, delays disease progression and improves overall survival (OS) in mCRPC; however, resistance and disease progression usually occur, highlighting a need for improved treatments (6–10). Conversely, PTEN loss may suppress AR transcriptional activity in tumors and is associated with advanced disease and poor prognosis (11–17). In abiraterone-treated patients with mCRPC, tumors with PTEN loss by IHC were associated with worse outcomes (12). Therefore, combined inhibition of the AR and PI3K–Akt–mTOR pathways may result in improved benefit for patients with mCRPC (1, 2, 18).

Ipatasertib (GDC-0068) is a potent, novel, selective ATP-competitive small-molecule inhibitor of all three isoforms of Akt. Sensitivity to ipatasertib is associated with high tumoral levels of phosphorylated Akt, PTEN protein loss or genetic mutations, and *PIK3CA* kinase domain mutations (19–21). Tumor biopsies from a phase I study demonstrated PI3K–Akt–mTOR pathway inhibition by ipatasertib at clinically achievable doses (21). A phase I study of single-agent ipatasertib in 52 pretreated patients with various tumor types demonstrated an acceptable tolerability profile, characterized by gastrointestinal effects, asthenia/fatigue, hyperglycemia, rash, and preliminary antitumor activity (22).

In this phase Ib/II study in patients with mCRPC (GO27983; NCT01485861), the combined inhibition of androgen signaling with abiraterone, and PI3K–Akt–mTOR signaling with ipatasertib, was investigated to assess tolerability and efficacy compared

[1]The Royal Marsden/Institute of Cancer Research, London, United Kingdom. [2]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, (IRST) IRCCS, Meldola, Italy. [3]Institut Gustave Roussy, Villejuif, France. [4]Medical Oncology, Ospedale San Donato, Azienda USL Toscana Sud-Est, Istituto Toscano Tumori, Arezzo, Italy. [5]Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain. [6]Hospital General Universitario Gregorio Marañón, Madrid, Spain. [7]Tennessee Oncology, Nashville, Tennessee. [8]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania. [9]Genentech, Inc., South San Francisco, California.

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Current address for D.J. Maslyar: Alector, South San Francisco, California.

Corresponding Author: Johann S. de Bono, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London SM2 5NG, UK. Phone: 4420-8722-4028; Fax: 4420-8642-7979; E-mail: Johann.DeBono@icr.ac.uk

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Translational Relevance

This study is the first to demonstrate that the combination of ipatasertib and abiraterone is superior to abiraterone alone, delaying rPFS particularly in mCRPC with PTEN loss. Both protein and DNA-based PTEN assays and clinical results support the biologic hypothesis of this combination.

with single-agent abiraterone. Tumor PTEN loss was also prospectively evaluated as a putative predictive marker.

Patients and Methods

Study design and patients

This multicenter, international, phase Ib/II trial consisted of two stages. In the phase Ib, open-label, dose escalation stage, the recommended phase II dose of ipatasertib in combination with abiraterone 1,000 mg once daily and prednisone/prednisolone 5 mg twice daily was determined. The phase Ib study was conducted in 5 sites in the United States. There was no dose-limiting toxicity with ipatasertib 400 mg, the highest evaluated dose (Supplementary Table S1). The phase Ib portion included a safety assessment of abiraterone plus GDC-0980, a dual PI3K/mTOR inhibitor, but this arm was discontinued due to poor tolerability (data not shown).

The phase II, three-arm, double-blind, randomized stage compared the efficacy and safety of ipatasertib with abiraterone and prednisone/prednisolone versus placebo with abiraterone and prednisone/prednisolone. This combination was evaluated in the intent-to-treat (ITT; unselected) population as well as in patients with PTEN-loss tumors. The phase II study was conducted in 49 sites in nine countries. The protocol was amended five times to update inclusion/exclusion criteria, increase the number of participating sites, add prednisolone as an alternative to prednisone, clarify the blinding process, specify the recommended phase II dose of ipatasertib, and update the phase II study design.

Eligible patients were aged $\geq$18 years with histologically confirmed metastatic or advanced prostate cancer previously treated with docetaxel-based therapy and progressing after $\geq$1 hormonal therapy (23), had an Eastern Cooperative Oncology Group performance status of 0 or 1 at screening, and adequate hematologic, liver, and kidney function. Patients were excluded if they had small cell or neuroendocrine prostate carcinoma, previous treatment for prostate cancer with abiraterone, PI3K–Akt–mTOR inhibitors, or any cancer therapy <2 weeks prior to initiation, type I or II diabetes mellitus requiring insulin (patients not requiring insulin were permitted), clinically significant cardiac or pulmonary dysfunction, active autoimmune disease, immunocompromised status, or liver disease. Patients were required to provide a tumor block or 15 to 20 unstained serial slides for evaluation of PTEN status and to support the biomarker-related exploratory objectives of the study (the vast majority of these specimens came from the patient's primary disease: 220/223, 91%; Supplementary Fig. S1).

This study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from patients prior to enrollment in agreement with approved protocols from the respective ethics committees.

Randomization and masking

Patients were randomized 1:1:1 via permuted block randomization through an interactive voice–web-based response system (IVRS/IWRS) to receive ipatasertib 400 mg, ipatasertib 200 mg, or placebo, in combination with abiraterone 1,000 mg once daily and prednisone/prednisolone 5 mg twice daily continuously in 28-day cycles (Supplementary Fig. S2). Ipatasertib and placebo were identical in appearance. Crossover was not permitted. Randomization was stratified by prior treatment with enzalutamide, number of prior chemotherapy regimens for metastatic disease (1 vs. >1), and progression factor (PSA only vs. other). Patients and investigators were blinded to treatment status (i.e., ipatasertib vs. placebo); however, they were aware of randomization to the different doses of ipatasertib/placebo (400 mg vs. 200 mg). Emergency unblinding was permitted and could be performed by the investigator through the IVRS/IWRS system. The PTEN loss status was not disclosed.

Procedures

Ipatasertib (400 or 200 mg), abiraterone 1,000 mg, and placebo were administered orally once daily, and prednisone/prednisolone 5 mg was administered orally twice daily. Patients received treatment until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion/termination. After study completion or termination, patients who continued to benefit from study treatment were given the opportunity to continue as part of an extension study. Per the discretion of the investigator, the dose of ipatasertib/placebo could be reduced by one dose level (100-mg increments). If the patients receiving the lowest dose had any reason for further dose reduction, ipatasertib was discontinued.

Tumor assessments were performed at screening; after cycles 3, 5, 7, and 9; every three cycles (12 weeks) thereafter; and at treatment completion. Radiographic progression-free survival (rPFS) was adapted from the Prostate Cancer Working Group 2 Criteria and assessed using RECIST version 1.1 for progressive disease of soft tissue, bone scan progressive disease (Supplementary Table S2), or death within 30 days of the last dose (24). Other study assessments included medical history, laboratory tests, adverse events (AE), pharmacokinetics, biomarkers, and patient-reported outcomes (see Supplementary Methods for further details). Cumulative dose intensity for each study drug (ipatasertib, placebo, or abiraterone) was calculated using the actual amount of study drug received in milligrams divided by the expected amount of study drug in milligrams. The expected amount of study drug was calculated on the basis of treatment duration (the interval between the first and last administered doses of study drug) and the initial dose and schedule specified in the protocol.

PTEN loss was assessed via IHC performed centrally at The Institute of Cancer Research (London, United Kingdom) through a validated assay, and the researchers were blinded to treatment assignment and clinical outcome data (12, 25). Additional protein- and DNA-based platforms to assess PTEN loss included an alternative PTEN IHC assay (Ventana), next-generation sequencing (NGS; Foundation Medicine), and FISH (Core Diagnostics). Additional details on these methodologies are listed in the Supplementary Methods.

Outcomes

The coprimary endpoints were rPFS in the ITT population and in patients whose tumors had PTEN loss. Secondary

endpoints in the ITT and PTEN-loss populations include OS, PSA response rate, objective tumor response, CTC conversion rate, and safety and tolerability. Exploratory endpoints were PSA progression and rPFS in PTEN loss and nonloss populations using alternative assays and platforms (see Supplementary Fig. S1 and Supplementary Table S3).

Safety was graded per the NCI Common Terminology Criteria for Adverse Events version 4.0. Preferred terms were assigned to the original entry, using the Medical Dictionary for Regulatory Activities version 18.1. Selected AEs were identified by AE group terms comprising preferred terms of similar medical concepts.

Statistical analysis

Efficacy comparisons between ipatasertib doses and the placebo cohort were planned, but not between ipatasertib cohorts. This trial was hypothesis generating and did not have adequate power to detect minimum clinically meaningful differences between cohorts at a statistically significant α (type I error) level of 5%. Instead, the 90% confidence intervals (CI) for the HR were calculated with the expectation that for clinically meaningful outcomes, the upper limit of the two-sided 90% CI will be close to 1. A true improvement of >3 months in median rPFS (from 6 to >9 months or HR < 0.67) was considered clinically meaningful for ipatasertib 400 or 200 mg versus placebo. The final analysis for the primary endpoint of rPFS was planned for 96 events in the PTEN-loss population, which gives 64 events per comparison; the corresponding two-sided upper 90% CI for a targeted HR ratio of 0.67 with 64 events is 1.01. Assuming a 60% prevalence of PTEN loss in prostate cancer, 162 overall events (108 per comparison) were expected in the overall population, giving the planned approximately 80 randomized patients per arm, or 240 randomized patients overall, to be enrolled. rPFS was evaluated using the following methods: A stratified Cox proportional hazards model estimated the HR and CI for each comparison, log-rank tests were used for each comparison, and the Kaplan–Meier approach estimated median rPFS for each cohort. Additional stratified sensitivity analyses were performed for the ITT population. For rPFS in PTEN-loss and nonloss populations, unstratified HRs and corresponding CIs were used.

Data for randomized patients without progressive disease or death were censored at the earliest date of the last assessments among the components of the rPFS endpoint. If neither of these assessments was performed after randomization, data were censored at the randomization date plus 1 day. PSA response rate and overall response rate (ORR) were estimated with corresponding 90% CIs. This trial is registered with ClinicalTrials.gov, number NCT01485861.

Results

A total of 253 patients were enrolled from July 30, 2013, through December 11, 2014, in the phase II study. Reasons for patients discontinuing ipatasertib/placebo were similar in all cohorts (Fig. 1) with the most common reason being disease progression (placebo, 73.2%; ipatasertib 200 mg, 59.8%; ipatasertib 400 mg, 51.2%). As anticipated for the trial size, some imbalances in patient characteristics were observed; however, overall, the arms were well balanced (Table 1).

A total of 173 rPFS events occurred in the ITT population: 59.5% of patients with ipatasertib 400 mg, 68.6% with ipatasertib 200 mg, and 77.1% with placebo. The median duration of rPFS was 8.18 months (90% CI, 6.67–10.87) for ipatasertib 400 mg and 6.37 months (90% CI, 4.60–8.34) for placebo in molecularly unstratified patients (HR = 0.75; 90% CI, 0.54–1.05; $P = 0.17$; Fig. 2A). With the ipatasertib 200 mg dose level, the median rPFS was 8.31 months (90% CI, 6.44–10.48) with HR = 0.94 (90% CI, 0.69–1.28; $P = 0.75$) relative to placebo (Fig. 2A). Subgroup analyses for rPFS were performed for baseline covariates. Similar trends in rPFS were observed for most subgroups treated with ipatasertib 400 mg compared with placebo; no differences were observed between patients who had or had not received prior enzalutamide, although these

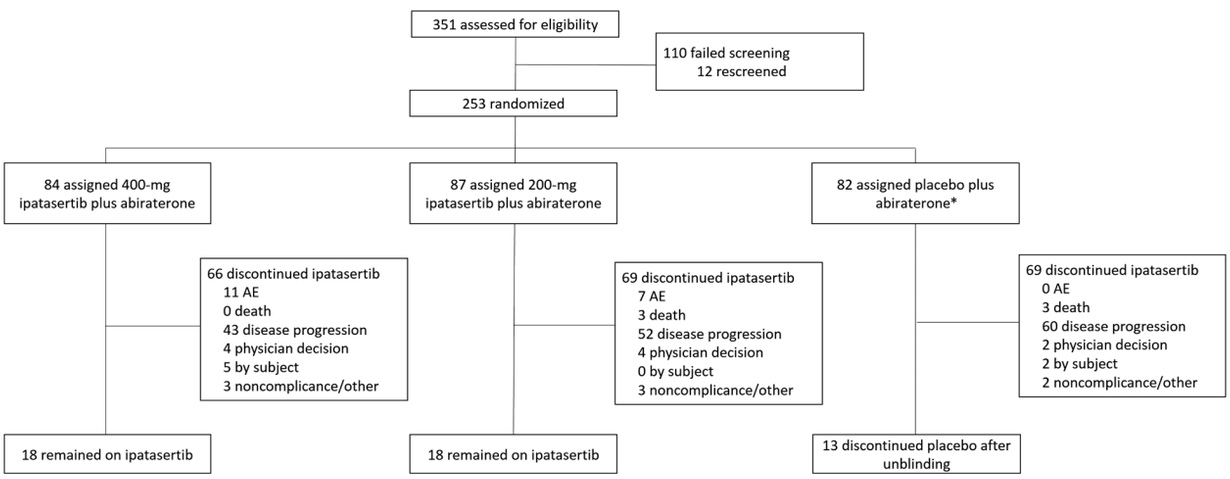

Figure 1.

Trial profile. *One patient was randomized to the placebo group but received 5 consecutive days of ipatasertib and therefore was assigned to ipatasertib 200 mg for safety analysis.

Table 1. Baseline demographics and clinical characteristics

Characteristics	Ipatasertib 400 mg + abiraterone ($n = 84$)	Ipatasertib 200 mg + abiraterone ($n = 86$)	Placebo + abiraterone ($n = 83$)
Stratification factors (%)			
Prior enzalutamide	7 (8)	9 (10)	7 (8)
Progression factor at trial entry, *n* (%)			
PSA + radiographic	42 (50)	42 (49)	47 (57)
PSA only	36 (43)	32 (37)	30 (36)
Radiographic only	6 (7)	12 (14)	6 (7)
Number of prior chemotherapy regimens for metastatic disease			
1	69 (82)	69 (80)	62 (75)
>1	15 (18)	17 (20)	21 (25)
Other factors			
Age, mean (SD), y	66.9 (8.5)	68.8 (7.2)	67.6 (7.8)
Stage IV at diagnosis, *n* (%)	52 (68)	40 (51)	45 (56)
ECOG PS at enrollment, *n* (%)			
0	43 (51)	38 (44)	32 (39)
1	41 (49)	47 (55)	51 (61)
Gleason score, *n* (%)			
≤7	31 (37)	30 (35)	34 (41)
≥8	48 (57)	52 (61)	46 (55)
Sites of metastatic disease, *n* (%)			
Liver	9 (11)	9 (10)	8 (10)
Lung	11 (13)	16 (19)	8 (10)
Bone	77 (93)	80 (93)	78 (94)
Lymph node	42 (51)	43 (50)	40 (48)
PSA, mean (SD), μg/L	379 (1012)	261 (623)	230 (329)
Alkaline phosphatase, IU/mL	198 (220)	217 (301)	251 (326)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; y, years.

results should be interpreted with caution due to small sample sizes (Supplementary Fig. S3).

A total of 104 OS events occurred in the ITT molecularly unstratified population: 35.7% of patients in the ipatasertib 400 mg, 41.9% in the ipatasertib 200 mg, and 45.8% in the placebo cohorts had events. The median duration of OS was 18.92 months (90% CI, 17.12–not estimable) with ipatasertib 400 mg and 15.64 months (90% CI, 13.77–19.42) with placebo (HR = 0.72; 90% CI, 0.47–1.11; $P = 0.22$; Fig. 2B). With the ipatasertib 200 mg dose level, the median OS was 21.5 months (90% CI, 13.27–not estimable) with HR = 0.94 (90% CI, 0.65–1.43; $P = 0.88$) relative to placebo (Fig. 2B).

A total of 168 patients experienced PSA progression: 57.1% with ipatasertib 400 mg, 69.8% with ipatasertib 200 mg, and 72.3% with placebo. The median PSA progression-free time was 5.55 months (90% CI, 4.17–7.39) with ipatasertib 400 mg, and 3.71 months (90% CI, 2.79–4.67) with placebo, in molecularly unstratified patients (HR = 0.70; 90% CI, 0.50–0.97; $P = 0.07$; Fig. 2C). No significant difference in PSA progression-free survival was observed in the ipatasertib 200-mg arm (HR = 0.95; 90% CI, 0.70–1.31; $P = 0.79$) with a median PSA progression-free time of 3.78 months (90% CI, 2.79–5.49; Fig. 2C).

PSA response rates (defined as ≥50% reduction from baseline) were similar across treatment arms: 36.9% in the ipatasertib 400 mg arm (84 total evaluable patients), 33.7% in the ipatasertib 200 mg arm (86 total evaluable patients), and 34.9% in the placebo arms (83 total evaluable patients; Supplementary Table S4); of note, in patients who previously received enzalutamide, PSA response rates were 42.8% (7 total evaluable patients), 33.3% (9 total evaluable patients), and 0% (7 total evaluable patients), respectively.

RECIST ORRs were 32.4% with ipatasertib 400 mg (37 total evaluable patients), 23.1% with ipatasertib 200 mg (39 total evaluable patients), and 22.9% with placebo (35 total evaluable patients; Supplementary Table S5). Circulating tumor cell conversion rates (defined by decline to <5 cells/7.5 mL postbaseline among patients with ≥5 cells/7.5 mL at baseline) were 43.9% in the ipatasertib 400 mg arm (41 total evaluable patients), 46.8% in the ipatasertib 200 mg arm (47 total evaluable patients), and 41.7% in the placebo arm (48 total evaluable patients; Supplementary Table S6).

rPFS in patients with PTEN-loss tumors was a coprimary endpoint. Patients with PTEN-loss tumors, identified by the predefined The Institute of Cancer Research PTEN IHC assay (ICR IHC; which employed the CST138G6 PTEN antibody), were 43.0% (71/165). Patients with PTEN-loss tumors who received ipatasertib 400 mg had an improved rPFS outcome (HR = 0.39; 90% CI, 0.22–0.70) compared with patients whose tumors had no PTEN loss (HR = 0.84; 90% CI, 0.51–1.37; Fig. 3, Table 2A). The association between tumor PTEN loss and rPFS was less pronounced in the ipatasertib 200 mg arm (HR = 0.46; 90% CI, 0.25–0.83 and HR = 1.13; 90% CI, 0.69–1.85, respectively). Applying the ICR IHC PTEN-loss assay used in the primary analysis as the reference standard, the concordance between the assays was 80% for Ventana IHC, 79% for FoundationOne NGS, and 69% for FISH (Supplementary Fig. S1). The prevalence of PTEN loss was 56.2% (82/146) by the Ventana IHC assay (using SP218 PTEN antibody), 43.8% (39/89) by the FoundationOne NGS assay, and 36.2% (71/196) by the FISH assay. The lower prevalence of PTEN loss observed using the DNA-based platforms was anticipated, given that PTEN loss at the protein level can occur through genetic and nongenetic mechanisms (26). No association was found between tumor PTEN loss and RECIST ORR, circulating tumor cell conversion rates, OS or PSA response (Supplementary Tables S5–S7; Table 2B) in this advanced patient population.

Associations were evaluated between genes of many different pathways and PFS and ORR in the NGS-evaluable population ($n = 89$) and a segment of the NGS-evaluable population with PTEN nonloss by the ICR IHC assay ($n = 39$). No associations were observed between individual gene alterations or alterations in the different pathways examined with rPFS or ORR (independent of study treatment) in either patient population (Supplementary Fig. S4). However, given the limited sample sizes of these populations caution should be used in this observation.

AEs were more common with ipatasertib versus placebo and were generally consistent with the PI3K–Akt–mTOR pathway inhibitor class and included diarrhea, nausea, vomiting, asthenia, rash (grouped term), decreased appetite, and hyperglycemia (Table 3, Supplementary Table S8). These AEs were dose dependent, manageable, and reversible, and did not impact on treatment dose intensity [mean (SD) ipatasertib 400 mg: 87.22 (16.68); ipatasertib 200 mg: 96.34 (17.62); placebo: 96.85 (9.63)]. Fifty-four patients (64.3%), 44 patients (50.6%), and 29 patients (35.4%) experienced a grade ≥3 AE in the ipatasertib 400 mg, ipatasertib 200 mg, and placebo cohorts, respectively. The most common grade ≥3 AEs in the ipatasertib cohorts were diarrhea, hyperglycemia, asthenia, rash, and

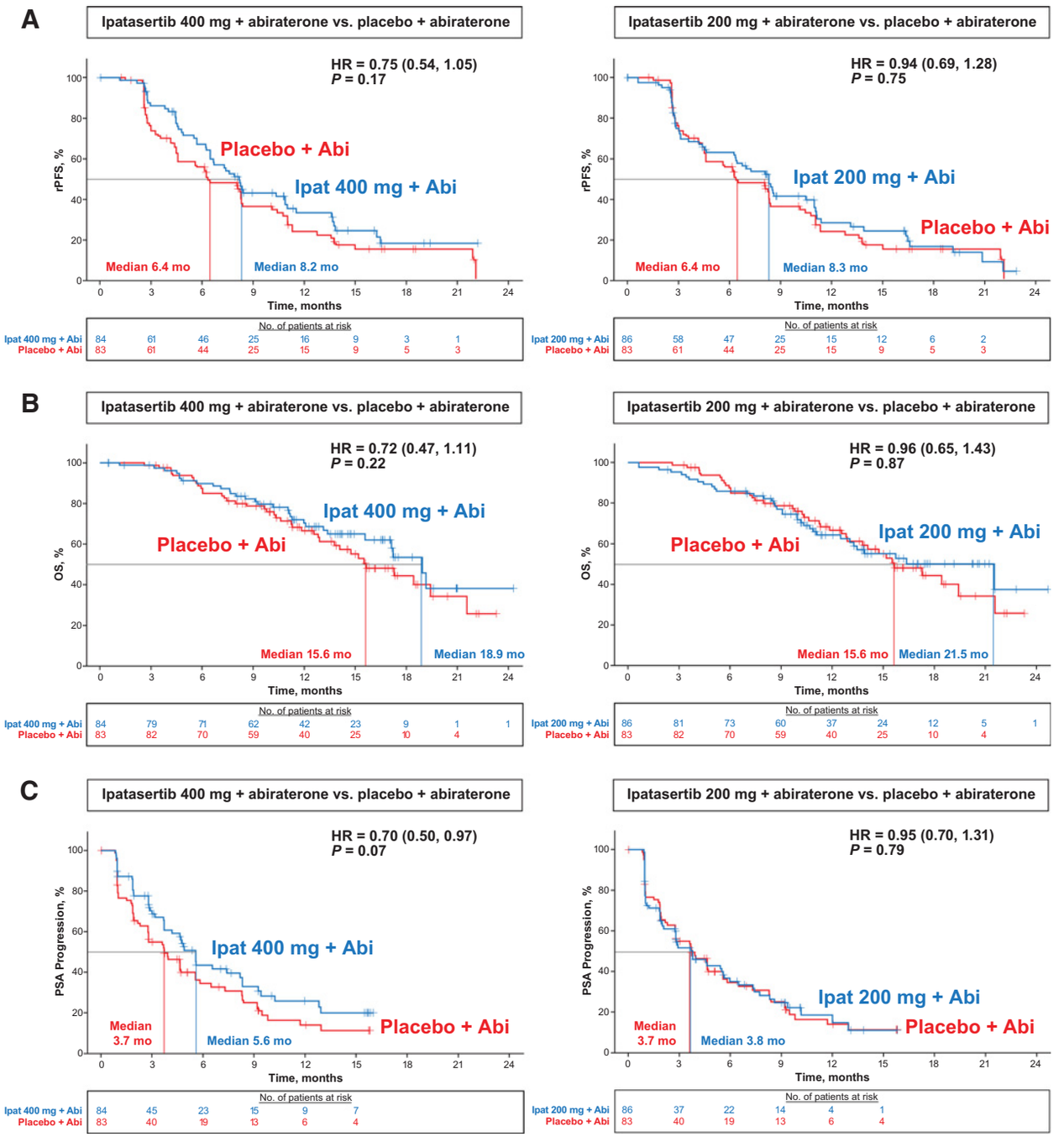

Figure 2.

Overall population: rPFS (**A**), OS (**B**), and time to PSA progression (**C**) Kaplan–Meier plots. An rPFS event is defined by RECIST progressive disease of soft tissue, bone scan progressive disease, or death within 30 days of last dose. PSA progression is defined as a ≥25% relative increase and an absolute increase of ≥2 ng/mL above the baseline or nadir that is confirmed by a second consecutive value ≥3 weeks later. All HRs are stratified with 90% CIs. Abi, abiraterone; Ipat, ipatasertib; mo, months.

pneumonia. Serious AEs (SAE) were higher in the ipatasertib cohorts (400 mg: 42.9%; 200 mg: 40.2%) versus placebo (18.3%). The most common SAE was pneumonia (ipatasertib 400 mg: 3.6%; ipatasertib 200 mg: 4.6%; placebo: 0). Other SAEs occurring in ≥2 patients in any arm included hematuria, urinary retention, pyrexia, anemia, urinary tract infections, sepsis, septic shock, diarrhea, rash, and pain. AEs that led to discontinuation occurred in 10 (11.9%) and 7 (8.0%) patients

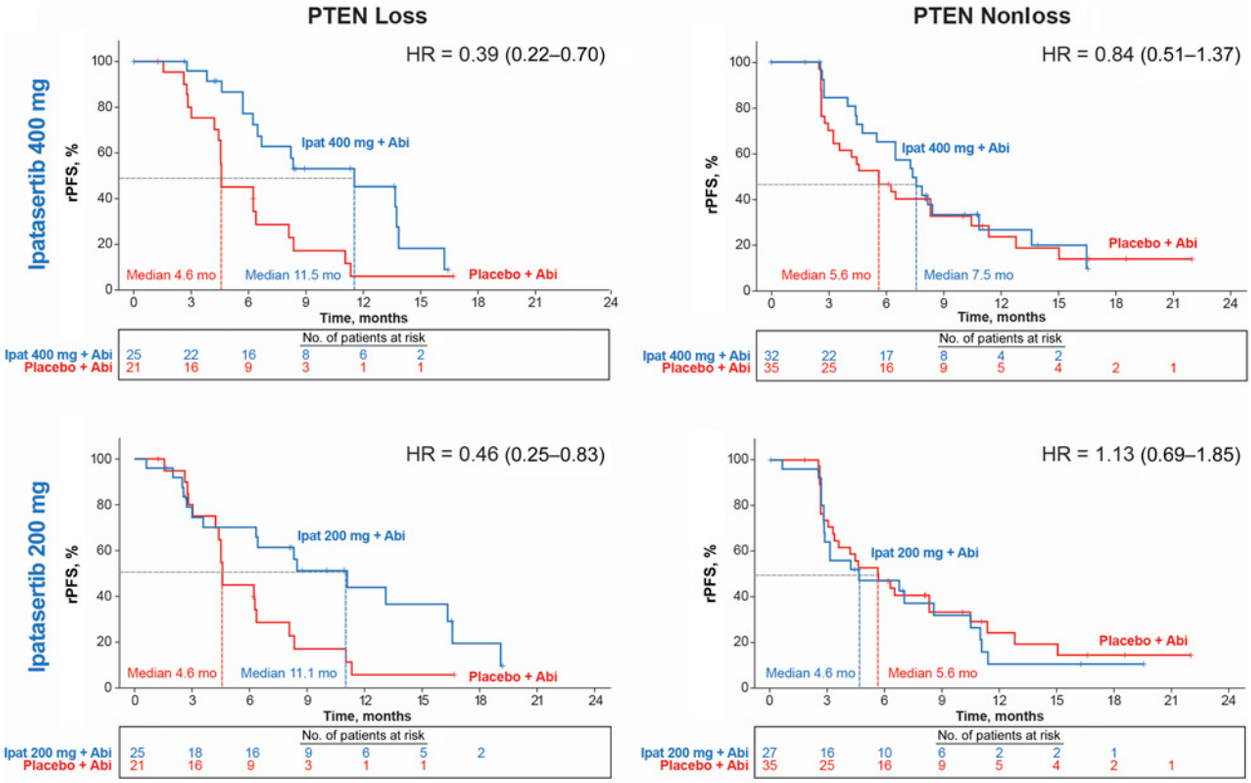

Figure 3.
PTEN loss and nonloss subpopulations (ICR IHC assay) for rPFS. Abi, abiraterone; Ipat, ipatasertib; mo, months.

in the ipatasertib 400 and 200 mg cohorts, respectively; no discontinuations due to AEs occurred with placebo. The most common AEs leading to discontinuation in the ipatasertib 400 mg arm were diarrhea (2/84 = 2.4%) and hyperglycemia (2/84 = 2.4%).

AEs leading to death were balanced among the three cohorts without any trend in causes of death. Of the 253 randomized patients, 104 (41.1%) died during survival follow-up including 30 patients (35.7%) receiving ipatasertib 400 mg, 36 (41.9%) receiving ipatasertib 200 mg, and 38 (45.8%) receiving placebo. Most deaths were due to disease progression [82/104 (78.8%)]. Of the 14 deaths that were due to AEs [14/253 (5.5%); 4.8% with ipatasertib 400 mg vs. 6.9% with ipatasertib 200 mg vs. 4.9% with placebo], five events were considered related to prostate cancer or prostate cancer progression. Of the remaining nine events, two occurred in the ipatasertib 400 mg arm (bradycardia and nervous system disorder), four occurred in the ipatasertib 200 mg arm [sepsis (2), aortic aneurysm rupture, and death not specified], and three occurred in the placebo arm (cerebral hemorrhage, acute heart failure, and death not specified). No deaths were related to study treatment.

Discussion

In this phase Ib/II trial that assessed the combination of ipatasertib with abiraterone acetate and prednisone in patients with mCRPC, the superiority of this combination over abiraterone alone was supported by a delayed rPFS, particularly in patients with PTEN-loss tumors treated with the higher ipatasertib dose. A dose-dependent numerical improvement was observed in OS and time to PSA progression in the ITT population, although neither was statistically significant in this exploratory randomized phase II study. These results support the hypothesis that combined PI3K–Akt–mTOR and AR blockade may be advantageous to patients suffering from PTEN-loss mCRPC.

PTEN loss is usually an early (truncal) event in prostate carcinogenesis resulting in little intratumor heterogeneity (12, 27). PTEN loss can be due to gene deletions, rearrangements including intronic rearrangements, and nongenomic aberrations such as methylation, microRNA, and pseudogene expression. Therefore, genomic analyses of the PTEN gene by FISH or NGS may underestimate PTEN loss. However, some genomic inactivating aberrations may still generate a detectable, but nonfunctioning, PTEN protein. DNA-based diagnostic analyses and PTEN protein levels were concordant, and superior antitumor activity for a combined use of ipatasertib 400 mg and abiraterone was demonstrated in mCRPC with PTEN loss detected with all the four PTEN assays. Our findings may underestimate the benefits of this combination because a significant proportion (15%–20%) of PTEN nonloss mCRPC can also have AKT hyperactivation through deleterious aberrations of other genes including

Table 2. PTEN loss and nonloss subpopulations by the four PTEN diagnostic assays tested for (**A**) rPFS and (**B**) OS

A

	Primary analysis		Exploratory analysis					
	ICR IHC		Ventana IHC		FISH		NGS	
	PTEN loss	PTEN nonloss	PTEN loss	PTEN nonloss	PTEN loss	PTEN nonloss	PTEN loss	PTEN nonloss
400 mg ipatasertib + abiraterone								
Patients, *n*	25	32	26	22	28	38	15	21
Patients with events, *n* (%)	15 (60.0)	20 (62.5)	16 (61.5)	14 (63.6)	15 (53.6)	25 (65.8)	7 (46.7)	14 (66.7)
rPFS, median months								
Ipatasertib	11.5	7.5	11.0	7.5	13.7	6.5	13.8	7.4
Placebo	4.6	5.6	4.6	5.7	6.5	5.6	6.2	4.5
rPFS HR	0.39	0.84	0.50	0.74	0.67	0.77	0.24	0.52
90% CI	0.22–0.70	0.51–1.37	0.29–0.87	0.41–1.32	0.36–1.24	0.50–1.20	0.10–0.60	0.25–1.02
200 mg ipatasertib + abiraterone								
Patients, *n*	25	27	31	16	22	47	13	16
Patients with events, *n* (%)	16 (64.0)	20 (74.1)	21 (67.7)	12 (75.0)	15 (68.2)	31 (66.0)	9 (69.2)	10 (62.5)
rPFS, median months								
Ipatasertib	11.1	4.6	8.5	6.4	10.5	6.7	8.3	8.6
Placebo	4.6	5.6	4.6	5.7	6.5	5.6	6.2	4.5
rPFS HR	0.46	1.13	0.66	1.04	0.87	0.74	0.55	0.53
90% CI	0.25–0.83	0.69–1.85	0.39–1.11	0.57–1.92	0.47–1.61	0.49–1.13	0.24–1.27	0.25–1.13
Placebo + abiraterone								
Patients, *n*	21	35	25	26	21	40	11	13
Patients with events, *n* (%)	18 (85.7)	26 (74.3)	20 (80.0)	19 (73.1)	14 (66.7)	31 (77.5)	10 (90.9)	11 (84.6)

B

	Primary analysis		Exploratory analysis					
	ICR IHC		Ventana IHC		FISH		NGS	
	PTEN loss	PTEN nonloss	PTEN loss	PTEN nonloss	PTEN loss	PTEN nonloss	PTEN loss	PTEN nonloss
Ipatasertib 400 mg + abiraterone								
Patients, *n*	25	32	26	22	28	38	15	21
Patients with events, *n* (%)	9 (36.0)	9 (28.1)	10 (38.5)	5 (22.7)	9 (32.1)	15 (39.5)	5 (33.3)	7 (33.3)
OS, median months								
Ipatasertib	19.15	17.22	19.15	15.57	19.15	17.22	NE	19.15
Placebo	14.75	13.77	12.81	13.77	18.43	11.83	14.75	13.77
OS HR	0.62	0.56	0.65	0.54	0.89	0.62	0.44	0.54
90% CI	(0.29–1.33)	(0.28–1.13)	(0.33–1.28)	(0.22–1.29)	(0.40–1.99)	(0.35–1.08)	(0.15–1.29)	(0.21–1.40)
Ipatasertib 200 mg + abiraterone								
Patients, *n*	25	27	31	16	22	47	13	16
Patients with events, *n* (%)	8 (32.0)	13 (48.1)	13 (41.9)	7 (43.8)	10 (45.5)	20 (42.6)	6 (46.2)	7 (43.8)
OS, median months								
Ipatasertib	NE	10.68	NE	13.44	13.44	16.36	NE	13.44
Placebo	14.75	13.77	12.81	13.77	18.43	11.83	14.75	13.77
OS HR	0.64	1.19	0.83	0.98	1.7	0.72	1.13	0.79
90% CI	(0.30–1.37)	(0.64–2.22)	(0.44–1.56)	(0.45–2.14)	(0.77–3.73)	(0.43–1.21)	(0.43–2.93)	(0.31–1.97)
Placebo + abiraterone								
Patients, *n*	21	35	25	26	21	40	11	13
Patients with events, *n* (%)	12 (57.1)	16 (45.7)	14 (56.0)	13 (50.0)	8 (38.1)	22 (55.0)	6 (54.5)	6 (46.2)

Abbreviation: NE, not estimable.

PIK3CA, *PIK3CB*, *AKT1*, *PIK3R1*, and *SPOP*. PTEN loss is associated with poor prognosis in mCRPC and correlates with a higher Gleason score, visceral disease, and more advanced stage at diagnosis (12, 14–17, 25, 28). Our data indicate that PTEN loss in tumors may be a predictive biomarker for this patient population, identifying cases benefiting from treatment with combined ipatasertib and abiraterone. Validation of these data are now required through phase III evaluation.

The safety results were consistent with previous clinical experience of ipatasertib, which was generally well tolerated. Common AEs in the ipatasertib combination regimen included gastrointestinal toxicity, asthenia/fatigue, decreased appetite, hyperglycemia, and rash. A small numerical increase in infections was identified, which has been previously reported for PI3K–Akt–mTOR pathway inhibitors (29). These AEs were largely grade 1/2, manageable, reversible, and did not impact the dose intensity of either drug.

The combination of ipatasertib with abiraterone acetate and prednisone showed trends toward improved rPFS in patients with mCRPC in this randomized phase II trial; however, in those with PTEN-loss tumors, measures of antitumor activity supported the superiority of the ipatasertib combination arms in patients with tumors with PTEN loss. As PTEN is one of the most important tumor suppressors in cancer, these data may also benefit patients with other PTEN-loss cancers.

Disclosure of Potential Conflicts of Interest

U. De Giorgi is a consultant/advisory board member for Astellas, Ipsen, Janssen, Bristol-Myers Squibb, Pfizer, Pierre-Fabre, and Sanofi. S. Bracarda is a consultant/advisory board member for and reports other remuneration from

Table 3. AEs (≥25% in any cohort) by preferred term

AE, *n* (%)	Ipatasertib 400 mg + abiraterone (*n* = 84)	Ipatasertib 200 mg + abiraterone (*n* = 87)	Placebo + abiraterone (*n* = 82)
Total patients with AEs	83 (98.8)	82 (94.3)	76 (92.7)
Total patients with grade ≥3 AEs	54 (64.3)	44 (50.6)	29 (35.4)
Total patients with SAEs	36 (42.9)	35 (40.2)	15 (18.3)
Deaths	30 (35.7)	36 (41.4)	38 (46.3)
Due to AEs	4 (4.8)	6 (6.9)	4 (4.9)
Diarrhea, any grade	64 (76.2)	39 (44.8)	21 (25.6)
Grade 3	10 (11.9)	2 (2.3)	1 (1.2)
Grade 4	0	0	0
SAE	2 (2.4)	1 (1.1)	0
Asthenia, any grade	23 (27.4)	17 (19.5)	13 (15.9)
Grade 3	5 (6.0)	1 (1.1)	1 (1.2)
Grade 4	0	0	0
SAE	1 (1.2)	0	0
Fatigue, any grade	21 (25.0)	22 (25.3)	24 (29.3)
Grade 3	3 (3.6)	3 (3.4)	2 (2.4)
Grade 4	0	0	0
SAE	0	0	1 (1.2)
Decreased appetite, any grade	21 (25.0)	19 (21.8)	12 (14.6)
Grade 3	1 (1.2)	0	0
Grade 4	0	0	0
SAE	0	0	0
Back pain, any grade	15 (17.9)	18 (20.7)	21 (25.6)
Grade 3	1 (1.2)	3 (3.4)	1 (1.2)
Grade 4	0	0	0
SAE	1 (1.2)	1 (1.1)	1 (1.2)
Nausea, any grade	44 (52.4)	30 (34.5)	20 (24.4)
Grade 3	2 (2.4)	0	0
Grade 4	0	0	0
SAE	0	0	1 (1.2)
Vomiting, any grade	26 (31.0)	24 (27.6)	12 (14.6)
Grade 3	0	1 (1.1)	0
Grade 4	0	0	0
SAE	0	0	1 (1.2)

Abbreviation: SAE, serious AE.

Astellas and Janssen. W.Y. Chan holds ownership interest (including patents) in Genentech. S. Gendreau is an employee of and holds ownership interest (including patents) in Genentech/Roche. D.J. Maslyar is an employee of and holds ownership interest (including patents) in Genentech/Roche. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.S. de Bono, U. De Giorgi, C. Massard, G.D. Radavoi, P.H. Patel, V. Jinga

Development of methodology: J.S. de Bono, D.N. Rodrigues, C. Massard, G.D. Radavoi, N. Xu, R. Riisnaes, P.H. Patel, V. Jinga

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.S. de Bono, U. De Giorgi, D.N. Rodrigues, C. Massard, S. Bracarda, A. Font, J.A.A. Arija, K.C. Shih, G.D. Radavoi, N. Xu, R. Riisnaes, V. Jinga

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.S. de Bono, U. De Giorgi, D.N. Rodrigues, C. Massard, S. Bracarda, J.A.A. Arija, G.D. Radavoi, N. Xu, W.Y. Chan, H. Ma, S. Gendreau, P.H. Patel, D.J. Maslyar, V. Jinga

Writing, review, and/or revision of the manuscript: J.S. de Bono, U. De Giorgi, D.N. Rodrigues, C. Massard, S. Bracarda, J.A.A. Arija, G.D. Radavoi, N. Xu, W.Y. Chan, H. Ma, S. Gendreau, R. Riisnaes, P.H. Patel, D.J. Maslyar, V. Jinga

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.S. de Bono, G.D. Radavoi, S. Gendreau, D.J. Maslyar, V. Jinga

Study supervision: J.S. de Bono, U. De Giorgi, C. Massard, G.D. Radavoi, W.Y. Chan, H. Ma, P. Patel, D.J. Maslyar, V. Jinga

Other (PTEN assay development): J.S. de Bono

Other (investigator of the trial): J.A.A. Arija

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