Original Study

Safety Profile of Ipatasertib Plus Abiraterone vs Placebo Plus Abiraterone in Metastatic Castration-resistant Prostate Cancer

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Abstract

In the phase III IPATential150 trial, ipatasertib-abiraterone significantly improved clinical outcomes vs. placebo-abiraterone for metastatic castration-resistant prostate cancer with PTEN-loss. While ipatasertib-abiraterone was overall tolerable, ipatasertib was associated with increased grade 3/4 adverse events and treatment discontinuation, and rates of diarrhea, hyperglycemia, rash and transaminase were increased (safety population: n = 1097). These adverse events would likely be lessened with prophylactic measures.

Purpose: Adding ipatasertib to abiraterone and prednisone/prednisolone significantly improved radiographic progression-free survival for patients with metastatic castration-resistant prostate cancer (mCRPC) with PTEN-loss tumours by immunohistochemistry in the IPATential150 trial (NCT03072238). Here we characterise the safety of these agents in subpopulations and assess manageability of key adverse events (AEs). **Materials and methods:** In this randomised, double-blind, phase 3 trial, patients with previously untreated asymptomatic or mildly symptomatic mCRPC were randomised 1:1 to receive ipatasertib-abiraterone or placebo-abiraterone (all with prednisone/prednisolone). AEs were analysed, focusing on key AEs of diarrhoea, hyperglycaemia, rash and transaminase increased. **Results:** 1097 patients received study medication and were assessed for safety (47% with PTEN-loss tumours by immunohistochemistry and 20% were Asian). Ipatasertib was associated with increased Grade 3/4 AEs and AEs leading to treatment discontinuation vs placebo. The rate of discontinuation of ipatasertib was 18% in patients with PTEN-loss and 21% overall. The frequencies of all-grade, Grade 3/4 and serious AEs were similar between the PTEN-loss and overall populations. Diarrhoea, hyperglycaemia, rash and transaminase elevation were more frequent in ipatasertib-treated patients, appearing rapidly after treatment initiation (median onset: 8-43 days for ipatasertib arm and 56-104 days for placebo). The ipatasertib discontinuation rate was 32% and 18% in Asian and non-Asian patients, respectively, despite similar baseline characteristics and Grade 3/4 AE frequencies between groups. **Conclusions:** Ipatasertib plus abiraterone had an overall tolerable safety profile consistent with known toxicities. More AEs leading to drug discontinuation were observed with ipatasertib than placebo, but incidence would likely be lessened with prophylactic measures.

Clinical Genitourinary Cancer, Vol. 21, No. 2, 230–237 © 2023 The Authors. Published by Elsevier Inc.

Keywords: AKT inhibition, IPATential150, Adverse events, mCRPC, Phase 3

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Submitted: Nov 16, 2022; Accepted: Jan 2, 2023; Epub: 7 January 2023

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1558-7673/$ - see front matter
https://doi.org/10.1016/j.clgc.2023.01.001

Introduction

AKT is a serine-threonine kinase that is part of the phosphatidylinositol-3-kinase (PI3K)/AKT pathway associated with tumor development and progression[1]; targeting this pathway is a proven anticancer strategy.[2,3] PTEN, a PI3K/AKT pathway regulator, is functionally lost in 40% to 50% of metastatic castration-resistant prostate cancer (mCRPC) and is associated with worse clinical outcomes.[4-6] PI3K/AKT pathway inhibitors have been approved to treat multiple cancer types; however, no AKT-specific targeted inhibitors have yet been approved as cancer therapy.[2,7]

Ipatasertib is a pan-AKT inhibitor with promising efficacy in mCRPC.[8,9] In a phase II study, the addition of ipatasertib to abiraterone resulted in prolonged radiographic progression-free survival (PFS) in men with mCRPC, with greater impact observed in men with PTEN-loss vs. PTEN-intact tumors as assessed by immunohistochemistry (IHC).[8] In IPATential150, the addition of ipatasertib to abiraterone resulted in a significant risk reduction of radiological disease progression or death vs. placebo plus abiraterone in patients with PTEN-loss tumors by IHC (HR, 0.77; 95% CI: 0.61, 0.98; $P = .034$), but not in the intention-to-treat population (HR, 0.84; 95% CI: 0.71, 0.99).[9] Risk was reduced in patients with PTEN loss as assessed by next-generation sequencing (HR, 0.65; 95% CI: 0.45, 0.95).

The safety profile associated with AKT inhibitors is an important consideration. Ipatasertib plus abiraterone demonstrated a safety profile consistent with each agent's known toxicities, with key adverse events (AEs) identified as associated with ipatasertib being hyperglycemia, diarrhea, rash and transaminase elevation.[8-14] In clinical studies evaluating ipatasertib in patients with breast cancer, prophylactic measures have been enacted to reduce the risk of onset and severity of these AEs.[11-14]

Overall, Asian populations have a different genomic profile than Western populations, including a lower prevalence of PTEN loss and a higher prevalence of *BRCA2* alteration in Asian men with mCRPC.[15,16] Due to variability between Asian and non-Asian patients with prostate cancer in response and tolerability to treatment,[17-19] it is clinically important to assess comparative toxicities between Asian and non-Asian populations. Further, there are limited data on AKT inhibition-induced toxicities between Asians and non-Asians.

Here we further characterize AEs associated with ipatasertib and abiraterone and assess the manageability of AEs in patients with previously untreated mCRPC from IPATential150.

Methods

Study Design and Patients

The design of the randomized, double-blind IPATential150 trial has been reported (Supplementary Figure 1).[9] Briefly, patients with previously untreated asymptomatic/mildly symptomatic mCRPC were randomized 1:1 to receive ipatasertib-abiraterone or placebo-abiraterone. Patients in the experimental arm received ipatasertib (400 mg once daily), and patients in the control arm received placebo. All patients received abiraterone (1000 mg once daily) plus prednisone/prednisolone (5 mg twice daily). Coprimary end points were investigator-assessed radiographic PFS assessed in the intention-to-treat population and investigator-assessed radiographic PFS in patients with PTEN-loss tumors by IHC. PTEN loss was defined as a minimum of 50% of the specimen's tumour area with no detectable PTEN staining by VENTANA IHC (SP218 antibody) assay. The trial was conducted according to Good Clinical Practice guidelines of the International Conference on Harmonisation and the principles of the Declaration of Helsinki. All patients provided written informed consent. An independent data-monitoring committee periodically reviewed safety data until primary analysis. The study was approved by independent review boards or ethics committees at all study sites.

Safety Assessments

The overall safety-evaluable (SE) population was all randomized patients who received any ipatasertib, placebo or abiraterone. Patients were assessed for AEs at each contact with investigators. The incidence, duration, nature and severity of AEs were assessed, with severity determined using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 and coded using the standard Medical Dictionary for Regulatory Activities preferred terms. Investigators assessed the seriousness, severity and causality. Severe liver injury by Hy's law and selected AEs defined by the authors were assessed (Supplemental Methods). Key AEs of diarrhea, hyperglycemia, rash, and transaminase increased were selected for detailed analysis. Baseline glycated hemoglobin A1c (HbA1c) of <5.7% was considered nondiabetic, ≥5.7% to <6.5% prediabetic and ≥6.5% diabetic. Race was self-identified.

Glucose Levels

Continuous glucose measurements were obtained in a separate cohort of patients from the A.MARTIN trial[8] who received treatment in 4 periods as follows: (1) ipatasertib monotherapy, AM dosing; (2) ipatasertib+prednisone/prednisolone, AM dosing; (3) ipatasertib+abiraterone+prednisone/prednisolone, AM dosing; (4) ipatasertib+abiraterone+prednisone/prednisolone, PM dosing (Supplementary Figure 2). AM dosing was ≥1 hour prior to first meal, and PM dosing was ≥2 hours after last meal with no overnight eating. Blood glucose levels were measured using blinded continuous glucose monitoring (CGM) via the Dexcom G6 CGM device. Average and peak glucose were assessed.

Global Health Status (GHS) Statistical Analysis

Statistical details have been described.[9] Safety was clinically assessed by review of all relevant parameters, including AEs, vital signs and laboratory values. Multiple occurrences of the same event in one individual were counted once at the highest grade.

Results

Patients and Trial Interventions

From June 30, 2017, to January 17, 2019, 1101 men with mCRPC were enrolled and 554 were assigned to placebo-abiraterone and 547 to ipatasertib-abiraterone (Supplementary Figure 3).[9] The clinical cutoff date was March 16, 2020. Among

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Table 1 Safety Summary in the Overall SE Population[a] and the PTEN-loss-by-IHC Population

AEs, *n* (%)	Overall SE Population (N = 1097)		PTEN-Loss by IHC SE Population (n = 520)	
	Pbo + Abi (*n*=546)	Ipat + Abi (*n*=551)	Pbo + Abi (*n*=257)	Ipat + Abi (*n*=263)
All-grade	519 (95)	548 (99)	243 (95)	262 (99.6)
All-grade selected[a]	406 (74)	537 (97)	185 (72)	253 (96)
Grade 3/4	193 (35)	362 (66)	91 (35)	170 (65)
Grade 3/4 selected[a]	75 (14)	294 (53)	37 (14)	133 (51)
Serious	124 (23)	218 (40)	64 (25)	102 (39)
Grade 5	20 (4)	24 (4)	9 (4)	9 (3)
Leading to discontinuation of pbo/ipat	28 (5)	116 (21)	13 (5)	48 (18)
Leading to dose reduction of pbo/ipat	34 (6)	220 (40)	15 (6)	104 (40)
Leading to dose interruption of pbo/ipat	125 (23)	319 (58)	52 (20)	143 (54)
Leading to discontinuation of abi	22 (4)	47 (9)	12 (5)	21 (8)
Leading to dose reduction of abi	27 (5)	64 (12)	13 (5)	33 (13)
Leading to dose interruption of abi	101 (18)	229 (42)	42 (16)	104 (40)

Abbreviations: Abi = abiraterone; AE = adverse event; IHC = immunohistochemistry; ipat = ipatasertib; pbo = placebo; SE = safety evaluable.
[a] Selected AEs were the grouped terms of asthenia, colitis, diarrhea, erythema multiforme, anaemia, hepatotoxicity, hyperglycemia, hyperlipidaemia, nausea, neutropenia, oral mucositis, peripheral neuropathy, pneumonia, pneumonitis, rash, thrombocytopenia, transaminase increased and vomiting.

enrolled patients, 1097 received ≥1 dose of trial treatment and were included in the safety analysis, 546 in the placebo-abiraterone and 551 in the ipatasertib-abiraterone SE populations. Five patients in the placebo-abiraterone arm received ≥1 dose of ipatasertib and were included in the ipatasertib-abiraterone SE population. Baseline patient demographics and disease characteristics were largely balanced between arms (Supplementary Figure 4A).

Safety Summary

As previously reported, abiraterone exposure was comparable between arms, whilst ipatasertib exposure was numerically lower than placebo exposure. Exposure to placebo, ipatasertib and abiraterone was comparable between patients with and without PTEN loss by IHC.[9] Ipatasertib-abiraterone had a similar safety profile in the overall SE population and in the PTEN-loss-by-IHC SE population (Table 1). AEs leading to discontinuation of placebo occurred in 5% (28/546) of patients, whilst AEs leading to discontinuation of ipatasertib occurred in 21% (116/551); in the PTEN-loss-by-IHC SE population, the rates were 5% (13/257) and 18% (48/263), respectively. A similar trend was observed with dose reductions and interruptions. Given the similarity of the safety profiles in the 2 populations, further analyses are shown only in the overall SE population.

Dose Reduction or Discontinuation of Treatment

In the safety population, the median treatment exposure of placebo was 14.0 months overall ($n = 546$) and 14.2 months in patients who did not discontinue placebo due to an AE ($n = 518$). The median treatment exposure to ipatasertib was 11.1 months overall ($n = 551$) and 14.0 months in patients who did not discontinue ipatasertib due to an AE ($n = 435$).

In patients who experienced an AE leading to discontinuation of ipatasertib ($n = 116$), the median time to discontinuation of ipatasertib was 1.76 months (95% CI: 1.41, 2.40) (Figure 1). Among 250 patients in the ipatasertib-abiraterone arm who had a dose reduction from 400 mg, the median time to first dose reduction was 1.84 months (95% CI: 1.48, 1.91); 53% (132/250) had a single dose reduction to 300 mg, 4% (9/250) to 200 mg, and 44% (109/250) had dose reductions to both 300 and 200 mg.

Key Adverse Events

The most frequent key AE was diarrhea, occurring in 23% (123/546) of patients receiving placebo-abiraterone and 80% (440/551) receiving ipatasertib-abiraterone (Table 3).

Hyperglycemia is an identified on-target effect of ipatasertib,[20] and 18% (100/546) of patients receiving placebo-abiraterone experienced any-grade hyperglycemia vs. 48% (264/551) receiving ipatasertib-abiraterone (Table 2). One patient receiving ipatasertib-abiraterone died from complications of hyperglycemia (related to treatment), and the study was amended to add additional monitoring in the first week and during all clinical visits to ensure fasting glucose levels were rigorously reviewed prior to dosing and discharge from the clinic. The glucose level assessment cohort included 24 patients. Among patients with available data, peak and average glucose levels were lower for patients who received evening dosing (Figure 3A and B).

Overall, 11% (62/546) of patients receiving placebo-abiraterone and 41% (228/551) receiving ipatasertib-abiraterone experienced rash (Table 3). Erythema multiforme occurred in <1% (any grade, 1/546; grade 3/4, 0; grade 5, 0) of patients receiving placebo-abiraterone and 1% (any grade, 6/551; grade 3/4, 5; grade 5, 0) receiving ipatasertib-abiraterone.

Incidences of transaminase increased were 12% (68/546) in the placebo-abiraterone arm and 24% (131/551) in the ipatasertib-abiraterone arm (Table 2). No cases met the criteria for Hy's law indicative of severe liver injury.

Amongst the key AEs, grade 3/4 AEs, serious AEs and AEs leading to discontinuation of placebo or ipatasertib were more

Figure 1 Time to discontinuation of ipatasertib in patients who discontinued ipatasertib due to an adverse event.

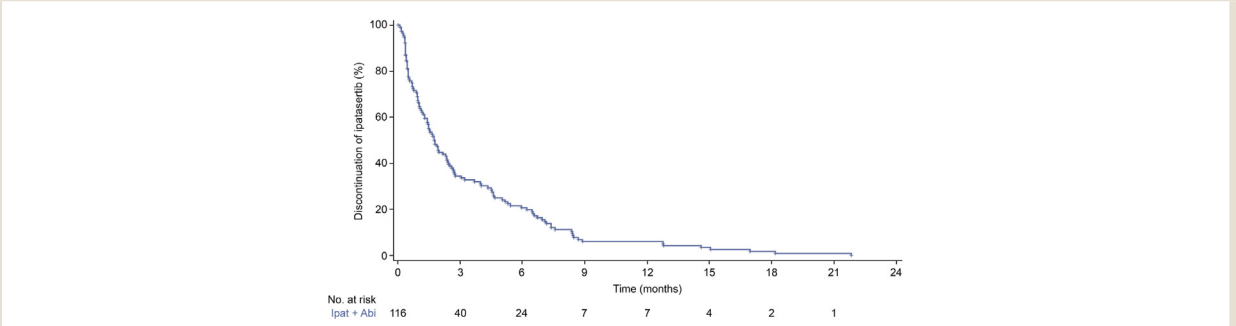


Table 2 Frequency of Key AEs

	Diarrhea		Hyperglycemia		Rash		Transaminase Increased	
	Pbo + Abi *n*=546	Ipat + Abi *n*=551	Pbo + Abi *n*=546	Ipat + Abi *n*=551	Pbo + Abi *n*=546	Ipat + Abi *n*=551	Pbo + Abi *n*=546	Ipat + Abi *n*=551
Any AE, *n* (%)	123 (23)	440 (80)	100 (18)	264 (48)	61 (11)	228 (41)	68 (12)	131 (24)
Grade 3/4	4 (1)	57 (10)	7 (1)	77 (14)	1 (<1)	90 (16)	27 (5)	67 (12)
Serious	0	12 (2)	1 (<1)	26 (5)	0	25 (5)	1 (<1)	8 (1)
Grade 5	0	0	0	1 (<1)[a]	0	0	0	0
Leading to pbo/ipat discontinuation	0	23 (4)	2 (<1)	19 (3)	1 (<1)	31 (6)	5 (1)	10 (2)
Leading to abi discontinuation	0	2 (<1)	0	1 (<1)	0	6 (1)	5 (1)	8 (1)

Abbreviations: Abi = abiraterone; AE = adverse event; Ipat = ipatasertib; Pbo = placebo.
[a] Treatment for hyperglycemia for this patient was delayed, as patient had left the clinic prior to laboratory test availability.

frequent in patients who received ipatasertib vs. placebo. Deaths due to AEs were infrequent, with none due to diarrhea, rash or transaminase increased (Table 2). Rates of grade 3/4 AEs were not impacted by baseline patient demographics or disease characteristics, except for increased hyperglycemia in patients with diabetes (Supplementary Figure 4B). Concomitant medications are in Supplementary Table I.

Time to Onset, Duration, Resolution and Recurrence of Key AEs

The median onset of diarrhea, hyperglycemia, rash and transaminase increased occurred very soon after treatment initiation, and median durations were generally short but with wide ranges (Figure 2). Most resolved without recurrence.

Safety Summary in Asian Patients

In the overall safety population, 218 patients (20%) were Asian, 109 in each arm (Table 3). In the ipatasertib-abiraterone arm, the rates of all-grade AEs, grade 3/4 AEs, and deaths due to AEs were similar between Asian and non-Asian patients. The rate of AEs leading to discontinuation of ipatasertib was higher in Asian patients at 32% (35/109) vs. 18% (74/407) in non-Asian patients; however, rates of AEs leading to dose reduction or dose interruption of ipatasertib were similar between the 2 groups (Table 3).

Differences in selected AEs were observed between Asian and non-Asian patients treated with ipatasertib for hyperglycemia, rash and transaminase increased (Supplemental Table II). Erythema multiforme was less frequent, but occurred in 6% of Asian patients treated with ipatasertib vs. none in non-Asian patients. The rate of asthenia was lower in Asian patients in both arms. Among patients who had a deterioration in GHS, 72% (46/64) of Asian and 67% (106/158) of non-Asian patients discontinued ipatasertib (Supplementary Figure 5).

Discussion

The addition of ipatasertib to abiraterone resulted in prolonged radiographic PFS in patients with PTEN-loss tumors by IHC, with a 23% reduced risk when given as first-line treatment.[9] Here we report that the safety profile of ipatasertib was manageable, but optimization of AE management strategies may provide further benefit to patients.

The overall safety profile in IPATential150 was consistent with the phase II A.MARTIN trial, where common AEs were gastrointestinal toxicity, asthenia or fatigue, decreased appetite, hyperglycemia and rash, and rates of grade 3/4 AEs, deaths due to AEs and serious AEs were similar.[8,9] In IPATential150, AEs leading to discontinuation of ipatasertib occurred in 21% of the SE population and in 18% of patients with PTEN-loss tumors by IHC (rate for placebo

Table 3 Safety Summary in the SE Population in Asian and Non-Asian Patients

AEs, *n* (%)	All Asian (n=218)		Non-Asian (n=812)	
	Pbo + Abi (*n*=109)	Ipat + Abi (*n*=109)	Pbo + Abi (*n*=405)	Ipat + Abi (*n*=407)
All-grade	103 (94)	109 (100)	384 (95)	404 (99)
All-grade selected[a]	78 (72)	108 (99)	300 (74)	394 (97)
Grade 3/4	40 (37)	69 (63)	141 (35)	268 (66)
Grade 3/4 selected[a]	23 (21)	61 (56)	48 (12)	212 (52)
Serious	24 (22)	39 (36)	90 (22)	164 (40)
Grade 5	2 (2)	2 (2)	17 (5)	19 (5)
Leading to discontinuation of pbo/ipat	4 (4)	35 (32)	23 (6)	74 (18)
Leading to dose reduction of pbo/ipat	11 (10)	43 (39)	20 (5)	161 (40)
Leading to dose interruption of pbo/ipat	31 (28)	64 (59)	82 (20)	231 (57)
Leading to discontinuation of abi	3 (3)	15 (14)	19 (5)	32 (8)
Leading to dose reduction of abi	11 (10)	17 (16)	15 (4)	47 (12)
Leading to dose interruption of abi	23 (21)	38 (35)	68 (17)	171 (42)

Abbreviations: Abi = abiraterone; AE = adverse event; Ipat = ipatasertib; Pbo = placebo.
[a] Selected AEs were the grouped terms of asthenia, colitis, diarrhea, erythema multiforme, anemia, hepatotoxicity, hyperglycemia, hyperlipidemia, nausea, neutropenia, oral mucositis, peripheral neuropathy, pneumonia, pneumonitis, rash, thrombocytopenia, transaminase increased and vomiting.

Figure 2 Time to onset, duration, resolution and recurrence of all-grade key adverse events in patients treated with placebo + abiraterone or ipatasertib + abiraterone. AE = adverse event; ipat = ipatasertib; pbo = placebo.

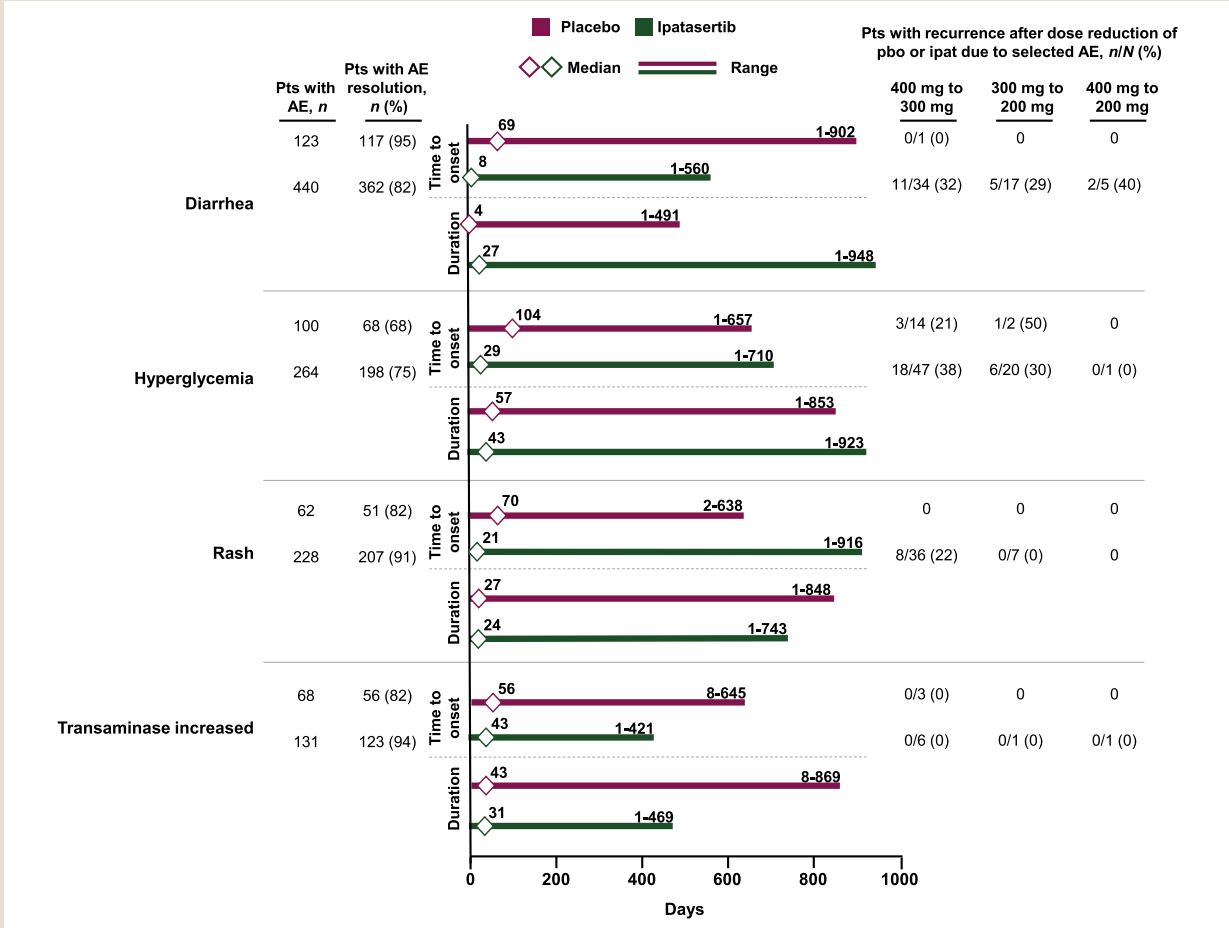
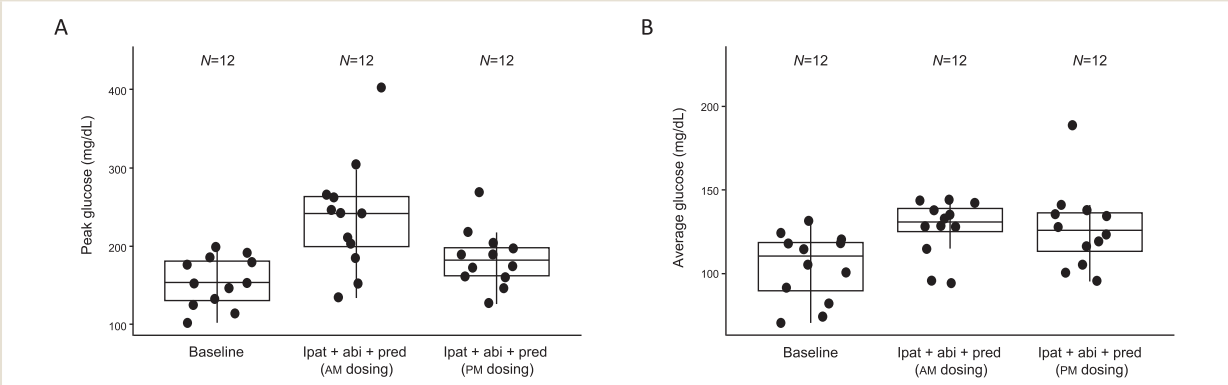


Figure 3 (A) Peak and (B) average glucose levels at baseline (Cycle 1 Day 1), after 7 days of ipat + abi am dosing (Cycle 1 Day 8) and after 7 days of ipat + abi pm dosing (Cycle 1 Day 25). abi = abiraterone; ipat = ipatasertib; pred = prednisone/prednisolone.



was 5% in each). Leading causes were rash, diarrhea, hyperglycemia and transaminase increased, in line with other AKT inhibitors in mCRPC.[21] The discontinuation rate was not impacted by PTEN-loss-by-IHC-status.

In triple-negative breast cancer (TNBC), the IPATunity130 and CO40151 trials evaluated combination therapies including ipatasertib, and included strategies such as prophylactic antidiarrheals or antihistamines for diarrhea and rash, respectively.[11-14] In IPATential150, guidelines for management of diarrhea, hyperglycemia and rash were in the protocol, but prophylactic measures were not. Despite this, most of these AEs resolved and recurrence was limited. However, rates here were slightly higher than in the TNBC trials, suggesting prophylactic antidiarrheals or antihistamines could reduce ipatasertib discontinuation rates in mCRPC.

The pathogenesis of diarrhea associated with AKT inhibitors is unknown, yet it is the most common AE reported in clinical trials evaluating ipatasertib.[9-11,14] Of note, 93% of patients with TNBC who received ipatasertib plus paclitaxel in the LOTUS trial experienced any-grade AE of diarrhea (23% grade ≥3), whilst the rate in the IPATunity130 trial (cohort A), which initiated prophylactic loperamide, was 80% (9% grade ≥3).[11,14] Despite the high rate (80% all grade) of diarrhea in IPATential150, 95% of patients had cases that resolved. Diarrhea was also the leading AE associated with the AKT inhibitor capivasertib, yet the rate was similar to placebo (66% vs. 60%, respectively).[21]

Hyperglycemia is a common AE associated with AKT and PI3K inhibitors and is considered an on-target effect.[20] The rates observed here (48% with ipatasertib-abiraterone;18% with placebo-abiraterone) are higher than those observed with ipatasertib in breast cancer trials, which were <15% in the ipatasertib-paclitaxel and placebo-paclitaxel arms.[11,14,22] The rates in the respective placebo arms between mCRPC and breast cancer studies suggest that differences in the patient populations, such as sex, age or other factors, are contributing. The rate observed here was lower than the 64% observed in the SOLAR-1 trial, which assessed alpelisib (a PI3K inhibitor) plus fulvestrant in patients with hormone receptor–positive advanced breast cancer.[23] Glucose assessment data reported here suggest offering ipatasertib as an evening dose may reduce the risk for hyperglycemia, particularly in patients with higher-risk status.

The mechanism of ipatasertib-associated rash is unclear. In clinical studies of AKT inhibitors, rash was commonly maculopapular with or without pruritis. Here, 41% of patients in the ipatasertib-abiraterone arm had AEs of rash (16% grade ≥3). In breast cancer studies, any-grade rash occurred in ≤26% of patients in ipatasertib-paclitaxel arms, yet grade ≥3 events were rare (~2%).[11,22] In SOLAR-1, patients who received prophylactic antirash medication had reduced incidence and severity of rash than patients who did not.[24]

Increased transaminase level has been associated with AKT inhibitors with no confirmed mechanism. Here, transaminase increased events were increased with ipatasertib, yet ipatasertib added to paclitaxel did not increase the rate of transaminitis in the IPATunity130 cohort B trial,[22] suggesting that ipatasertib may aggravate abiraterone-mediated hepatotoxicity.

Overall, the safety profile of ipatasertib-abiraterone was comparable between Asian and non-Asian patients, excluding increased rates of discontinuation of ipatasertib or abiraterone due to AEs in Asian patients. This may be due to multiple factors, including dose, hepatic metabolism, physician reporting of AEs, or other factors. In patients with a self-reported decrease in quality of life (deterioration in GHS), there was no substantial difference in the rate of discontinuation of ipatasertib between Asian and non-Asian patients, suggesting the higher discontinuation rate in Asians was not due to patient factors, but instead physician decision. The treatment combination used in this study previously demonstrating good tolerability in Japanese patients,[25] and a population pharmacokinetic analysis of ipatasertib found, race was not a significant covariate impacting exposure of ipatasertib or its metabolite.[26] In some Asian populations, there is an associa-

tion between specific human leukocyte antigen alleles and erythema multiforme.[27,28]

Overall, AEs were manageable and reversible in IPATential150 and were consistent with the phase II A.MARTIN trial.[8] These AEs appeared rapidly after the initiation of treatment with limited recurrence, suggesting that predefined prophylactic measures can help mitigate their impact. Although more AEs leading to drug discontinuation were observed with ipatasertib plus abiraterone than placebo plus abiraterone, we anticipate this will be lessened with prophylactic measures, such as antidiarrheals and antihistamines, which were successfully used in breast cancer studies with ipatasertib.[11-14]

Clinical Practice Points

- PI3K/AKT pathway inhibitors have been approved to treat multiple cancer types; however, no AKT-specific targeted inhibitors have been approved as cancer therapy. Numerous registrational studies are ongoing for inhibitors of this pathway, including AKT inhibitors alone or in combination with other agents. The safety profile associated with AKT inhibitors for the treatment of metastatic castration-resistant prostate cancer (mCRPC) is an important consideration. Ipatasertib is a pan-AKT inhibitor that has shown efficacy in patients with mCRPC. In IPATential150, the addition of ipatasertib to abiraterone resulted in a significant risk reduction of radiological disease progression or death vs. placebo plus abiraterone in patients with PTEN-loss tumors.
- In this safety analysis of the IPATential150 trial, adverse events (AEs) were assessed and characterized, with a focus on key AEs of diarrhea, hyperglycemia, rash, and transaminase increased. Ipatasertib-abiraterone had an overall tolerable safety profile consistent with the known toxicities of the individual agents. Increased incidence of grade 3/4 AEs and AEs leading to discontinuation were associated with ipatasertib. Key AEs of diarrhea, hyperglycemia, rash and transaminase elevation were more frequent in ipatasertib-treated patients, appearing rapidly after treatment initiation. It is likely that prophylactic measures, such as antidiarrheals and antihistamines, which were used in clinical trials of ipataseritb for breast cancer, would lessen the incidence and severity of these AEs, potentially increasing treatment exposure and leading to a greater clinical benefit. This study adds to the knowledge of AKT inhibition and could help inform AE management guidelines in clinical practice and future clinical trial design.

Data-Sharing Statement

With publication, individual patient-level data will be available to qualified researchers who request access through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Acknowledgments

We thank the patients who participated in the trial and the clinical site investigators. Medical writing assistance for this manuscript was provided by Scott Battle, PhD, of Health Interactions, Inc, and funded by F. Hoffmann-La Roche Ltd. The IPATential150 study was sponsored by F. Hoffmann-La Roche Ltd/Genentech Inc., a member of the Roche group. The study sponsor was involved in the study design, data interpretation and decision to submit for publication in conjunction with the authors.

Disclosure

This work was supported by F. Hoffmann-La Roche Ltd, Basel, Switzerland; and Genentech Inc., South San Francisco, CA, USA [no grant number applicable]. All authors report editorial assistance from F. Hoffmann-La Roche. NM reports grants and nonfinancial support from F. Hoffmann-La Roche during the conduct of the study; grants and/or personal fees from Janssen, MSD, Chugai, Astellas, Lilly, Taiho, Pfizer, Sanofi, Eisai and AstraZeneca outside the submitted work. JdB reports personal fees from F. Hoffmann-La Roche/Genentech and grants from F. Hoffmann-La Roche/Genentech during the conduct of the study; grants, personal fees and other from AstraZeneca, GSK, Pfizer, Taiho, Daiichi-Sankyo, Bayer, Orion Pharma, F. Hoffmann-La Roche/Genentech, Merck Serono, Sierra Oncology, MSD, Astellas, CellCentric, MSD, Sanofi, Vertex Pharmaceuticals; personal fees and other from Terumo, Menarini/Silicon Biosystems, Bioexcel Therapeutics, Eisai, Qiagen, outside the submitted work; in addition, has a patent for DNA damage repair inhibitors for treatment of cancer (patent number WO 2005 053662 licensed to AstraZeneca), and a patent for 17-substituted steroids useful in cancer treatment (patent number US 5604213 licensed to Janssen). CS reports grants and/or personal fees from Janssen, F. Hoffmann-La Roche/Genentech, Sanofi, Astellas, Pfizer, Bayer, and Lilly, during the conduct of the study; has a patent for abiraterone plus cabozantinib issued to Exelixis, a patent for parthenolide as treatment for cancer licensed to Indiana University, and a patent for dimethylaminoparthenolide as treatment for cancer licensed to Leuchemix. KNC reports grants from F. Hoffmann-La Roche, during the conduct of the study; grants and/or personal fees from Astellas, AstraZeneca, Constellation Pharma, Daiichi Sankyo, Janssen, Merck, Novartis, Pfizer, Point Biopharma, F. Hoffmann-La Roche, Sanofi, outside the submitted work. DO reports grants and nonfinancial support from F. Hoffmann-La Roche, during the conduct of the study; grants/personal/nonfinancial support from Astellas Pharma, Bayer, Janssen, AstraZeneca, Clovis Oncology, Astellas Medivation, F. Hoffmann-La Roche/Genentech, Pfizer, Tokai Pharmaceuticals, Ipsen, MSD, Daiichi Sankyo, outside the submitted work. SS reports grants and nonfinancial support from F. Hoffmann-La Roche, during the conduct of the study; grants and/or personal fees from Amgen, MSD, Merck Serono, F. Hoffmann-La Roche/Genentech, AstraZeneca, AAA/Novartis directly to the institution, outside the submitted work. CM reports grants and nonfinancial support from F. Hoffmann-La Roche, during the conduct of the study; personal fees from Amgen, Astellas Pharma, AstraZeneca, Bayer, BeiGene, Blueprint Medicines, BMS, Celgene, Debiopharm Group, F. Hoffmann-LaRoche/Genentech, Innate Pharma, Ipsen,

Janssen, Lilly, MSD, Novartis, Orion, Pfizer, PharmaMar, Sanofi, Taiho, outside the submitted work. JG, FS, and HH are employees of F. Hoffmann-La Roche, and GC and AH are employees of Genentech. SB reports serving as advisory board member for Astellas, Janssen, Pfizer, BMS, F. Hoffmann-La Roche, Ipsen, MSD, Merck, AAA, AstraZeneca. CNS reports grants and nonfinancial support from F. Hoffmann-La Roche during the study, personal fees from Pfizer, MSD, Merck, AstraZeneca, Astellas, Sanofi/Genzyme, F. Hoffmann-La Roche/Genentech, Immunomedics, Janssen, BMS, Foundation Medicine.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2023.01.001.