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ORIGINAL ARTICLE

Antitumor activity of ipatasertib combined with chemotherapy: results from a phase Ib study in solid tumors

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Background: This phase Ib study evaluated the safety, tolerability, pharmacokinetics, and preliminary efficacy of the oral AKT inhibitor ipatasertib and chemotherapy or hormonal therapy in patients with advanced or metastatic solid tumors to determine combined dose-limiting toxicities (DLTs), maximum tolerated dose, and recommended phase II doses and schedules.

Patients and methods: The clinical study comprised four combination treatment arms: arm A (with docetaxel), arm B [with mFOLFOX6 (modified leucovorin, 5-fluorouracil, and oxaliplatin)], arm C (with paclitaxel), and arm D (with enzalutamide). Primary endpoints were safety and tolerability; secondary endpoints were pharmacokinetics, clinical activity per Response Evaluation Criteria in Solid Tumors v1.1, and prostate-specific antigen levels.

Results: In total, 122 patients were enrolled. Common adverse events were diarrhea, nausea, vomiting, decreased appetite, and fatigue. The safety profiles of the combination regimens were consistent with those of the background regimens, except for diarrhea, hyperglycemia, and rash, which were previously observed with ipatasertib treatment. The only combination DLT across all treatment arms was one event of grade 3 dehydration (ipatasertib 600 mg and paclitaxel). Recommended phase II doses for ipatasertib were 600 mg (and mFOLFOX6) and 400 mg (and paclitaxel), respectively. The maximum assessed dose of ipatasertib 600 mg combined with docetaxel or enzalutamide was well tolerated. Coadministration with enzalutamide (a cytochrome P450 3A inducer) resulted in approximately 50% lower ipatasertib exposure.

Conclusions: Ipatasertib in combination with chemotherapy or hormonal therapy was well tolerated with a safety profile consistent with that of ATP-competitive AKT inhibitors.

Clinical trial number: NCT01362374.

Key words: AKT inhibitor, phase I, advanced cancer

INTRODUCTION

The phosphoinositide 3-kinase (PI3K)/AKT pathway is frequently activated in cancer,[1,2] promoting tumor survival, proliferation, metabolism, and growth.[2] AKT is negatively regulated by the tumor suppressor phosphatase and tensin homolog (PTEN). AKT inhibition potentiates the effects of cytotoxic agents and hormonal therapies.[3–7] Baseline or induced AKT activity by anticancer agents may be an intrinsic or adaptive resistance mechanism that can be exploited to increase therapeutic efficacy.

Ipatasertib (GDC-0068)—a selective, ATP-competitive, small-molecule inhibitor of all three AKT isoforms—is being developed for the treatment of cancers in which PI3K/AKT pathway activation may be relevant for tumor growth or therapeutic resistance and has demonstrated PI3K/AKT pathway inhibition in preclinical studies.[8–10] A phase I study of single-agent ipatasertib in 52 pre-treated patients with various cancers showed an

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acceptable tolerability profile and preliminary antitumor activity.[11]

This study was designed to obtain safety data for ipatasertib when combined with therapeutic regimens commonly used as standard of care to treat diverse advanced malignancies including castrate-resistant prostate cancer (CRPC; docetaxel and enzalutamide), advanced colorectal cancer [mFOLFOX6 (modified regimen of leucovorin, 5-fluorouracil, and oxaliplatin)], and advanced breast cancer (paclitaxel).

We present results from preclinical studies assessing antitumor efficacy of the combinations and their individual components and from a phase Ib trial of ipatasertib combined with chemotherapy or hormonal therapy in patients with advanced or metastatic solid tumors.

PATIENTS AND METHODS

Preclinical studies

Methods are described in the supplementary Methods, available at *Annals of Oncology* online.

Study design and treatment

This open-label, multicenter, phase Ib, dose-escalation trial enrolled patients with advanced or metastatic tumors and assessed ipatasertib in combination with docetaxel (arm A), mFOLFOX6 (arm B), paclitaxel (arm C), or enzalutamide in patients with metastatic CRPC (arm D). The primary objectives were to evaluate safety and tolerability, estimate the maximum tolerated dose, and identify dose-limiting toxicities (DLTs) and a recommended phase II dose of ipatasertib in combination with chemotherapy or hormonal therapy. Each arm comprised dose escalation (stage 1) and cohort expansion (stage 2) (supplementary Figure S1, supplementary Appendix, available at *Annals of Oncology* online).

This study (NCT01362374) was approved by the institutional review board or ethics committee at participating centers and was conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients

Eligible patients were aged $\geq$18 years and had Eastern Cooperative Oncology Group performance status of 0 or 1, histologically or cytologically documented advanced or metastatic solid tumors for which established therapy either did not exist or proved ineffective or intolerable, life expectancy of $\geq$12 weeks, adequate hematologic and end-organ function, and resolution to grade $\leq$1 of all acute, clinically significant treatment-related toxicities from prior therapy. Key exclusion criteria were history of type 1 or 2 diabetes mellitus requiring insulin, chronic corticosteroid use (20 mg of prednisone equivalent per day), history of malabsorption syndromes, and exclusions for combination regimens generally consistent with practice guidelines (e.g. no prior seizures for patients receiving enzalutamide). All patients provided written informed consent.

Assessments

Adverse events (AEs) and laboratory abnormalities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 and tumor response assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see supplement, available at *Annals of Oncology* online).

Analyses

Analyses were based on the safety-evaluable population comprising all patients who received any dose of ipatasertib. The pharmacokinetic analysis population included all patients with a measurable concentration at $\geq$1 collection time point. Efficacy analyses were carried out on the intent-to-treat population (see supplement, available at *Annals of Oncology* online).

RESULTS

Preclinical studies

A combination of ipatasertib with chemotherapeutics and hormonal therapy *in vitro* revealed synergism in most cancer cell lines tested based on a combination index of $<$1 using the Chou-Talalay method (supplementary Figure S2, available at *Annals of Oncology* online). *In vivo*, ipatasertib plus docetaxel showed enhanced efficacy compared with either agent alone in the HCI-001 triple-negative breast cancer (TNBC) patient-derived xenograft (PDX) model (low PTEN protein levels as determined by immunohistochemistry) (supplementary Figure S3A, available at *Annals of Oncology* online). Ipatasertib + paclitaxel showed enhanced efficacy compared with either agent alone in the MCF-7 hormone receptor-positive breast cancer model harboring the E545K *PIK3CA* mutation (supplementary Figure S3B, available at *Annals of Oncology* online). Ipatasertib + the FOLFOX-containing regimen showed enhanced efficacy compared with either agent alone in the STO#240 gastric PDX model (PTEN null/human epidermal growth factor receptor 2 negative) (supplementary Figure S4, available at *Annals of Oncology* online). Lastly, ipatasertib + enzalutamide showed enhanced efficacy compared with either agent alone in the LuCaP 35V CRPC PDX model (androgen receptor positive/PTEN low) (supplementary Figure S5, available at *Annals of Oncology* online).

Patient characteristics

As of 2 May 2016, 122 patients were enrolled: 27 in arm A (3 at ipatasertib 100 mg, 4 at 200 mg, 7 at 400 mg, and 13 at 600 mg), 34 in arm B (6 at 100 mg, 9 at 200 mg, 6 at 400 mg, and 13 at 600 mg), 27 in arm C (21 at 400 mg and 6 at 600 mg), and 34 in arm D (6 at 400 mg, 7 at 600 mg, and 21 at 400 mg, with the option to increase to 600 mg pursued in only three patients). All patients discontinued study treatment except for 3 in arm D mostly due to disease progression (supplementary Table S1, available at *Annals of Oncology* online). Baseline demographic characteristics are shown in Table 1.

Table 1. Patient baseline demographics and characteristics

Characteristic	Arm A (docetaxel) *n* = 27	Arm B (mFOLFOX6) *n* = 34	Arm C (paclitaxel) *n* = 27	Arm D (enzalutamide) *n* = 34
Age, median (range), years	62.0 (28–75)	58.5 (33–77)	58.0 (41–80)	71.0 (56–83)
Male, *n* (%)	20 (74.1)	19 (55.9)	10 (37.0)	34 (100.0)
ECOG PS, *n* (%)				
0	12 (44.4)	13 (38.2)	12 (44.4)	19 (55.9)
1	15 (55.6)	21 (61.8)	15 (55.6)	15 (44.1)
Race, *n* (%)				
Asian	0	0	1 (3.7)	1 (2.9)
Black or African American	1 (3.7)	1 (2.9)	0	1 (2.9)
Multiracial	0	1 (2.9)	0	0
White	25 (92.6)	32 (94.1)	26 (96.3)	31 (91.2)
Other	1 (3.7)	0	0	1 (2.9)
Number of prior systemic therapies, median (range)	4.0 (0–12)	4.5 (0–11)	3.0 (0–12)	5.5 (1–15)
Prior radiotherapy, *n* (%)	16 (59.3)	15 (44.1)	17 (63.0)	31 (91.2)
Prior PI3K inhibitor therapy, *n* (%)	2 (7.4)	3 (8.8)	8 (29.6)	1 (2.9)
Most common location(s) of primary tumors, *n* (%)				
Lung	5 (18.5)	—	2 (7.4)	—
Breast	5 (18.5)	1 (2.9)	15 (55.6)	—
Colorectal	—	14 (41.2)	—	—
Esophageal	4 (14.8)	3 (8.8)	—	—
Prostate	—	—	—	34 (100.0)
Bladder	3 (11.1)	—	2 (7.4)	—
Pancreas	—	2 (5.9)	1 (3.7)	—

ECOG PS, Eastern Cooperative Oncology Group performance status; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin; PI3K, phosphoinositide 3-kinase.

Safety

Almost all patients experienced ≥1 AE (Table 2). Incidence of grade 3/4 laboratory abnormalities was generally low, and no apparent dose relationship was observed. Ipatasertib-related AEs observed in ≥10% of all patients and by dose level are shown in supplementary Tables S2 and S3, respectively, available at *Annals of Oncology* online.

Arm A (ipatasertib + docetaxel). A median of 4.0 cycles of ipatasertib treatment was administered with a median duration of treatment of 10.9 weeks (supplementary Table S4, available at *Annals of Oncology* online). Common AEs (mostly grade 1/2) occurring in ≥50% of patients were diarrhea (85.2%), nausea (74.1%), vomiting (66.7%), and neutropenia (59.3%). Twenty-one patients (77.8%) experienced grade ≥3 AEs; of these, only 4 AEs occurred in >1 patient: neutropenia in 15 patients (55.6%), febrile neutropenia in 3 patients (11.1%), and hypophosphatasemia and diarrhea each in 2 patients (7.4%), which was consistent with the known safety profile of docetaxel and showed no relationship with ipatasertib doses. Fifteen patients (55.6%) experienced SAEs; 4 (14.8% overall) experienced 6 SAEs considered related to study treatment, including rash/rash maculopapular (2), diarrhea (1), hypocalcemia (1), hypomagnesemia (1), and hypophosphatemia (1). No DLTs occurred; the maximum assessed dose (MAD) of ipatasertib with docetaxel was 600 mg daily on days 2–15 per 21-day cycle. Patients in the expansion cohort were treated at the MAD of 600 mg. One death—due to septic shock—occurred and was considered unrelated to ipatasertib or docetaxel.

Table 2. Overview of safety

Total patients with ≥1 AE, *n* (%)	Arm A (docetaxel) *n* = 27	Arm B (mFOLFOX6) *n* = 34	Arm C (paclitaxel) *n* = 27	Arm D (enzalutamide) *n* = 34
Any AE	27 (100.0)	34 (100.0)	26 (96.3)	34 (100.0)
Grade ≥3 AE	21 (77.8)	26 (76.5)	14 (51.9)	15 (44.1)
Serious AE	15 (55.6)	16 (47.1)	10 (37.0)	8 (23.5)
Treatment-related AE	26 (96.3)	30 (88.2)	25 (92.6)	33 (97.1)
AE leading to discontinuation of ipatasertib	2 (7.4)	2 (5.9)	3 (11.1)	3 (8.8)
AE leading to dose reduction or interruption of ipatasertib	15 (55.6)	24 (70.6)	17 (62.9)	17 (50.0)
AE leading to discontinuation of other study drug	2 (7.4)	3 (8.8)[a,b] 6 (17.6)[c]	4 (14.8)	2 (5.9)
AE leading to dose reduction or interruption of other study drug	13 (48.1)	24 (70.6)[a] 17 (50.0)[b] 24 (70.6)[c]	15 (55.5)	13 (38.2)
Death	1 (3.7)	2 (5.9)	3 (11.1)	1 (2.9)

AE, adverse event; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin.
[a] Discontinuation, dose reduction, or dose interruption of 5-fluorouracil.
[b] Discontinuation, dose reduction, or dose interruption of leucovorin.
[c] Discontinuation, dose reduction, or dose interruption of oxaliplatin.

Arm B (ipatasertib + mFOLFOX6). A median of 4.5 cycles of ipatasertib treatment was administered with a median duration of treatment of 8.2 weeks (supplementary Table S4, available at *Annals of Oncology* online). Common AEs (mostly grade 1/2) occurring in ≥50% of patients were nausea (85.3%), diarrhea (76.5%), vomiting (70.6%), and decreased appetite (50.0%); 26 patients (76.5%) experienced grade ≥3 AEs. Sixteen patients (47.1%) experienced SAEs, one (2.9% of total) of whom had hypokalemia considered related to study treatment. The only grade 3/4 laboratory abnormality (>15%) reported was neutropenia (23.5%). No DLTs occurred; the MAD of ipatasertib with mFOLFOX6 was 600 mg daily on days 1–7 per 14-day cycle. Patients in the expansion cohort were treated at the MAD of 600 mg. Two deaths—due to adenocarcinoma progression and progressive liver metastasis, respectively—occurred and were considered unrelated to ipatasertib or mFOLFOX6.

Arm C (ipatasertib + paclitaxel). A median of 3.0 cycles of ipatasertib treatment was administered with a median duration of treatment of 11.0 weeks (supplementary Table S4, available at *Annals of Oncology* online). Common AEs (mostly grade 1/2) occurring in ≥50% of patients were diarrhea (81.5%) and nausea (55.6%); 14 patients (51.9%) experienced AEs of grade ≥3. Ten patients (37.0%) experienced SAEs, two (7.4% of total) of whom experienced three SAEs considered related to study treatment, including dehydration (2) and diarrhea (1). No grade 3/4 laboratory abnormalities (>15%) were reported. One patient in the 600-mg group experienced a DLT of dehydration. The MAD of ipatasertib with paclitaxel was 600 mg. Patients in the expansion cohort were treated with ipatasertib 400 mg based on the totality of the safety data. Three deaths—due to pancreatic carcinoma progression, mesothelioma progression, and respiratory failure, respectively—occurred and were considered unrelated to ipatasertib or paclitaxel.

Arm D (ipatasertib + enzalutamide). A median of 3.0 cycles of ipatasertib treatment was administered with a median duration of treatment of 12.8 weeks (supplementary Table S4, available at *Annals of Oncology* online). Common AEs (mostly grade 1/2) occurring in ≥50% of patients were diarrhea (91.2%), fatigue (58.8%), and nausea (50.0%); 15 patients (44.1%) experienced AEs of grade ≥3. Eight patients (23.5%) experienced SAEs, one (2.9% of total) of whom had pulmonary embolism considered related to study treatment. There were no grade 3/4 laboratory abnormalities with a frequency of >15%. No DLTs occurred; the MAD of ipatasertib with enzalutamide was 600 mg daily on days 1–28 per 28-day cycle. Patients in the expansion cohort were treated with a starting dose of ipatasertib 400 mg based on the totality of the safety data. In the expansion cohort, three patients had intrapatient ipatasertib dose escalation from 400–600 mg. One death due to cardiac arrest occurred following disease progression and study drug discontinuation and was considered unrelated to ipatasertib or enzalutamide.

Pharmacokinetics

In arm A, the day 1 mean maximum plasma concentration (C_{max}) and mean area under the concentration time curve over 24 hours (AUC_{0-24h}) of ipatasertib following a single dose of 600 mg ipatasertib were 496 ng/mL (39.6%) and 2720 ng·h/mL (41.2%), respectively, comparable with single-agent data [C_{max}, 488 ng/mL (41.4%) and AUC_{0-24h}, 2670 ng·h/mL (39.4%)]. In arm B, the day 1 exposure of ipatasertib increased in an approximately dose-proportional manner; however, ipatasertib exposures following the 600-mg dose were higher compared with single-agent data [C_{max}, 619 ng/mL (50.2%) and AUC_{0-24h}, 4580 ng·h/mL (38.5%)]. In arm C, the steady-state exposure of ipatasertib was comparable with single-agent data. The mean C_{max} and AUC_{0-24h} at steady state following once-daily dosing of ipatasertib 400 mg were 388 (84.4%) ng/mL and 3180 (38.9%) ng·h/mL, respectively. In arm D, the steady-state exposure of ipatasertib was reduced by ≈50% with ipatasertib plus enzalutamide, but the exposure of its metabolite G-037720 was ≈20% higher compared with the exposures following single-agent ipatasertib. Ipatasertib is primarily a substrate of CYP3A, and its exposure was expected to be reduced when co-administered with enzalutamide, a strong CYP3A inducer. Exposures of docetaxel, mFOLFOX6 (5-fluorouracil and free and total oxaliplatin), paclitaxel (and its metabolite), and enzalutamide (and its metabolite) were comparable with those reported in the literature (supplementary Table S5, available at *Annals of Oncology* online).[12–17]

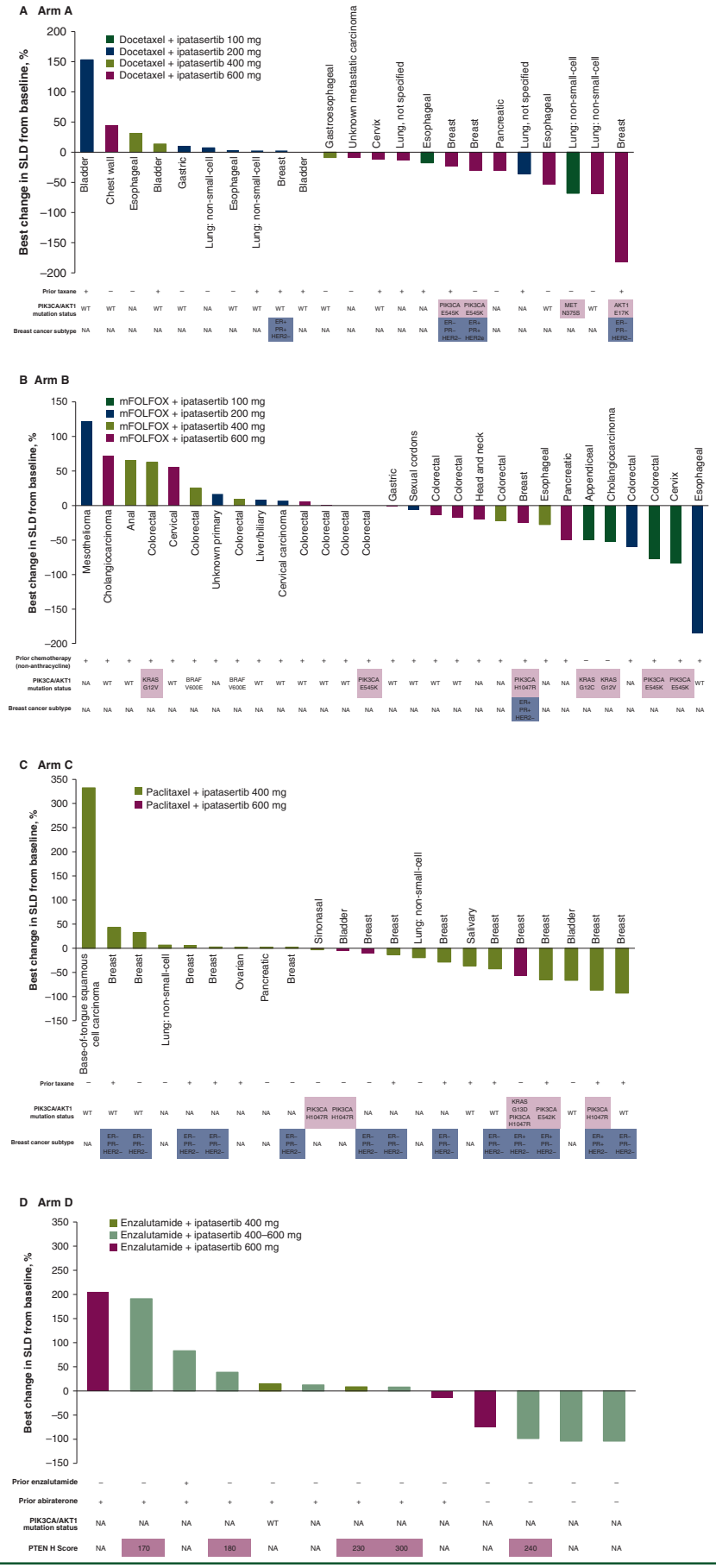
Efficacy

In total, 101 efficacy-evaluable patients had baseline measurable disease. Eight patients (7.9%; two in each arm) experienced a best overall response of partial response (PR) by RECIST v1.1 (Figures 1 and 2; supplementary Table S6, available at *Annals of Oncology* online). The objective response rate per RECIST v1.1 was proportionally higher in patients with *AKT1/PIK3CA*-activating mutations, but sample sizes were small (supplementary Table S7, available at *Annals of Oncology* online).

Arm A (ipatasertib + docetaxel; *n* = 26). The maximum investigator-assessed progression-free survival (PFS) was ≈10.2 months in a patient with lung cancer; three patients had PFS of >6 months. Two patients (7.7%) had a PR, 14 (53.8%) achieved stable disease (SD), and 7 (26.9%) had disease progression.

Arm B (ipatasertib + mFOLFOX6; *n* = 33). Maximum investigator-assessed PFS was ≈50 months in a patient with appendiceal cancer; six patients had PFS of >6 months. Two patients (6.1%) had a PR, 17 (51.5%) achieved SD, and 10 (30.3%) had disease progression.

Arm C (ipatasertib + paclitaxel; *n* = 25). Maximum investigator-assessed PFS was ≈14.2 months in a patient with breast cancer; three patients had PFS of >6 months. Two patients (8.0%) had a PR, 14 (56.0%) had SD, and 6 (24.0%) had disease progression.


A Arm A
Docetaxel + ipatasertib 100 mg
Docetaxel + ipatasertib 200 mg
Docetaxel + ipatasertib 400 mg
Docetaxel + ipatasertib 600 mg
Best change in SLD from baseline, %
Prior taxane
PIK3CA/AKT1 mutation status
Breast cancer subtype
B Arm B
mFOLFOX + ipatasertib 100 mg
mFOLFOX + ipatasertib 200 mg
mFOLFOX + ipatasertib 400 mg
mFOLFOX + ipatasertib 600 mg
Best change in SLD from baseline, %
Prior chemotherapy (non-anthracycline)
PIK3CA/AKT1 mutation status
Breast cancer subtype
C Arm C
Paclitaxel + ipatasertib 400 mg
Paclitaxel + ipatasertib 600 mg
Best change in SLD from baseline, %
Prior taxane
PIK3CA/AKT1 mutation status
Breast cancer subtype
D Arm D
Enzalutamide + ipatasertib 400 mg
Enzalutamide + ipatasertib 400–600 mg
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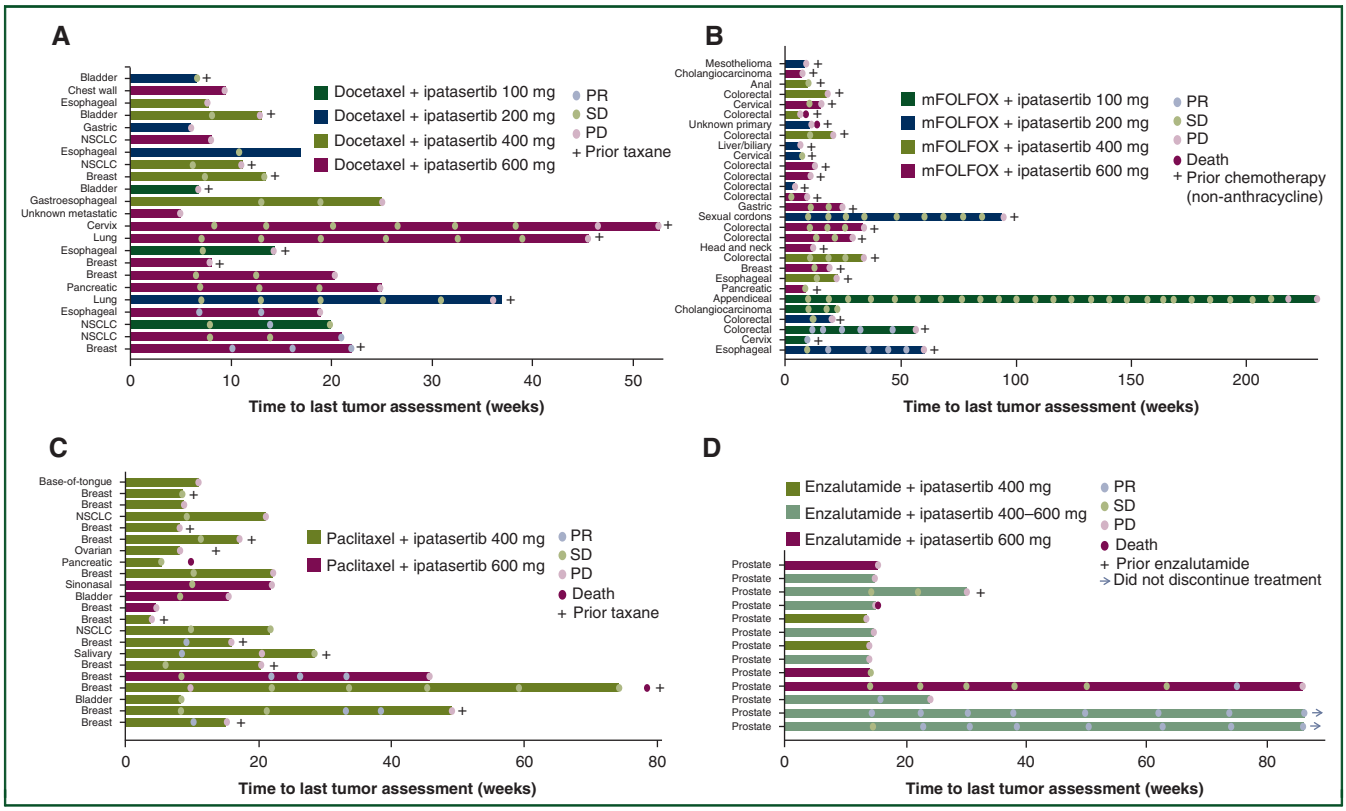

Figure 2. Response duration from treatment start in patients with reported sum of longest tumor diameter.
Lanes represent individual patients. (A) Patients enrolled in arm A received docetaxel + ipatasertib. (B) Patients enrolled in arm B received mFOLFOX6 + ipatasertib. (C) Patients enrolled in arm C received paclitaxel + ipatasertib. (D) Patients enrolled in arm D received enzalutamide + ipatasertib. Arm D comprised only patients with prostate cancer. mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin; NSCLC, non-small-cell lung carcinoma; PD, progressive disease; PR, partial response; SD, stable disease.

Arm D (ipatasertib + enzalutamide; *n* = 17). Maximum investigator-assessed PFS was ≈19.5 months in one patient; four patients had PFS of >6 months. Two patients (11.8%) had a PR, four (23.5%) had SD, and seven (41.2%) had disease progression. Antitumor activity measured by the maximum change in PSA from baseline in patients with/without prior abiraterone therapy is shown in supplementary Figure S6, available at *Annals of Oncology* online.

DISCUSSION

A first-in-human study showed that ipatasertib—an ATP-competitive AKT inhibitor—attained significant pathway inhibition in well-tolerated doses and achieved meaningful disease control in a subgroup of patients.[11] Because AKT affects not only tumor growth but also resistance to anticancer therapies, ipatasertib combinations may enhance the antitumor effect. Our preclinical data suggest that ipatasertib combinations may result in growth inhibition and antitumor efficacy *in vitro* and *in vivo*, supporting evaluation of ipatasertib combinations in patients.

Overall, ipatasertib was well tolerated at ≤600 mg with manageable and reversible AEs. The most common investigator-assessed AEs (>30%) related to ipatasertib were diarrhea, nausea, vomiting, decreased appetite, and asthenia/fatigue. This safety profile was consistent with the established profiles of single-agent ipatasertib, the PI3K-AKT-mTOR inhibitor class, and the drugs used as combination partners. The only DLT in this study was dehydration occurring in one patient in arm C. Seven deaths occurred in this study, but none were treatment related.

Based on the safety results in arm C, the recommended dose for the phase II study of ipatasertib + paclitaxel for the treatment of TNBC was 400 mg daily for days 1—21 of each 28-day cycle.[18] Based on the safety results in arm B, the recommended phase II dose for the study of ipatasertib+ mFOLFOX6 in gastric cancer was 600 mg daily (NCT01896531).[19]

This phase Ib patient population had heterogeneous tumor types with largely treatment-refractory disease based on the median number of prior therapies. Because a proportion of patients with prior exposure to the same therapy or other investigational PI3K inhibitors was included, their expected response outcome was low. Combination therapy

Figure 1. Best reduction in sum of longest tumor diameters in patients with baseline measurable disease.
(A) Patients enrolled in arm A received docetaxel + ipatasertib. (B) Patients enrolled in arm B received mFOLFOX6 + ipatasertib. (C) Patients enrolled in arm C received paclitaxel + ipatasertib. (D) Patients enrolled in arm D received enzalutamide + ipatasertib. Arm D comprised only patients with prostate cancer. Phosphatase and tensin homolog (PTEN) absence/presence was assessed by an H score ranging from 0 (complete loss) to 400 (full expression). ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HER2e, HER2 equivocal; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin; NA, not available; PR, progesterone receptor; SLD, sum of longest diameters; WT, wild type.

with ipatasertib showed a partial efficacy response in patients with advanced and late-line breast, colorectal, esophageal, and prostate cancers. The safety and tolerability profile of ipatasertib—when combined with chemotherapeutic or endocrine agents—allows for further evaluations in multiple cancers, including breast and prostate cancers with high intrinsic PI3K/AKT pathway activation due to aberrant activation of the pathway via activating mutations in *AKT1/PIK3CA* or PTEN loss via multiple mechanisms.

Limitations of this study include small sample size, absence of a comparative treatment arm, and inability to assess mutational status in some patients due to insufficient tissue samples. Overall, the manageable and tolerable safety profile of ipatasertib and preliminary evidence of antitumor activity support further evaluation of combination ipatasertib therapy in multiple solid tumors for which ipatasertib has the potential to block both intrinsic and adaptive treatment resistance.

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DISCLOSURES

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REFERENCES

1. Khan KH, Yap TA, Yan L, Cunningham D. Targeting the PI3K-AKT-mTOR signaling network in cancer. *Chin J Cancer.* 2013;32:253—265.
2. Manning BD, Toker A. AKT/PKB signaling: navigating the network. *Cell.* 2017;169:381—405.

3. Garcia MG, Alaniz LD, Cordo Russo RI, et al. PI3K/Akt inhibition modulates multidrug resistance and activates NF-kappaB in murine lymphoma cell lines. *Leuk Res*. 2009;33:288—296.
4. Wallin JJ, Guan J, Prior WW, et al. Nuclear phospho-Akt increase predicts synergy of PI3K inhibition and doxorubicin in breast and ovarian cancer. *Sci Transl Med*. 2010;2:48ra66.
5. Wang YA, Johnson SK, Brown BL, et al. Enhanced anti-cancer effect of a phosphatidylinositol-3 kinase inhibitor and doxorubicin on human breast epithelial cell lines with different p53 and oestrogen receptor status. *Int J Cancer*. 2008;123:1536—1544.
6. Yu HG, Ai YW, Yu LL, et al. Phosphoinositide 3-kinase/Akt pathway plays an important role in chemoresistance of gastric cancer cells against etoposide and doxorubicin induced cell death. *Int J Cancer*. 2008;122:433—443.
7. Clark AS, West K, Streicher S, Dennis PA. Constitutive and inducible Akt activity promotes resistance to chemotherapy, trastuzumab, or tamoxifen in breast cancer cells. *Mol Cancer Ther*. 2002;1:707—717.
8. Blake JF, Xu R, Bencsik JR, et al. Discovery and preclinical pharmacology of a selective ATP-competitive Akt inhibitor (GDC-0068) for the treatment of human tumors. *J Med Chem*. 2012;55:8110—8127.
9. Yan Y, Serra V, Prudkin L, et al. Evaluation and clinical analyses of downstream targets of the Akt inhibitor GDC-0068. *Clin Cancer Res*. 2013;19:6976—6986.
10. Lin J, Sampath D, Nannini MA, et al. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. *Clin Cancer Res*. 2013;19:1760—1772.
11. Saura C, Roda D, Rosello S, et al. A first-in-human phase I study of the ATP-competitive AKT inhibitor ipatasertib demonstrates robust and safe targeting of AKT in patients with solid tumors. *Cancer Discov*. 2017;7:102—113.
12. *TAXOL US Package Insert*. Princeton, NJ: Bristol-Myers Squibb Company; 2011.
13. *XTANDI US Package Insert*. Northbrook, IL: Astellas Pharma US, Inc; 2018.
14. Bruno R, Hille D, Riva A, et al. Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. *J Clin Oncol*. 1998;16:187—196.
15. Huizing MT, Keung AC, Rosing H, et al. Pharmacokinetics of paclitaxel and metabolites in a randomized comparative study in platinum-pretreated ovarian cancer patients. *J Clin Oncol*. 1993;11:2127—2135.
16. Lévi F, Metzger G, Massari C, Milano G. Oxaliplatin: pharmacokinetics and chronopharmacological aspects. *Clin Pharmacokinet*. 2000;38:1—21.
17. Michael M, Gibbs P, Smith R, et al. Open-label phase I trial of vandetanib in combination with mFOLFOX6 in patients with advanced colorectal cancer. *Invest New Drugs*. 2009;27:253—261.
18. Kim SB, Dent R, Im SA, et al. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2017;18:1360—1372.
19. Bang YJ, Kang YK, Ng M, et al. A phase II, randomised study of mFOLFOX6 with or without the Akt inhibitor ipatasertib in patients with locally advanced or metastatic gastric or gastroesophageal junction cancer. *Eur J Cancer*. 2018;108:17—24.