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CLINICAL TRIAL

Final results of the double-blind placebo-controlled randomized phase 2 LOTUS trial of first-line ipatasertib plus paclitaxel for inoperable locally advanced/metastatic triple-negative breast cancer

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Abstract

Purpose In LOTUS (NCT02162719), adding the oral AKT inhibitor ipatasertib to first-line paclitaxel for locally advanced/metastatic triple-negative breast cancer (aTNBC) improved progression-free survival (PFS; primary endpoint), with an enhanced effect in patients with *PIK3CA/AKT1/PTEN*-altered tumors (FoundationOne next-generation sequencing [NGS] assay). We report final overall survival (OS) results.

Methods Eligible patients had measurable previously untreated aTNBC. Patients were stratified by prior (neo)adjuvant therapy, chemotherapy-free interval, and tumor immunohistochemistry PTEN status, and were randomized 1:1 to paclitaxel 80 mg/m^2 (days 1, 8, 15) plus ipatasertib 400 mg or placebo (days 1–21) every 28 days until disease progression or unacceptable toxicity. OS (intent-to-treat [ITT], immunohistochemistry PTEN-low, and PI3K/AKT pathway-activated [NGS *PIK3CA/AKT1/PTEN*-altered] populations) was a secondary endpoint.

Results Median follow-up was 19.0 versus 16.0 months in the ipatasertib–paclitaxel versus placebo–paclitaxel arms, respectively. In the ITT population ($n=124$), median OS was numerically longer with ipatasertib–paclitaxel than placebo–paclitaxel (hazard ratio 0.80, 95% CI 0.50–1.28; median 25.8 vs 16.9 months, respectively; 1-year OS 83% vs 68%). Likewise, median OS favored ipatasertib–paclitaxel in the PTEN-low ($n=48$; 23.1 vs 15.8 months; hazard ratio 0.83) and *PIK3CA/AKT1/PTEN*-altered ($n=42$; 25.8 vs 22.1 months; hazard ratio 1.13) subgroups. The ipatasertib–paclitaxel safety profile was unchanged.

Conclusions Final OS results show a numerical trend favoring ipatasertib–paclitaxel and median OS exceeding 2 years with ipatasertib–paclitaxel. Overall, results are consistent with the reported PFS benefit; interpretation within biomarker-defined subgroups is complicated by small sample sizes and TNBC heterogeneity.

Keywords Ipatasertib · Oral · PI3K/AKT · Triple-negative breast cancer · First-line therapy

Abbreviations

AKT	Protein kinase B
CI	Confidence interval
IQR	Interquartile range
ITT	Intent-to-treat
LAR	Luminal androgen receptor
OS	Overall survival
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PTEN	Phosphatase and tensin homolog
TNBC	Triple-negative breast cancer

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Introduction

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway is a key regulator of several normal cellular processes, including cell growth, proliferation, metabolism, and survival [1, 2]. AKT is one of

the most frequently activated protein kinases in human cancers; its activation is potentiated by PI3K and inhibited by phosphatase and tensin homolog (PTEN). Aberrant activation of the PI3K/AKT pathway promotes resistance to anti-cancer therapies in many human cancers, including breast and prostate, and often results from genomic and molecular alterations of the key genes phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), *AKT1*, and *PTEN* [2–8]. AKT can be activated by: loss of function of negative regulators (PTEN, INPP4B, PHLPP, PP2A); gain of function of positive regulators (PI3K, AKT, receptor tyrosine kinases [e.g., HER2]); and therapy-induced survival response (chemotherapy, endocrine therapy) [2, 9].

Ipatasertib, an investigational orally administered ATP-competitive selective AKT inhibitor, has been explored as treatment for breast cancer in various preclinical studies and phase 1 studies [10–12]. In the subsequent randomized phase 2 clinical trial (LOTUS) evaluating ipatasertib as first-line therapy for locally advanced/metastatic triple-negative breast cancer (TNBC), combining ipatasertib with paclitaxel significantly improved progression-free survival (PFS)—the primary endpoint—compared with paclitaxel alone [13]. The PFS benefit from ipatasertib was observed in the intent-to-treat (ITT) population and was more pronounced in the *PIK3CA/AKT1/PTEN*-altered subgroup at the primary analysis, leading to initiation of phase 3 evaluation in a biomarker-selected population of patients with *PIK3CA/AKT1/PTEN*-altered locally advanced or metastatic breast cancer. Results from the PAKT randomized phase 2 trial of paclitaxel with or without the AKT inhibitor capivasertib as first-line therapy for metastatic TNBC also showed an improvement in PFS and interim overall survival (OS; median follow-up 18.2 months), with a more pronounced effect in patients with *PIK3CA/AKT1/PTEN*-altered tumors [14].

At the time of the primary PFS analysis of LOTUS, OS results were immature (deaths in 21% of the ITT population). In an updated analysis of OS after deaths in 55% of patients, the stratified OS hazard ratio in the ITT population was 0.62 (95% confidence interval [CI] 0.37–1.05%), and median OS was 23.1 months with ipatasertib–placebo versus 18.4 months with placebo–paclitaxel [15]. In the *PIK3CA/AKT1/PTEN*-altered population, the median OS was 19.7 months in the ipatasertib–paclitaxel arm and was not reached in the placebo–paclitaxel arm; the OS hazard ratio was 0.90 (95% CI 0.38–2.15) and 1-year OS rates were 88% versus 63% in the ipatasertib–paclitaxel versus placebo–paclitaxel arms, respectively (Supplementary Table S1).

Here, we report the final OS results from the LOTUS trial.

Patients and methods

The design of the LOTUS (NCT02162719) trial has been described in detail previously [13]. In brief, this double-blind placebo-controlled randomized phase 2 trial enrolled women with measurable locally advanced/metastatic TNBC not amenable to curative resection who had received no prior systemic therapy for advanced/metastatic disease. Prior (neo)adjuvant chemotherapy and/or radiotherapy was permitted if completed ≥ 6 months before the first dose. Eligible patients were aged ≥ 18 years with Eastern Cooperative Oncology Group performance status 0/1. All patients provided written informed consent before undergoing any study-specific procedures. Independent institutional review boards at all participating centers approved the protocol and all study-related documents.

Patients were stratified according to tumor PTEN status (assessed centrally by immunohistochemistry in archival or newly obtained tumor tissue samples; *H*-score 0 vs 1–150 vs > 150), prior (neo)adjuvant chemotherapy (yes vs no), and chemotherapy-free interval (≤ 12 vs > 12 months vs no prior chemotherapy). Patients were randomly assigned in a 1:1 ratio to receive intravenous paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle in combination with either oral ipatasertib 400 mg/day or placebo, administered on days 1–21 of each 28-day cycle. Treatment was continued until disease progression, intolerable toxicity, or withdrawal of consent. Ipatasertib or placebo could be temporarily interrupted for up to 4 consecutive weeks if patients experienced toxicity considered related to the study drug. Primary prophylactic anti-diarrheal drugs were not specified as part of safety management guidelines in the protocol. Diarrhea was managed with loperamide or according to institutional guidelines and standard of care, including but not limited to therapy with diphenoxylate and atropine, codeine, or octreotide. If symptoms persisted despite adequate (combination) anti-diarrheal medications and dose interruptions, dose reductions were implemented. Tumors were assessed every 8 weeks according to Response Evaluation Criteria in Solid Tumours (version 1.1). Safety was evaluated on an ongoing basis until the study drug discontinuation visit (or resolution or stabilization of ongoing related adverse events). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. After discontinuing treatment, patients were followed for OS and subsequent therapy every 3 months until death, withdrawal from study participation, or study closure.

Tumor samples (collected from either primary tumor or metastatic sites at any time before treatment) were evaluated for genetic alterations using Foundation

Medicine's FoundationOne® NGS assay (Foundation Medicine, Cambridge, MA, USA) and for gene expression by RNA sequencing (RNASeq) using TruSeq RNA Access (Illumina, Inc., San Diego, CA, USA) and Expression Analysis (Morrisville, NC, USA). *PIK3CA/AKT1/PTEN*-altered tumors were defined as those with one or more of the following alterations: *PTEN* homozygous/heterozygous deletions; *PTEN* deleterious mutations with loss of heterozygosity (LOH); *PIK3CA*-activating mutations; or *AKT1*-activating mutations (described in detail elsewhere [16]). Samples were classified into subtypes by gene expression based on the Absolute Intrinsic Molecular Subtyping (AIMS) method [17] and that developed by Lehmann and Pietenpol [18, 19].

The co-primary endpoints were PFS in the ITT population and PFS in the subgroup of patients with PTEN-low tumors identified by immunohistochemistry, results of which were published previously [13]. Secondary efficacy endpoints included objective response rate, duration of response (both reported previously) and OS in the ITT population, the population with PTEN-low tumors, and the population with PI3K/AKT pathway-activated tumors. OS was estimated using Kaplan–Meier methodology, with hazard ratios estimated based on Cox regression; 95% CIs were calculated for medians and hazard ratios. Treatment arms were compared using log-rank tests. In post hoc analyses, baseline and molecular characteristics were explored in patients with long-term response to treatment (defined retrospectively as OS of > 30 months) to assess potential imbalances between treatment arms and identify profiles potentially associated with better outcomes, for hypothesis generation. Safety objectives included evaluation of the incidence, nature, and severity of adverse events.

Efficacy analyses were based on all randomized patients according to the randomized treatment. Safety analyses were based on all treated patients (at least one dose of ipatasertib, placebo, or paclitaxel) with patients analyzed according to the treatment actually received.

Results

Patient population, treatment exposure, and follow-up

A total of 124 patients were enrolled from 44 sites in Europe, the USA, and Asia. Demographic and clinical characteristics at baseline were generally balanced between the treatment arms (Supplementary Table S2). At the date of study closure (September 3, 2019), all patients had discontinued all study treatment, most commonly because of disease progression. The median duration of follow-up at this date was 19.0 months in the ipatasertib–paclitaxel arm versus 16.0 months in the placebo–paclitaxel arm. The median duration of paclitaxel exposure was 5.1 months (interquartile range [IQR] 3.2–8.8 months) versus 3.5 months (IQR 1.4–5.6 months), respectively. The median duration of ipatasertib/placebo was 5.3 (IQR 3.4–9.2) versus 3.5 (IQR 1.6–6.0) months, respectively.

Figure 1 shows the molecular profile of the treated population. Genetic alterations varied substantially across the cohort; beyond the top five genes (*TP53*, *PTEN*, *MYC*, *PIK3CA*, *RB1*), genetic profiles were diverse and unique across the study. Within the *PIK3CA/AKT1/PTEN*-non-altered population, there was no clear pattern of molecular subtype. However, in the *PIK3CA/AKT1/PTEN*-altered population, *AKT1* mutations occurred almost exclusively in luminal androgen receptor (LAR) subtype TNBC (five [83%] of the six patients with an *AKT1* mutation), whereas *PTEN* alterations were enriched in the basal-like 1 subtype (five [45%] of 11 patients with *PTEN* mutations had basal-like mutations). In addition, there was an imbalance in the distribution of the LAR subtype favoring the control arm in the *PIK3CA/AKT1/PTEN*-altered population (six [46%] of 13 evaluable patients in the control arm vs three [20%] of 15 in the ipatasertib–paclitaxel arm).

Overall survival

At the final data cutoff, 41 patients (66%) in the ipatasertib–paclitaxel arm and 46 (74%) in the placebo–paclitaxel arm had died. Of the remaining patients, 10 had withdrawn from the study (eight [13%] vs two [3%] in the ipatasertib–paclitaxel vs placebo–paclitaxel arms, respectively), four were lost to follow-up (one [2%] vs three [5%]), three had discontinued from the study for 'other' reasons (two [3%] vs one [2%]) and 20 (10 patients [16%] in each arm) who were alive in survival follow-up at the data cutoff discontinued because of study closure.

The stratified hazard ratio for OS in the ITT population was 0.80 (95% CI 0.50–1.28). Median OS was 25.8 months (95% CI 18.6–28.6 months) with ipatasertib–paclitaxel versus 16.9 months (95% CI 14.6–24.6 months) with placebo–paclitaxel (Fig. 2a). The 1-year OS rates were 83% (95% CI 73–93%) versus 68% (95% CI 56–80%), respectively. In all prespecified biomarker-defined subgroups (*PTEN* normal or low, *PIK3CA/AKT1/PTEN* altered or non-altered), median OS favored the ipatasertib–paclitaxel arm (Fig. 2b and c). Exploratory subgroup analyses according to TNBC subtype suggested no benefit from ipatasertib and a very good prognosis in the subgroup of 13 patients with LAR TNBC and in the (largely overlapping) subgroup of 14 patients with non-basal TNBC (11 of whom were also classified as LAR TNBC). There was a benefit from ipatasertib in the larger subgroups with non-LAR or basal TNBC (Fig. 2d and e), albeit these findings should be treated with

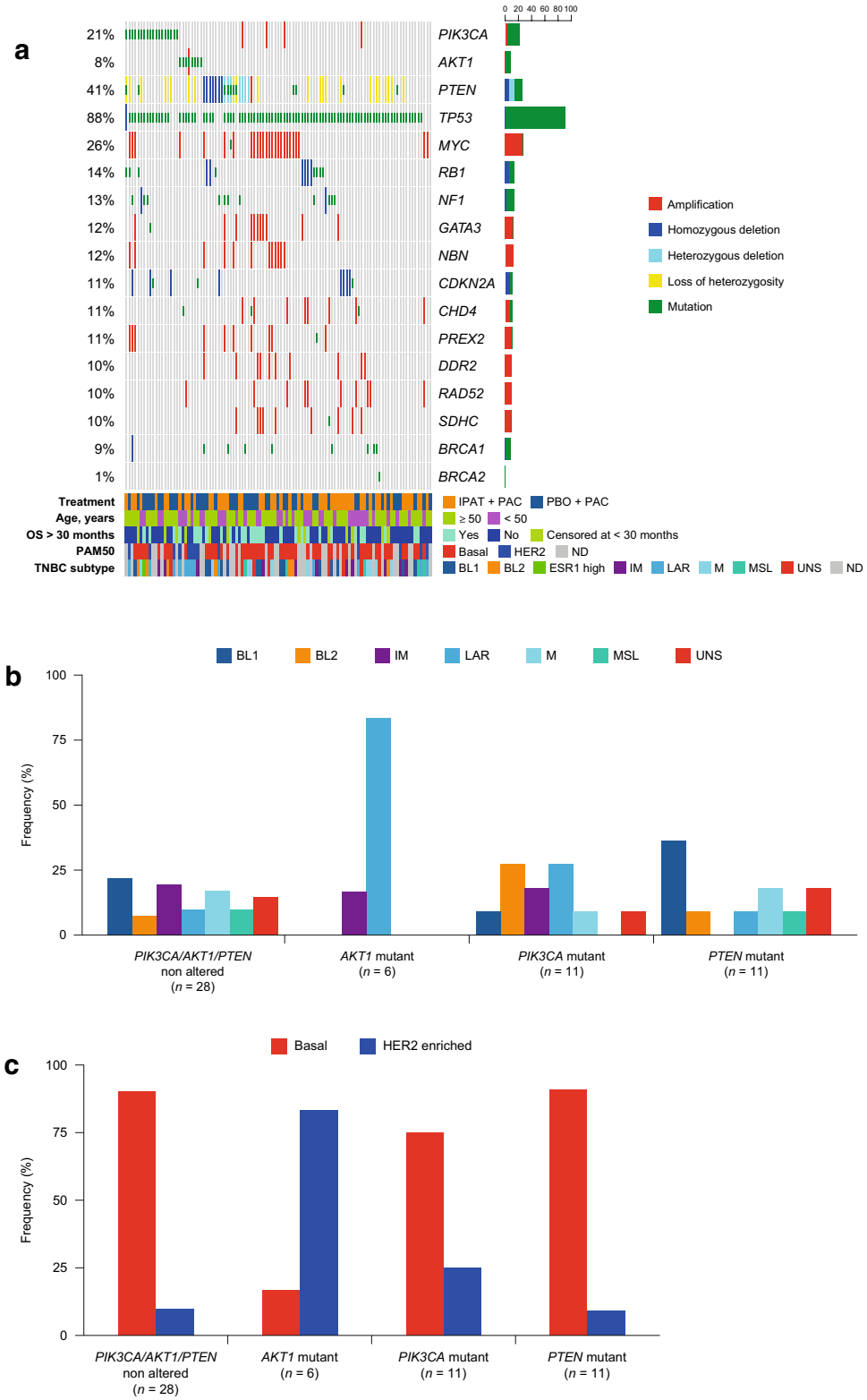

Fig. 1 Molecular profile of treated population. **a** Tile plot of transcriptional subtypes and most frequent genetic alterations according to treatment, age, OS, and molecular subtype, **b** TNBC subtype according to alteration, **c** intrinsic subtype according to alteration. *BL* basal like, *ESR1* estrogen receptor 1, *IM* immunomodulatory, *IPAT* ipatasertib, *LAR* luminal androgen receptor, *M* mesenchymal, *MSL* mesenchymal stem-like, *ND* no data, *NGS* next-generation sequencing, *OS* overall survival, *PAC* paclitaxel, *PAM50* prediction analysis of microarray 50, *PBO* placebo, *TNBC* triple-negative breast cancer, *UNS* unstable subtype

caution given the very small patient numbers in the LAR and non-basal subtype populations. Subgroup analyses of OS according to clinical and disease characteristics were consistent, favoring the ipatasertib–paclitaxel arm (Fig. 3). There appeared to be a more pronounced effect of ipatasertib in younger patients (< 50 years) than in older patients.

By the data cutoff, most patients had received at least one subsequent systemic anti-cancer therapy during

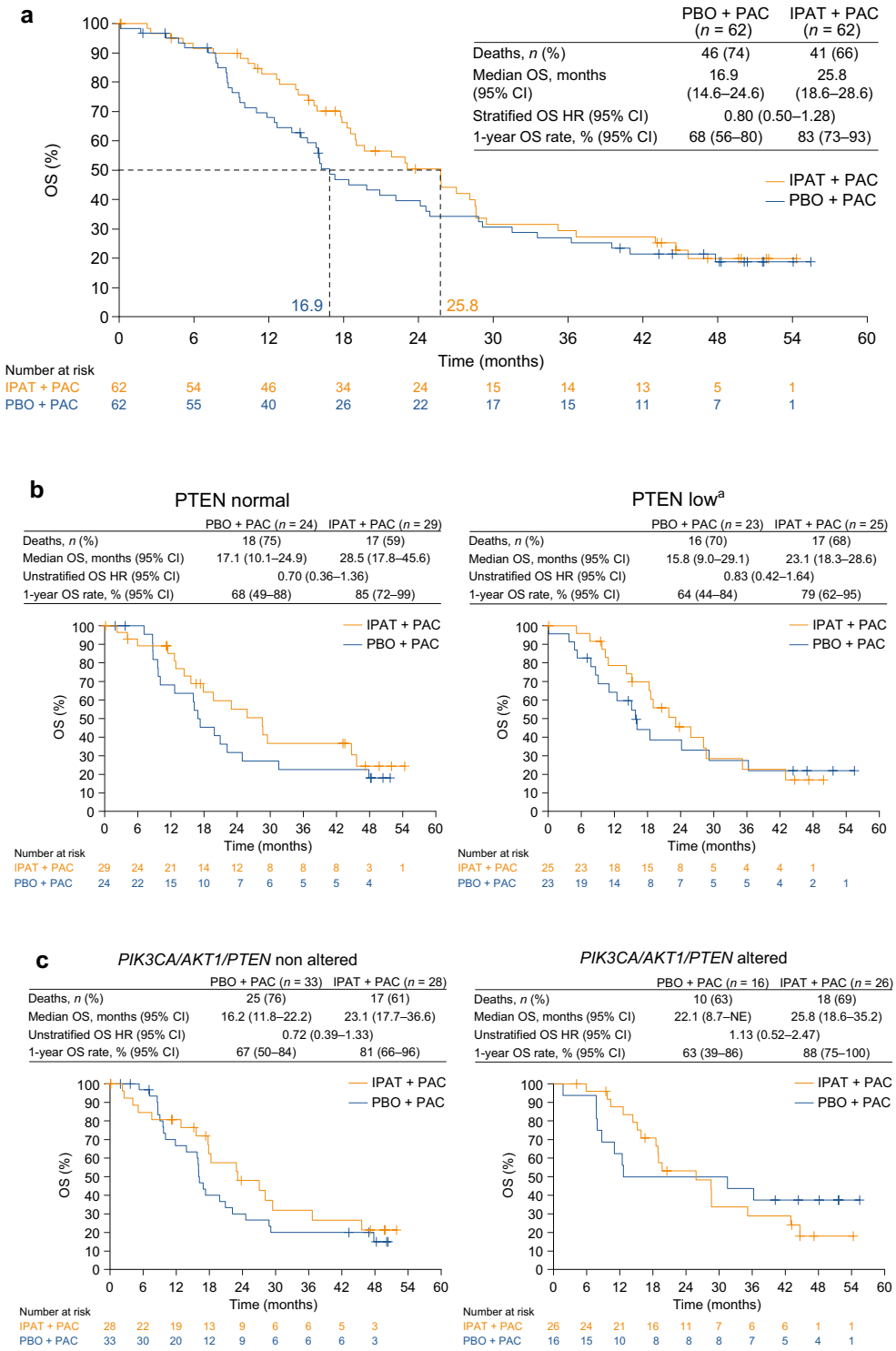

Fig. 2 Overall survival (data cutoff September 3, 2019), **a** ITT population, **b** according to PTEN status, **c** according to *PIK3CA/AKT1/PTEN* alteration status, **d** according to LAR subtype, **e** according to basal subtype. *CI* confidence interval, *HR* hazard ratio, *IHC* immunohistochemistry, *IPAT* ipatasertib, *ITT* intent-to-treat, *LAR* luminal androgen receptor, *NE* not estimable, *NGS* next-generation sequencing, *OS* overall survival, *PAC* paclitaxel, *PBO* placebo. [a]IHC H-score > 0 in ≥ 50% of tumor cells (VENTANA IHC)

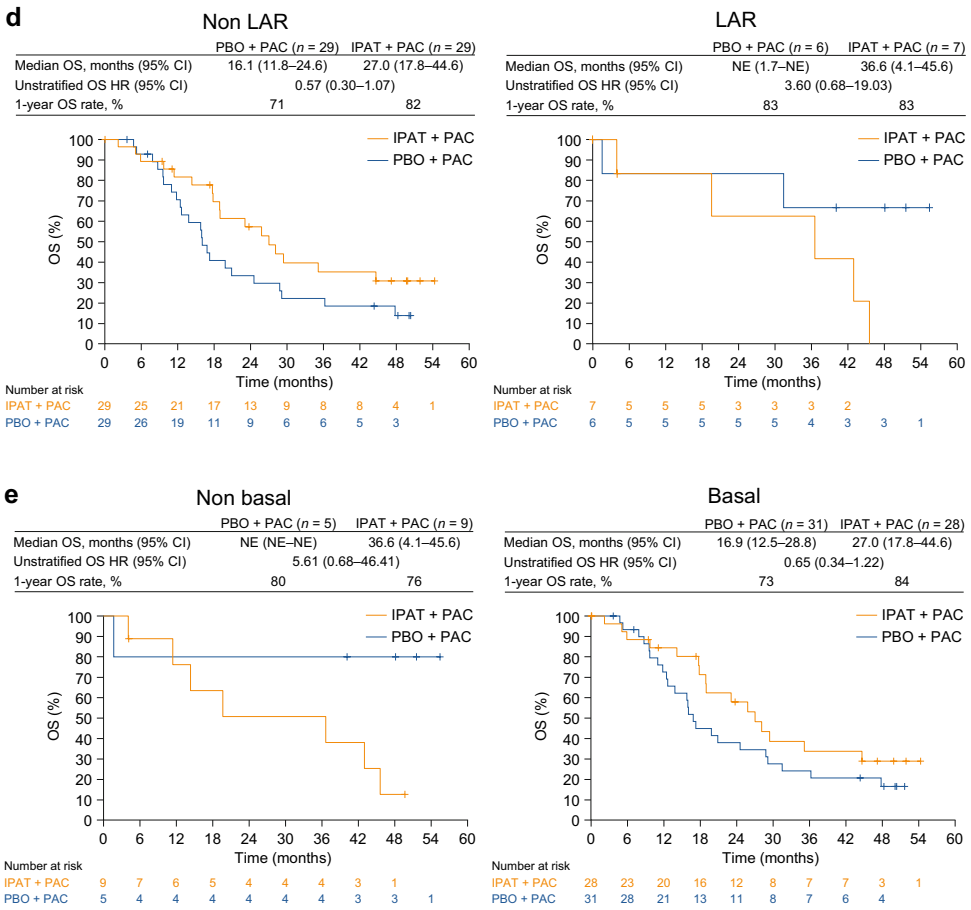

Fig. 2 (continued)

Factor	Subgroup	No. of events/No. of patients (%) PBO + PAC	No. of events/No. of patients (%) IPAT + PAC	Median OS, months PBO + PAC	Median OS, months IPAT + PAC	HR (95% Wald CI)
All	–	46/62 (74)	41/62 (66)	16.9	25.8	0.81 (0.53–1.23)
Age, years	< 50	20/24 (83)	12/22 (54)	15.1	35.2	0.41 (0.20–0.85)
	≥ 50	26/38 (68)	29/40 (73)	20.9	21.8	1.21 (0.71–2.07)
Region	Asia	23/30 (77)	20/29 (69)	18.4	25.8	0.77 (0.42–1.40)
	EU	12/16 (75)	11/18 (61)	16.2	25.8	0.66 (0.29–1.51)
	USA	11/16 (69)	10/15 (67)	15.8	19.7	1.08 (0.46–2.55)
Prior (neo)adjuvant chemotherapy (eCRF)	Yes	33/42 (79)	28/42 (67)	15.8	23.1	0.67 (0.40–1.11)
	No	13/20 (65)	13/20 (65)	18.4	25.8	1.15 (0.53–2.51)
DFI since last chemotherapy, months (eCRF)	≤ 12	11/14 (79)	8/11 (73)	11.3	14.4	0.54 (0.20–1.45)
	> 12	22/28 (79)	20/31 (65)	22.2	25.8	0.77 (0.42–1.41)
	No prior chemotherapy	13/20 (65)	13/20 (65)	18.4	25.8	1.15 (0.53–2.51)
Stage at initial diagnosis	0–III	35/45 (78)	32/48 (67)	15.8	22.9	0.74 (0.45–1.19)
	IV	11/17 (65)	9/14 (64)	20.9	27.0	1.06 (0.43–2.58)
Time from initial to metastatic diagnosis	≤ 3 years	29/35 (83)	26/36 (72)	14.6	19.0	0.63 (0.37–1.08)
	> 3 years	10/15 (67)	7/16 (44)	36.2	45.6	0.58 (0.22–1.53)
	de novo metastatic	3/5 (60)	5/6 (83)	16.0	24.1	1.05 (0.25–4.43)
	Unknown	4/7 (57)	3/4 (75)	41.0	16.5	6.07 (0.62–59.28)

Fig. 3 OS in clinically relevant subgroups (ITT population). *CI* confidence interval, *DFI* disease-free interval, *eCRF* electronic case report form, *HR* hazard ratio, *IPAT* ipatasertib, *ITT* intent-to-treat, *OS* overall survival, *PAC* paclitaxel, *PBO* placebo

follow-up (77% in the ipatasertib–paclitaxel arm, 90% in the placebo–paclitaxel arm). Slightly more patients in the placebo–paclitaxel arm than the ipatasertib–paclitaxel arm had received subsequent chemotherapy or immunotherapy (Table 1), possibly reflecting a higher proportion with disease progression.

Closer examination of patients at the tails of the curves suggests that patients in the control arm with particularly long OS (> 30 months) were enriched with the LAR TNBC subtype. In the placebo–paclitaxel control arm, seven of the eight patients with OS > 30 months were evaluable by RNASeq and of these, five (71%) had LAR subtype (compared with an expected LAR subtype prevalence of approximately 15%). Three of these eight patients had *AKT1*-mutated tumors, two had *PIK3CA*-mutated tumors, and three had *PTEN* homozygous deletions. In the ipatasertib–paclitaxel arm, six of seven patients with OS > 30 months were evaluable by RNASeq, of whom only one had LAR subtype. Among these seven patients, none had *AKT1*-mutated tumors, four had *PIK3CA* mutations, and three had *PTEN* mutations (two with homozygous deletion and one with mutation and LOH).

Among the 22 younger patients in the ipatasertib–paclitaxel arm, 11 (50%) had *PIK3CA/AKT1/PTEN*-altered tumors (three with *PIK3CA* mutations; four with *PTEN* mutations and LOH; two with *PTEN* heterozygous deletions; and two with *PTEN* homozygous deletions). Among the 24 younger patients in the placebo–paclitaxel arm, six (25%) had *PIK3CA/AKT1/PTEN*-altered tumors (two with *AKT1* mutations; one with *PTEN* mutation and LOH, and *PIK3CA* mutation; one with *PTEN* heterozygous deletion; and two with *PTEN* homozygous deletions).

Safety

Safety results at the final analysis were very similar to those reported at the primary analysis [13]. Since the primary analysis, grade ≥ 3 adverse events were reported in one additional patient in the ipatasertib–paclitaxel arm and two additional patients in the placebo–paclitaxel arm. In the ipatasertib–paclitaxel arm, adverse events led to paclitaxel discontinuation in three additional patients and paclitaxel interruption in one additional patient since the primary analysis (vs one and two, respectively, in the placebo arm as well as one patient requiring paclitaxel dose reduction). There were no additional adverse events necessitating ipatasertib dose modification or discontinuation.

Consistent with the previously reported primary analysis, the most common adverse event (any grade) with ipatasertib–paclitaxel was diarrhea (93% of patients compared with 21% of those receiving placebo–paclitaxel), followed by alopecia (54% vs 47%, respectively), nausea (53% vs 34%), and fatigue (30% vs 32%). The most common grade ≥ 3 adverse events were diarrhea (23% vs 0%), neutropenia (10% vs 2%), and neutrophil count decreased (8% vs 6%) (Supplementary Fig. S1). There were four fatal adverse events, all of which were reported at the time of the primary analysis: one case of pneumonia in the ipatasertib–paclitaxel arm, which was considered unrelated to treatment, and three deaths in the placebo–paclitaxel arm.

Table 1 Subsequent anti-cancer therapy

Therapy, *n* (%)	Placebo + paclitaxel (*n* = 62)	Ipatasertib + paclitaxel (*n* = 62)
Any systemic anti-cancer therapy[a]	56 (90)	48 (77)
Any chemotherapy	55 (89)	48 (77)
Platinum containing	32 (52)	33 (53)
Non-platinum containing	55 (89)	48 (77)
Immunotherapy	11 (18)	7 (11)

[a]Patients may have received more than one therapy

Discussion

At the final analysis of the placebo-controlled randomized phase 2 LOTUS trial after deaths in 70% of patients, OS was numerically longer with ipatasertib–paclitaxel than with placebo–paclitaxel (25.8 vs 16.9 months, respectively; hazard ratio 0.80 [95% CI 0.50–1.28]). In all biomarker-defined subgroups (PTEN normal or low, *PIK3CA/AKT1/PTEN* altered or non-altered), median OS favored ipatasertib–paclitaxel. However, the enhanced efficacy of ipatasertib in patients with *PIK3CA/AKT1/PTEN*-altered tumors in the primary PFS analysis was not observed in the final OS analysis. While this finding should be interpreted with caution given the small and imbalanced sample sizes in non-stratified subgroups (randomization in LOTUS was stratified by tumor immunohistochemistry PTEN status and not by NGS), and the design of the trial as a proof-of-concept study that was not powered for OS (or PFS), it raises questions about TNBC more generally. Initial results from LOTUS (and also from the PAKT trial [14]) suggested that perhaps *PIK3CA/AKT1/PTEN* alterations may represent a new and actionable target in metastatic TNBC. However, observations from the final OS analysis of LOTUS challenge this hypothesis. The marked heterogeneity and complexity of TNBC, even within molecular subtypes [20], make it difficult to control for all of the potential molecular and intrinsic factors that may play a role in outcomes. Therefore, even in larger trials, imbalances in molecular profiles as well as differences in the types of molecular alterations could

influence outcomes and have an impact on interpretation. Other potential confounding factors, such as the impact of subsequent therapy and possible imbalances in the type(s) of subsequent therapy administered, also influence OS. Of note, the 21% prevalence of *PIK3CA* alterations did not differ between primary tumor and metastatic samples (21% and 20%, respectively), as reported previously [16].

Notwithstanding the limitations of the small sample sizes in biomarker subgroups, it is interesting to see an OS benefit from ipatasertib in the non-luminal and basal subtypes. The LAR subtype, characterized by androgen receptor expression and its downstream effects, is associated with a better prognosis [21]. Patients with LAR TNBC may represent a distinct biology, with more indolent, slowly progressing disease that may be less susceptible to AKT-mediated chemotherapy resistance. In LOTUS, the subsets of patients achieving a long-lasting response to therapy (with or without ipatasertib) appear to include a high proportion of patients with luminal subtypes. Characterization of patients with more favorable outcomes in LOTUS suggest that the heterogeneity of TNBC, even within an apparently biomarker-selected population, may play an important role in outcomes and could also contribute to unexpected findings in these subgroups with very small patient numbers and imbalances according to molecular subtype.

There was also a suggestion of an enhanced effect of ipatasertib in younger patients (aged < 50 years) than older patients, which may be explained by differing biology. There appeared to be slight enrichment for LAR in the older subgroup, potentially contributing to the suggested differential effect of ipatasertib according to age, but this modest bias is unlikely to fully explain the apparent difference in treatment effect between younger and older patients, and these retrospective observations in very small numbers of patients should be interpreted with caution.

Median OS of > 2 years with the combination of ipatasertib and paclitaxel represents a clinically relevant and meaningful outcome in metastatic TNBC. Until the IMpassion130 trial, which demonstrated median OS of 25.0 months with atezolizumab plus nab-paclitaxel in the subgroup of patients with PD-L1-positive TNBC [22], no regimen had exceeded this threshold.

Safety results are consistent with previous reports [13, 15]; no new safety signals were observed. Of note, the safety profile in LOTUS suggests that ipatasertib blocks AKT, a recognized driver of carcinogenesis, with less toxicity than is observed with other classes of drugs targeting this pathway.

In conclusion, final OS results from LOTUS provide an encouraging signal of efficacy, irrespective of biomarker status, but the heterogeneity of metastatic TNBC and the small sample sizes of subgroups complicate interpretation. Future trials of TNBC may require greater selection and/or stratification according to prognostic molecular and genomic markers and adequate power if we are to unravel the potential role of targeted agents in this extremely complex and heterogeneous disease.

Supplementary Information The online version of this article (https://doi.org/10.1007/s10549-021-06143-5) contains supplementary material, which is available to authorized users.

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Author contributions RD, MO, SJI, CS, and S-BK were involved in the design of the study. RD, MO, SJI, S-AI, ME, SB, ART, CS, and S-BK obtained the data. MJW, NX, DB, S-JR, and AM analyzed the data. All authors interpreted the data, reviewed, and revised the draft manuscripts, and approved the final version for submission.

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Data availability Qualified researchers may request access to individual patient level data 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).

Compliance with ethical standards

Conflict of interest R Dent has received honoraria from Roche, Novartis, Lilly, Pfizer, Eisai, Merck, and AstraZeneca. M Oliveira has received honoraria from Roche, has served in a consultancy/advisory role for Roche/Genentech, GlaxoSmithKline, and Puma, and has received travel/accommodation/expenses from Roche, Novartis, Grünenthal Group, Pierre Fabre, and GP Pharm; her institution has received research funding from AstraZeneca, Philips Healthcare, Genentech, Roche, Novartis, Immunomedics, Seattle Genetics, GSK, Boehringer Ingelheim, and Puma Biotechnology. SJ Isakoff has received honoraria from Genentech, Hengrui, Puma, Immunomedics, Myriad and OncoPep, Inc.; his institution has received research funding from Genentech, PharmaMar, AstraZeneca, and Merck. S-A Im has served in a consultancy/advisory role for AstraZeneca, Amgen, Eisai, Lilly, MedPacto, Novartis, Daiichi-Sankyo, Pfizer, and Roche; his institution has received research funding from AstraZeneca, Pfizer, and Roche. M Espié has received research funding from Roche, Novartis, and Pfizer. S Blau reports that her husband is the owner of

the company All4Cure. AR Tan has served in a consultancy/advisory role for Immunomedics, Celgene, Pfizer, Genentech/Roche, Novartis, AbbVie, and Eisai; her institution has received research funding from Merck, Pfizer, Tesaro, Genentech/Roche, G1 Therapeutics, and Daiichi-Sankyo. C Saura has received honoraria from AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, Roche, Genomic Health, Novartis, Pfizer, Pierre Fabre, Puma, and Synthon, has served in a consultancy/advisory role for AstraZeneca, Eisai, Roche, Genomic Health, Novartis, Pfizer, Puma, Sanofi, and Synthon, and has received research funding from Genentech and AstraZeneca. MJ Wongchenko, N Xu, and A Mani are employed by Genentech/Roche and hold shares in Roche. D Bradley is employed by Roche Products Ltd, holds shares in Roche, and is named as an inventor on a Roche/Genentech patent application. S-J Reilly is employed by Roche Products Ltd and holds shares in Roche. S-B Kim has served in a consulting/advisory role for Novartis, AstraZeneca, Lilly, Enzychem Lifesciences, Dae Hwa Pharmaceutical Co. Ltd, ISU Abxis, and Daiichi-Sankyo and has received research funding from Novartis, Sanofi Aventis, Kyowa Kirin Inc, and DongKook Pharma Co, Ltd.

Ethical approval We obtained independent Institutional Review Board approval of the protocol and all study-related documents from each participating institution, and written informed consent from all participants. The trial was performed in accordance with the Helsinki declaration and all amendments.

Informed consent All patients provided written informed consent before undergoing any study-specific procedures.

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