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ORIGINAL ARTICLE

Phase III randomized study of taselisib or placebo with fulvestrant in estrogen receptor-positive, *PIK3CA*-mutant, HER2-negative, advanced breast cancer: the SANDPIPER trial☆

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Background: The phase III SANDPIPER study assessed taselisib (GDC-0032), a potent, selective PI3K inhibitor, plus fulvestrant in estrogen receptor-positive, HER2-negative, *PIK3CA*-mutant locally advanced or metastatic breast cancer.

Patients and methods: Postmenopausal women with disease recurrence/progression during/after an aromatase inhibitor were randomized 2 : 1 to receive taselisib (4 mg; taselisib arm) or placebo (placebo arm) plus fulvestrant (500 mg). Stratification factors were visceral disease, endocrine sensitivity, and geographic region. Patients with *PIK3CA*-mutant tumors (central cobas® PIK3CA Mutation Test) were randomized separately from those without detectable mutations. The primary endpoint was investigator-assessed progression-free survival (INV-PFS) in patients with *PIK3CA*-mutant tumors. Secondary endpoints included objective response rate, overall survival, clinical benefit rate, duration of objective response, PFS by blinded independent central review (BICR-PFS), safety, and time to deterioration in health-related quality of life.

Results: The *PIK3CA*-mutant intention-to-treat population comprised 516 patients (placebo arm: $n = 176$; taselisib arm: $n = 340$). INV-PFS was significantly improved in the taselisib {7.4 months [95% confidence interval (CI), 7.26-9.07]} versus placebo arm (5.4 months [95% CI, 3.68-7.29]) (stratified hazard ratio [HR] 0.70; 95% CI, 0.56-0.89; $P = 0.0037$) and confirmed by BICR-PFS (HR 0.66). Secondary endpoints, including objective response rate, clinical benefit rate, and duration of objective response, showed consistent improvements in the taselisib arm. Safety was assessed in all randomized patients who received at least one dose of taselisib/placebo or fulvestrant regardless of *PIK3CA*-mutation status ($n = 629$). Serious adverse events were lower in the placebo versus taselisib arm (8.9% versus 32.0%). There were more discontinuations (placebo arm: 2.3%; taselisib arm: 16.8%) and dose reductions (placebo arm: 2.3%; taselisib arm: 36.5%) in the taselisib arm.

Conclusion: SANDPIPER met its primary endpoint; however, the combination of taselisib plus fulvestrant has no clinical utility given its safety profile and modest clinical benefit.

Key words: *PIK3CA* mutations, taselisib, PI3K inhibitors, advanced breast cancer

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☆ **Note:** This study was previously presented as trials in progress posters for SANDPIPER at the American Society of Clinical Oncology (ASCO) Congress 2015 (29 May to 2 June 2015), San Antonio Breast Cancer Symposium (SABCS) Congress 2015 (8-12 December 2015), ASCO Congress 2016 (3-7 June 2016), European Society for Medical Oncology (ESMO) Congress 2016 (7-11 October 2016), SABCS Congress 2016 (6-10 December 2016) and ASCO Congress 2017 (2-6 June 2017). Key data from SANDPIPER were presented in an oral session at the ASCO Congress 2018 (1-5 June 2018).

INTRODUCTION

The phosphatidylinositol 3-kinase (PI3K) pathway is involved in tumor growth, proliferation, and survival and is activated frequently in solid tumors.[1] Mechanisms activating this pathway include gain-of-function mutations and/or amplification of the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene.[1-5] *PIK3CA* encodes the α-isoform of the catalytic subunit of PI3K (PI3Kα)[2] and mutations are detected in ∼40% of estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancers (BCs).[6] Preclinical data have demonstrated significant crosstalk between ER and PI3K pathways, and inhibition of PI3K results in an adaptive upregulation of ER signaling.[7,8] Additionally, PI3K inhibition augments ER function and dependence in hormone receptor-positive BC.[7,8]

Taselisib (GDC-0032), a potent, selective inhibitor of class I PI3Kα-, δ-, and γ-isoforms,[9-12] has greater efficacy *in vitro* against mutant PI3Kα isoforms and cells than those with wildtype PI3Kα.[9-11,13] A phase I study of single-agent taselisib suggested activity in *PIK3CA*-mutant BC.[13] The safety profile was tolerable, with expected PI3K inhibitor class adverse events (AEs), including hyperglycemia, diarrhea, rash, and stomatitis.[13-16] In a single-arm phase II study, response rates were higher in patients with *PIK3CA*-mutated advanced BC treated with taselisib plus fulvestrant than those with *PIK3CA*-mutation-not-detected (MND) tumors.[17] In the neoadjuvant LORELEI study, taselisib plus letrozole (versus placebo plus letrozole) had a significantly improved objective response rate (ORR) in the ER-positive, HER2-negative intention-to-treat population; this was more pronounced in the *PIK3CA*-mutant population.[18]

The phase III SANDPIPER study (ClinicalTrials.gov: NCT02340221) aimed to assess the clinical efficacy of taselisib plus fulvestrant versus placebo plus fulvestrant in patients with ER-positive, HER2-negative, *PIK3CA*-mutant locally advanced or metastatic BC. An exploratory evaluation in patients with *PIK3CA*-MND tumors was also carried out.

PATIENTS AND METHODS

Study design and patients

SANDPIPER was a phase III, randomized, multicenter, international, double-blind, placebo-controlled trial (Supplementary Figure S1 available at https://doi.org/10.1016/j.annonc.2020.10.596). Patients received 500 mg intramuscular fulvestrant (cycle 1, days 1 and 15; day 1 of each subsequent 28-day cycle) plus either taselisib (the taselisib arm) or placebo (the placebo arm) until progressive disease or unacceptable toxicity. Patients received either 4 mg taselisib tablets orally, once daily, or matching placebo. Dose interruptions and reductions of taselisib or placebo were permitted for treatment-related toxicities (Supplementary Table S1 available at https://doi.org/10.1016/j.annonc.2020.10.596). Fulvestrant dose interruptions, but not reductions, were permitted. Patients discontinued study drugs if they experienced any medical condition that the investigator/sponsor determined may jeopardize patient safety, radiographic progressive disease (or clinical progression at the discretion of the investigator), unacceptable toxicity, or if they were not compliant with protocol-specified drug administration and follow-up tests, or if they withdrew consent. Study procedures are provided in the published protocol.

Eligible patients, enrolled at 155 centers in 28 countries (Supplementary Protocol available at https://doi.org/10.1016/j.annonc.2020.10.596), were female, postmenopausal, and had histologically or cytologically confirmed invasive, ER-positive metastatic or inoperable locally advanced BC. A valid, centralized cobas® PIK3CA Mutation Test result from formalin-fixed paraffin-embedded tissue was required before randomization. Patients had radiologic/objective evidence of BC recurrence or progression while on or within 12 months of the end of adjuvant treatment with an aromatase inhibitor, or progression while on or within 1 month of the end of prior aromatase inhibitor treatment of locally advanced or metastatic BC. Patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status of zero or one and measurable disease via Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) or non-measurable, evaluable disease with at least one evaluable bone lesion via RECIST v1.1. Patients were also candidates for endocrine therapy alone at the time of study entry (per treatment guidelines).

Patients were ineligible if they had received prior fulvestrant, a PI3K inhibitor, a mammalian target of rapamycin inhibitor, or an AKT (protein kinase B) inhibitor. Patients requiring chemotherapy for visceral crisis per their physician's judgment, who had received >1 prior cytotoxic chemotherapy regimen for metastatic BC, or who had HER2-positive disease by local testing were ineligible.

SANDPIPER was approved by an institutional review board and conducted per the principles of the Declaration of Helsinki, International Council for Harmonisation Guidelines, and the laws and regulations of the countries in which it was conducted. All patients provided written informed consent.

Randomization and masking

Patients were randomly assigned 2 : 1 to either the taselisib or placebo arm; patients with *PIK3CA*-mutant tumors or *PIK3CA*-MND tumors (based on tumor tissue) were randomized separately using a permuted-block randomization method.

Stratification factors were visceral disease (visceral versus non-visceral), geographic region [Asia versus Western Europe/USA/Canada/Australia versus the rest of the world (RoW)], and endocrine sensitivity (sensitive versus non-sensitive).

Endocrine sensitivity was defined as either no endocrine treatment in advanced or metastatic BC and ≥24 months of adjuvant endocrine treatment before recurrence or documented clinical benefit [complete response (CR), partial response (PR), or stable disease ≥24 weeks] to most recent endocrine treatment in advanced or metastatic BC.

Outcomes

The primary endpoint was investigator-assessed progression-free survival (INV-PFS) in patients with *PIK3CA*-mutant tumors. Secondary endpoints included ORR, overall survival (OS), clinical benefit rate (CBR), duration of objective response (DoR), and PFS by blinded independent central review (BICR-PFS) in patients with *PIK3CA*-mutant tumors. Safety was assessed in all patients who received at least one dose of taselisib/placebo or fulvestrant, regardless of *PIK3CA* mutation status. Exploratory endpoints included efficacy in patients with *PIK3CA*-MND tumors and in patients whose *PIK3CA* mutation status was determined by circulating tumor DNA (ctDNA) analysis. Time to deterioration (TTD) in health-related quality of life (HRQoL) was also assessed.

Safety

Safety was evaluated by monitoring all AEs, standard laboratory abnormalities, and vital signs. AEs were defined and graded per National Cancer Institute — Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. 'Group' terms were defined based on the Medical Dictionary for Regulatory Activities (MedDRA; Supplementary Protocol available at https://doi.org/10.1016/j.annonc.2020.10.596).

Biomarker assessments

PIK3CA mutation status was determined centrally using the cobas® PIK3CA Mutation Test from formalin-fixed paraffin-embedded primary or metastatic tissue, according to the manufacturer's instructions (Roche Molecular Systems, Branchburg, NJ, USA). This test detects the following *PIK3CA* mutations: R88Q, N345K, C420R, E542K, E545A/G/K/D, Q546K/R/E/L, M1043I, H1047L/R/Y, and G1049R. Tumors were classified as '*PIK3CA*-mutant' based on a positive result or '*PIK3CA*-MND' if no mutations were detected.

PIK3CA mutations were also analyzed in plasma ctDNA using the FoundationOne® Liquid assay (Foundation Medicine, Inc., Cambridge, MA) as described previously.[19]

Tumor assessments

All known sites of disease were documented at screening (within 28 days before cycle 1, day 1) and reassessed at each subsequent tumor evaluation (every 8 weeks ±5 days from the date of randomization). Response assessments were made by the investigator based on physical examinations, computerized tomography scans, or magnetic resonance imaging, and/or bone scans per RECIST v1.1. The same radiographic procedure used to assess disease sites at screening was used throughout the study.

Statistical analysis

Planned enrollment was 600 patients, with a 4 : 1 enrichment of patients with *PIK3CA*-mutant (480 patients) versus *PIK3CA*-MND (120 patients) tumors (exploratory endpoint population). The sample size of 480 patients with *PIK3CA*-mutant tumors was determined based on a power calculation (primary endpoint analysis population). In these patients, approximately 287 INV-PFS events were required to detect the treatment difference under a target HR of 0.59 in PFS (3.1 months of improvement in median PFS) with 95% power at the α two-sided significance level of 1%, assuming a median PFS of 4.5 months in the control arm. One interim INV-PFS efficacy analysis was conducted at 60% of the planned PFS events for the primary analysis.

The intention-to-treat population included all randomized patients regardless of whether they received any amount of the assigned treatment. The primary and secondary efficacy populations comprised patients with *PIK3CA*-mutant tumors only. The safety-evaluable population included all randomized patients who received at least one dose of taselisib/placebo or fulvestrant regardless of *PIK3CA*-mutation status, with patients allocated to the treatment arm associated with the regimen received.

Median PFS (INV and BICR), OS, and DoR were estimated using the Kaplan—Meier approach in each treatment arm. Cox proportional hazards models were used to estimate the HR with 95% CI.

The Blyth—Still—Casella method was used to estimate the ORR and CBR and the corresponding 95% CI for each treatment arm. The stratified Cochran—Mantel—Haenszel test was used to compare ORR and CBR between treatment arms. The 95% CI for the difference in ORRs and CBRs between the two treatment arms was determined using the normal approximation to the binomial distribution. CBR was defined as CR, PR, or stable disease lasting ≥24 weeks. TTD in HRQoL was compared between treatment arms using the stratified Cox proportional hazards model.

RESULTS

Patient characteristics

Between 9 April 2015 and 4 September 2017, 631 patients were randomized to either the taselisib ($n = 417$) or placebo arm ($n = 214$) (Supplementary Figure S2 available at https://doi.org/10.1016/j.annonc.2020.10.596). Of the 516 patients with *PIK3CA*-mutant tumors, 176 and 340 were randomized to the placebo and taselisib arms, respectively; the data reported here focus on these patients unless otherwise specified. Baseline characteristics were well balanced between treatment arms (Table 1). Patients were enrolled from Western Europe, USA, Canada, or Australia (49.6%), Asia (15.7%), and RoW (34.7%); a numerically greater proportion of patients in the RoW versus non-RoW had an ECOG PS of one and had received prior tamoxifen in the placebo arm (Supplementary Table S2 available at https://doi.org/10.1016/j.annonc.2020.10.596). Median time on study was 10.8 months (range, 1.2-31.7 months) in the placebo arm and 11.2 months (range, 0-30.3 months) in the taselisib arm.

Efficacy

At clinical cutoff (15 October 2017), 67.6% of patients in the placebo arm versus 57.1% in the taselisib arm had

Table 1. Baseline demographic and disease characteristics in patients with *PIK3CA*-mutant tumors

	Placebo + fulvestrant (n = 176)	Taselisib + fulvestrant (n = 340)
Age in years, median (range)	61 (39-85)	60 (32-84)
ECOG PS		
0	93 (52.8)	185 (54.4)
1	83 (47.2)	155 (45.6)
Visceral disease[a]	103 (58.5)	201 (59.1)
Bone-only disease	32 (18.2)	70 (20.6)
Bone metastasis	127 (72.2)	267 (78.5)
Measurable disease	134 (76.1)	264 (77.6)
Endocrine sensitivity[a]	129 (73.3)	251 (73.8)
Prior endocrine therapy		
Prior adjuvant endocrine therapy	120 (68.2)	203 (59.7)
Prior endocrine therapy for MBC	121 (68.8)	254 (74.7)
Prior tamoxifen (regardless of setting)	86 (48.9)	168 (49.4)
Prior CDK4/6 inhibitor	3 (1.7)	12 (3.5)
Prior chemotherapy		
Prior chemotherapy in MBC	49 (27.8)	109 (32.1)
Prior systemic therapy in MBC	128 (72.7)	265 (77.9)
Number of regimens in MBC, median (25%, 75%)	1 (0, 2)	1 (1, 2)
Range	0-6	0-5
Region[a]		
Western Europe/USA/Canada/ Australia	86 (48.9)	170 (50.0)
Asia	29 (16.5)	52 (15.3)
Rest of the world	61 (34.7)	118 (34.7)

Data are *n* (%)unless otherwise specified.
CDK, cyclin-dependent kinases; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MBC, metastatic breast cancer; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
[a] Stratification factor.

experienced a PFS event (Figure 1A). In patients with PIK3CA-mutant tumors, the median INV-PFS in the placebo arm was 5.4 months (95% CI, 3.68-7.29) versus 7.4 months (95% CI, 7.26-9.07) in the taselisib arm (stratified HR 0.70; 95% CI, 0.56-0.89; P = 0.0037). BICR-PFS was consistent with INV-PFS and confirmed the magnitude of benefit (Figure 1B). Across most subgroups evaluated, results were consistent with the overall PIK3CA-mutant cohort with a treatment benefit in favor of the taselisib versus placebo arm (Figure 2).

Exploratory analyses of INV-PFS by geographic region showed a consistent benefit of taselisib versus placebo, except for patients from the RoW (Supplementary Figure S3A; Asia: Supplementary Figure S3B; Western Europe/USA/Canada/Australia: Supplementary Figure S3C available at https://doi.org/10.1016/j.annonc.2020.10.596). The RoW accounted for 34.7% of the patients with *PIK3CA*-mutant tumors overall and was the only region with an INV-PFS HR >1 (1.18). Consistent with the lack of INV-PFS benefit, patients in the RoW had a longer median BICR-PFS in the placebo versus taselisib arm compared with patients in other regions (Supplementary Table S3 available at https://doi.org/10.1016/j.annonc.2020.10.596).

In patients with *PIK3CA*-MND tumors, median INV-PFS was 4.0 months in the placebo arm and 5.6 months in the taselisib arm (stratified HR 0.69; 95% CI, 0.44-1.08) (Supplementary Figure S4A available at https://doi.org/10.1016/j.annonc.2020.10.596). Baseline demographics in patients with *PIK3CA*-MND tumors were generally balanced between arms (Supplementary Table S4 available at https://doi.org/10.1016/j.annonc.2020.10.596).

Among patients in the *PIK3CA*-mutant cohort with measurable disease, the objective response (CR or PR) was 16.1% higher in the taselisib arm (28.0%) versus the placebo arm (11.9%; 95% CI, 8.4-23.8) (Table 2). In the placebo arm, 11.9% of patients had a PR versus 27.3% in the taselisib arm (Table 2). Among patients with measurable disease at baseline, the CBR was lower in the placebo arm (37.3%) versus the taselisib arm (51.5%) (Table 2). The median DoR was 7.2 months (95% CI, 6.51-not evaluable) in the placebo arm and 8.7 months (95% CI, 5.72-11.24) in the taselisib arm (Table 2).

In patients with measurable disease in the *PIK3CA*-MND cohort, the ORR was 14.3% in the placebo arm versus 19.7% in the taselisib arm (Supplementary Figure S4B available at https://doi.org/10.1016/j.annonc.2020.10.596).

At clinical cutoff, OS data were immature. A total of 116 patients in the *PIK3CA*-mutant cohort had died (placebo arm: 24.4%; taselisib arm: 21.5%) (Table 2).

Safety

Most patients reported at least one AE, regardless of causality (Table 3). The most frequent all-grade AEs were gastrointestinal disorders (placebo arm: 55.4%; taselisib arm: 81.7%). The most common AEs in the taselisib arm (≥15% of patients) were diarrhea, hyperglycemia, nausea, decreased appetite, fatigue, headache, stomatitis, vomiting, asthenia, and rash (Table 3). Grade 3-5 AEs were experienced by 16.4% and 49.5% of patients in the placebo and taselisib arms, respectively, with diarrhea and hyperglycemia most commonly reported in the taselisib arm (Table 3).

The proportion of serious AEs was lower in the placebo arm versus the taselisib arm (8.9% versus 32.0%, respectively; Table 3). The most frequent serious AEs were gastrointestinal disorders (placebo arm: 0.9%; taselisib arm: 15.1%).

All-grade and serious infection occurred in 23.9% and 0.9% in the placebo arm, respectively (versus 41.8% and 7.5% of patients in the taselisib arm, respectively). Urinary tract infection was most frequently reported, with respiratory tract, gastrointestinal tract, and skin infections also common; no pattern of infection was identified.

Grade 5 AEs were observed in both the placebo (0.5%) and taselisib arms (1.9%) (Table 3). While there was no pattern in the cause of deaths, underlying disease was identified as a factor in several cases.

A lower proportion of patients in the placebo arm experienced AEs leading to taselisib/placebo discontinuation (2.3% versus 16.8% in the taselisib arm) and dose reduction (2.3% versus 36.5% in the taselisib arm) (Table 3).

AEs, including grade ≥3, serious AEs, and AEs leading to dose discontinuation, reduction, and interruption, were less frequent in the placebo versus taselisib arm in patients with *PIK3CA* mutations when analyzed by geographical region

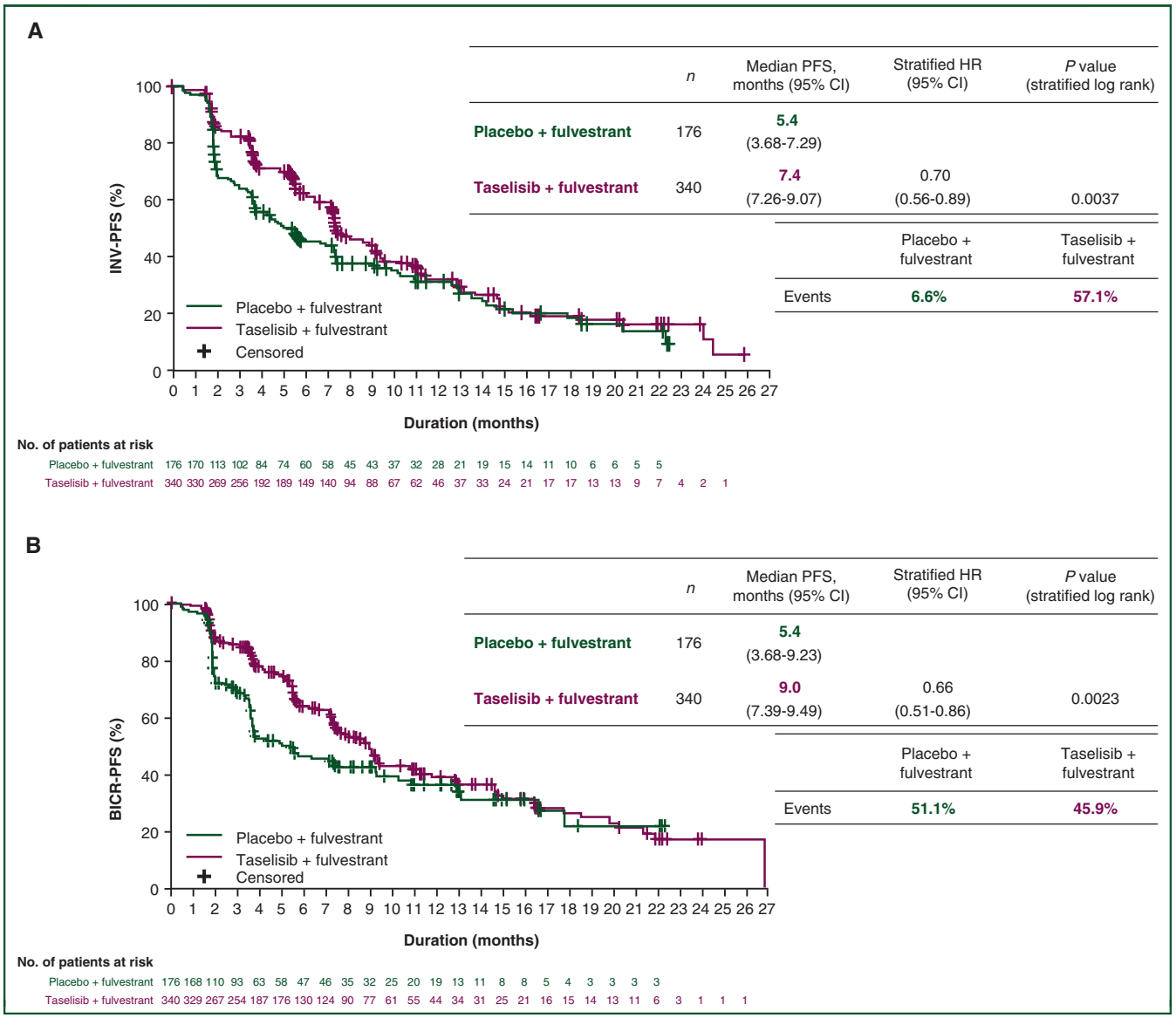

Figure 1. Kaplan–Meier plots for PFS in patients with *PIK3CA*-mutant tumors: (A) investigator-assessed PFS; (B) BICR-PFS.
PFS was defined as the time from randomization to first disease progression as determined by the investigator using RECIST v1.1, or death from any cause.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; INV, investigator-assessed; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

(Supplementary Table S5 available at https://doi.org/10.1016/j.annonc.2020.10.596). Relative to Western Europe/USA/Canada/Australia, patients from the RoW experienced fewer grade ≥3 AEs and AEs leading to taselisib discontinuation in the taselisib arm.

PIK3CA ctDNA biomarker assessment

Of the 631 patients enrolled, 339/598 plasma samples analyzed had detectable *PIK3CA* mutations, with 66 having ≥2 *PIK3CA* mutations. Overall concordance between tumor and ctDNA *PIK3CA* mutation positivity was 79.7% (Supplementary Tables S6 and S7 available at https://doi.org/10.1016/j.annonc.2020.10.596). Where tumors were classified as *PIK3CA*-mutant based on tissue analysis, 78.2% of patients also had detectable *PIK3CA* mutations by ctDNA analysis. Ninety-one patients with *PIK3CA*-mutant tumor tissue had no detectable ctDNA *PIK3CA* mutations (21.8%). Where tumors were classified as *PIK3CA*-MND based on tumor tissue analysis, 86.7% of patients also had no detectable *PIK3CA* mutations by ctDNA analysis. Twelve patients with *PIK3CA*-MND based on tumor tissue analysis had detectable *PIK3CA* mutations by ctDNA analysis (13.3%).

Based on ctDNA analysis, the INV-PFS HRs for patient subgroups with *PIK3CA*-mutant and *PIK3CA*-MND tumors were 0.62 (95% CI, 0.47-0.83) and 0.86 (95% CI, 0.57-1.27), respectively (Figures 3A and 3B; Supplementary Table S8 available at https://doi.org/10.1016/j.annonc.2020.10.596). The HR for INV-PFS in the taselisib and placebo arms was higher where patients had one *PIK3CA* mutation (HR 0.68, 95% CI, 0.49-0.93), compared with patients with ≥2 *PIK3CA* mutations (HR 0.37; 95% CI, 0.18-0.77)

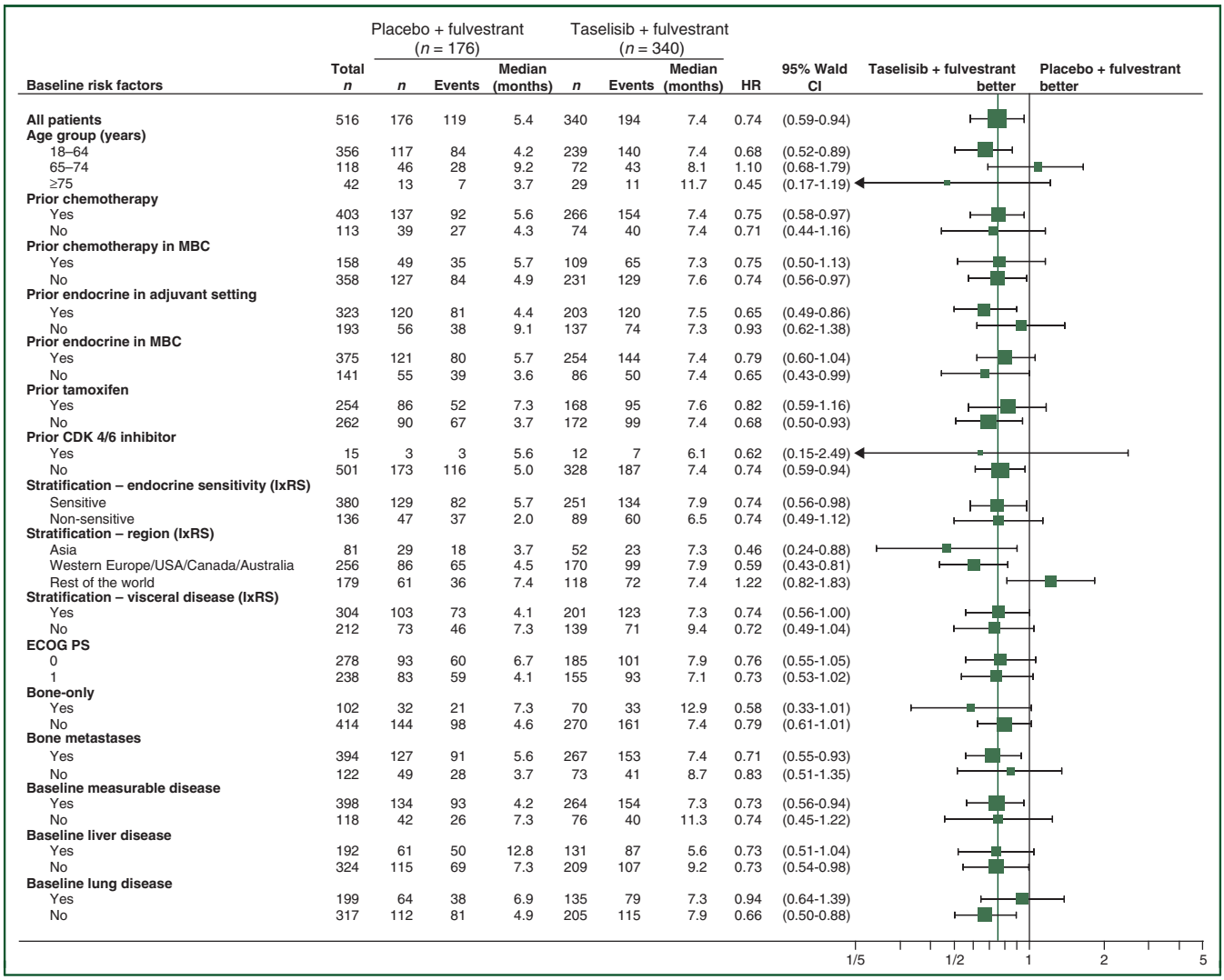

Figure 2. Forest plot of investigator-assessed PFS in patients with *PIK3CA*-mutant tumors.
PFS was defined as the time from randomization to first disease progression as determined by the investigator using RECIST v1.1, or death from any cause.
CI, confidence interval; CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IxRS, Interactive Voice/Web Response System; MBC, metastatic breast cancer; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

(Supplementary Figures S5A and S5B and Supplementary Table S8 available at https://doi.org/10.1016/j.annonc.2020.10.596). Similar geographic regional differences were observed with ctDNA analysis (Supplementary Table S9 available at https://doi.org/10.1016/j.annonc.2020.10.596).

The frequency of *PIK3CA* mutations across treatment arms did not differ when analyzed by geographical region (Supplementary Table S10 available at https://doi.org/10.1016/j.annonc.2020.10.596).

TTD in HRQoL

At clinical cutoff, TTD-HRQoL data were immature. Fifty-eight of 176 (33.0%) and 120/340 (35.3%) patients with *PIK3CA* mutations in the placebo and taselisib arms, respectively, had a deterioration in HRQoL. Median TTD in HRQoL was 6.5 months (95% CI, 3.8-11.1) in the placebo arm versus 8.1 months (95% CI, 7.3-9.7) in the taselisib arm (not statistically significant; stratified HR, 0.84; 95% CI, 0.60-1.16; $P = 0.28$; Supplementary Table S11 available at https://doi.org/10.1016/j.annonc.2020.10.596).

DISCUSSION

SANDPIPER was a phase III, double-blind, randomized study of taselisib/placebo plus fulvestrant in patients with ER-positive, HER2-negative, locally advanced or metastatic BC. SANDPIPER met its primary endpoint: the addition of taselisib to fulvestrant showed a statistically significant improvement in INV-PFS in patients with *PIK3CA*-mutant tumors. However, despite this improvement (HR 0.70), addition of taselisib to fulvestrant did not result in a clinically meaningful improvement given the short PFS observed. Taselisib plus fulvestrant had an expected safety profile, but with a higher proportion of discontinuations and dose reductions compared with the placebo arm.

Table 2. Secondary efficacy in patients with *PIK3CA*-mutant tumors

	Placebo + fulvestrant	Taselisib + fulvestrant
Patients with measurable disease	(*n* = 134)	(*n* = 264)
Responders	16 (11.9%)	74 (28.0%)
Difference in response rates (95% CI)	16.1 (8.4-23.8)	
P value (Cochran—Mantel—Haenszel)	0.0002	
CR	0	2 (0.8%)
PR	16 (11.9%)	72 (27.3%)
CBR	50 (37.3%)	136 (51.5%)
Patients with and without measurable disease	**(*n* = 176)**	**(*n* = 340)**
CBR	73 (41.5%)	185 (54.4%)
DoR	**(*n* = 16)**	**(*n* = 74)**
Median, months (95% CI)	7.2 (6.51-NE)	8.7 (5.72-11.24)
OS	**(*n* = 176)**	**(*n* = 340)**
Events	43 (24.4%)	73 (21.5%)

CBR was defined as objective response or no disease progression for ≥24 weeks since randomization; confirmation not needed for CR and PR.

CI, confidence interval; CBR, clinical benefit rate; CR, complete response; DoR, duration of objective response; NE, not evaluable; OS, overall survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PR, partial response.

Across most subgroups evaluated for INV-PFS, results were generally consistent with the overall *PIK3CA*-mutant cohort, with a treatment benefit in favor of the taselisib arm. A major exception was the RoW subgroup, where there was no benefit of adding taselisib to fulvestrant (HR 1.18). The reasons for this difference remain unknown and could not be readily explained by differential regional baseline characteristics or safety profiles. There was also no evidence of systemic bias since BICR-PFS analysis confirmed these regional differences.

In the SANDPIPER placebo arm, median INV- and BICR-PFS in patients with *PIK3CA*-mutant tumors were longer than expected based on subgroup analyses from the BELLE-2 and PALOMA-3 studies,[20,21] and this may have confounded the overall results. The longer median PFS in the placebo arm of SANDPIPER could not be explained by differences in baseline characteristics between treatment arms.

Secondary endpoints, including ORR, CBR, DoR, and BICR-PFS, showed consistent improvement with taselisib plus fulvestrant. OS data are immature at the time of this primary PFS analysis. Taselisib plus fulvestrant led to a numerical but not statistically significant improvement versus placebo in TTD in HRQoL; however, data were immature at the time of primary analysis.

The clinical efficacy of fulvestrant plus alpelisib, a selective inhibitor of PI3Kα, was reported in the phase III, randomized, placebo-controlled SOLAR-1 trial, which had a similar patient population to SANDPIPER.[22] Both SANDPIPER and SOLAR-1 met their primary endpoints, with statistically significant improvements in INV-PFS in the *PIK3CA*-mutant population (SANDPIPER: HR 0.70; $P = 0.0037$; SOLAR-1: HR 0.65; $P = 0.001$). However, patients treated with alpelisib plus fulvestrant had a PFS of 11 months (versus 5.7 months with placebo plus fulvestrant), which was longer than the 7.4 months observed in the taselisib arm of SANDPIPER (versus 5.4 months in the placebo arm).[22] The Kaplan—Meier PFS curves for the alpelisib plus fulvestrant versus placebo plus fulvestrant arms in SOLAR-1 remained separated, whereas the curves for the taselisib versus placebo arms in SANDPIPER converged, consistent with a clinically more meaningful benefit in SOLAR-1.[22] Interestingly, regional variations in PFS were reported in both SOLAR-1 and SANDPIPER: there was no treatment benefit with alpelisib in the Latin American region (9% of patients) or taselisib in the RoW (35% of patients), which included Latin America.[22] Direct comparisons of the data should be made with caution given the differential PI3K inhibitor profile of alpelisib versus taselisib and the differing definitions of endocrine sensitivity in the two trials.[22]

In our exploratory analysis of plasma collected immediately before enrollment, HR was more favorable for patients who had *PIK3CA* mutations detected by ctDNA analysis versus those detected in tissue (0.62 versus 0.70, respectively). The numerically lower INV-PFS in the placebo arm when *PIK3CA* mutations were detected by ctDNA versus tumor tissue analysis (3.6 versus 5.4 months, respectively) is consistent with the fulvestrant control arm in the BELLE-2 study (hormone receptor-positive, HER2-negative advanced BC; 3.2 versus 4.0 months, respectively),[23] potentially identifying a higher-risk population. Notably, patients with ≥2 detectable *PIK3CA* mutations by ctDNA analysis had a more favorable HR for INV-PFS and a higher ORR versus those with a single mutation,[24] suggesting that patients with ≥2 *PIK3CA* mutations may derive a larger clinical benefit from PI3K inhibition.

Taselisib plus fulvestrant had an expected safety profile,[13,17] with gastrointestinal toxicities and hyperglycemia being the most frequent AEs. Potential new safety signals with a higher frequency in the taselisib arm included infections, alopecia, pyrexia, decreased weight, and dyspepsia. Although there was a higher proportion of AEs leading to study drug discontinuation and dose reduction in the SOLAR-1 alpelisib arm (25.0% and 63.9%, respectively) versus the SANDPIPER taselisib arm (16.8% and 36.5%, respectively), this did not lead to poorer efficacy.[22]

In conclusion, SANDPIPER met its primary endpoint; however, taselisib plus fulvestrant has no clinical utility given its safety profile and modest clinical benefit.

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Table 3. Safety summary, including the most frequent all-grade AEs and grade ≥ 3 AEs (regardless of causality; safety-evaluable patients regardless of *PIK3CA*-mutant tumor status)

Safety summary	Placebo + fulvestrant (n = 213)	Taselisib + fulvestrant (n = 416)
All-grade AEs	191 (89.7)	397 (95.4)
All-grade selected AEs (associated with PI3K inhibition)[a]	86 (40.4)	356 (85.6)
Grade ≥3 AEs	35 (16.4)	206 (49.5)
Grade ≥3 selected AEs (associated with PI3K inhibition)[a]	4 (1.9)	130 (31.3)
SAEs[b]	19 (8.9)	133 (32.0)
Grade 5 AEs	1 (0.5)[c]	8 (1.9)[d]
Dose modifications		
AEs leading to taselisib/placebo discontinuation	5 (2.3)	70 (16.8)[e]
AEs leading to taselisib/placebo dose interruption	24 (11.3)	169 (40.6)
AEs leading to taselisib/placebo dose reduction	5 (2.3)	152 (36.5)
AEs leading to fulvestrant discontinuation	5 (2.3)	18 (4.3)
AEs leading to fulvestrant interruption	10 (4.7)	57 (13.7)
Most frequent any-grade AEs in ≥10% in the taselisib arm		
Diarrhea[f]	42 (19.7)	250 (60.1)
Hyperglycemia[f]	20 (9.4)	168 (40.4)
Nausea	52 (24.4)	142 (34.1)
Decreased appetite	22 (10.3)	110 (26.4)
Fatigue	38 (17.8)	101 (24.3)
Headache	25 (11.7)	84 (20.2)
Stomatitis[f]	18 (8.5)	138 (33.2)
Vomiting	24 (11.3)	78 (18.8)
Asthenia	39 (18.3)	77 (18.5)
Rash[f]	24 (11.3)	105 (25.2)
Cough	28 (13.1)	54 (13.0)
Back pain	24 (11.3)	54 (13.0)
Abdominal pain	19 (8.9)	51 (12.3)
Dry mouth	16 (7.5)	51 (12.3)
Arthralgia	27 (12.7)	48 (11.5)
Alopecia	6 (2.8)	47 (11.3)
Pruritus	16 (7.5)	46 (11.1)
Pyrexia	7 (3.3)	44 (10.6)
Dyspnea	17 (8.0)	43 (10.3)
Most frequent grade ≥3 AEs in ≥1% in the taselisib arm		
Diarrhea[f]	2 (0.9)	48 (11.5)
Hyperglycemia[f]	1 (0.5)	45 (10.8)
Rash[f]	—	16 (3.8)
Stomatitis[f]	—	15 (3.6)
Colitis[f]	—	13 (3.1)
Hypertension	7 (3.3)	10 (2.4)
Dehydration	1 (0.5)	8 (1.9)
ALT increase	—	8 (1.9)
Lipase increased	2 (0.9)	7 (1.7)
Neutropenia	2 (0.9)	7 (1.7)
Vomiting	2 (0.9)	7 (1.7)
Pneumonia	—	7 (1.7)
Pneumonitis[f]	1 (0.5)	7 (1.7)
AST increase	1 (0.5)	6 (1.4)
Sepsis	1 (0.5)	5 (1.2)
Diarrhea infectious	—	5 (1.2)
Hypokalemia	—	5 (1.2)

Data are *n* (%).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PI3K, phosphatidylinositol 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SAE, serious adverse event.

[a] Selected toxicities of interest for taselisib included diarrhea, colitis, pneumonitis, rash, stomatitis, and hyperglycemia.

[b] SAE: includes events that are fatal, life-threatening, require or prolong hospitalization, are considered a significant medical event (investigator judgment), or result in significant disability.

[c] Pneumonitis.

[d] Alcoholic pancreatitis, acute kidney injury/sepsis, acute respiratory failure, respiratory tract infection, unexplained death (2), hepatotoxicity, myocardial infarction.

[e] 51.4% of patients discontinued taselisib due to gastrointestinal toxicities, with diarrhea being the most frequent reason.

[f] Frequencies of selected AEs are based on 'group' terms of relevant events associated with taselisib, not preferred terms. Group terms are defined in the Supplementary materials available at https://doi.org/10.1016/j.annonc.2020.10.596.

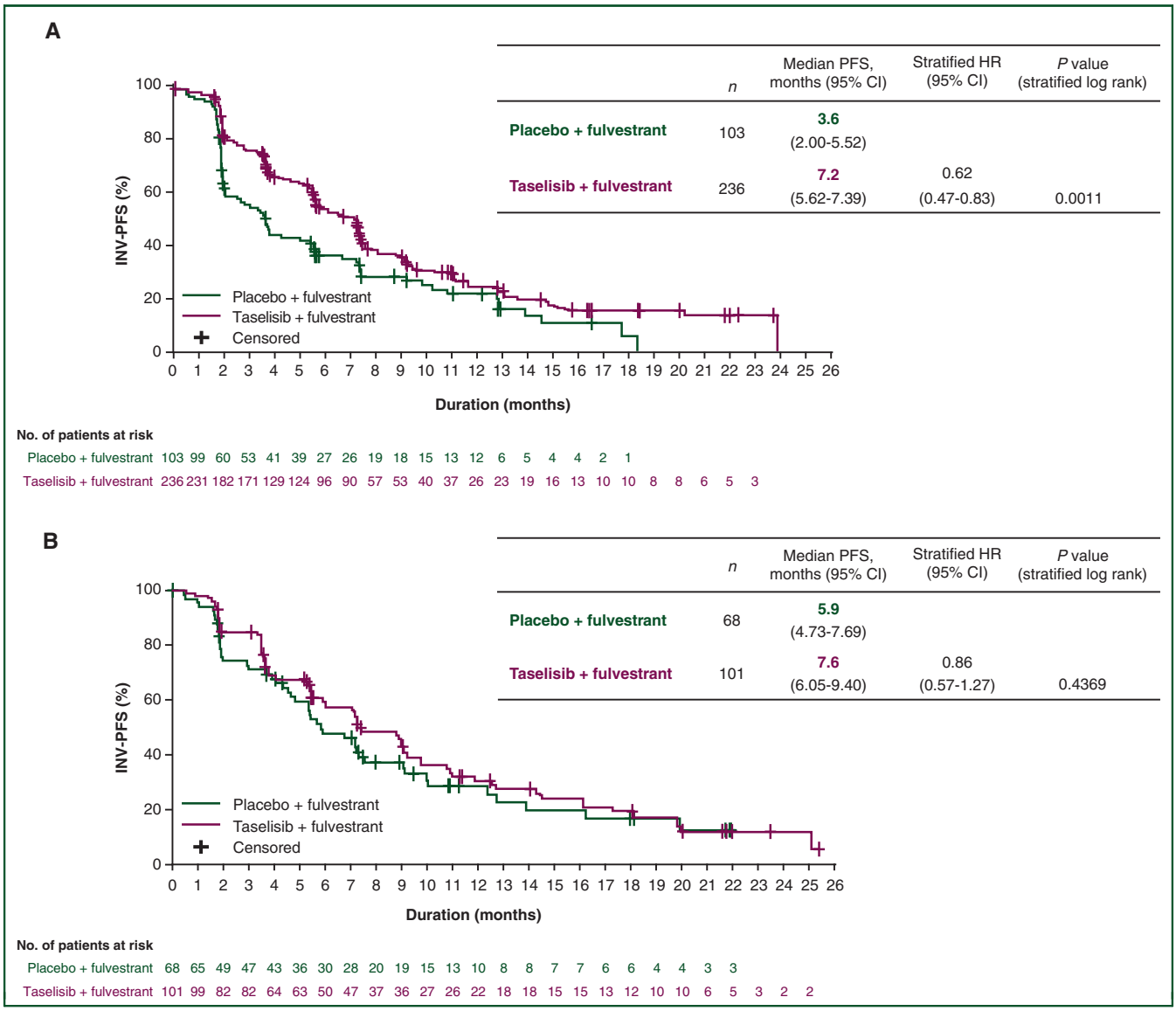

Figure 3. Kaplan–Meier plots for INV-PFS in patients with *PIK3CA* mutation status determined by ctDNA analysis: (A) patients with *PIK3CA*-mutant tumors and (B) patients with MND.

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; INV, investigator-assessed; MND, mutation not detected; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

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DATA SHARING

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).

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