ORIGINAL ARTICLE

Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer

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ABSTRACT

BACKGROUND

Inavolisib is a highly potent and selective inhibitor of the alpha isoform of the p110 catalytic subunit of the phosphatidylinositol 3-kinase complex (encoded by *PIK3CA*) that also promotes the degradation of mutated p110α. Inavolisib plus palbociclib–fulvestrant has shown synergistic activity in preclinical models and promising antitumor activity in early-phase trials.

METHODS

In a phase 3, double-blind, randomized trial, we compared first-line inavolisib (at an oral dose of 9 mg once daily) plus palbociclib–fulvestrant (inavolisib group) with placebo plus palbociclib–fulvestrant (placebo group) in patients with *PIK3CA*-mutated, hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative locally advanced or metastatic breast cancer who had had relapse during or within 12 months after the completion of adjuvant endocrine therapy. The primary end point was progression-free survival as assessed by the investigator.

RESULTS

A total of 161 patients were assigned to the inavolisib group and 164 to the placebo group; the median follow-up was 21.3 months and 21.5 months, respectively. The median progression-free survival was 15.0 months (95% confidence interval [CI], 11.3 to 20.5) in the inavolisib group and 7.3 months (95% CI, 5.6 to 9.3) in the placebo group (hazard ratio for disease progression or death, 0.43; 95% CI, 0.32 to 0.59; P<0.001). An objective response occurred in 58.4% of the patients in the inavolisib group and in 25.0% of those in the placebo group. The incidence of grade 3 or 4 neutropenia was 80.2% in the inavolisib group and 78.4% in the placebo group; grade 3 or 4 hyperglycemia, 5.6% and 0%, respectively; grade 3 or 4 stomatitis or mucosal inflammation, 5.6% and 0%; and grade 3 or 4 diarrhea, 3.7% and 0%. No grade 3 or 4 rash was observed. Discontinuation of any trial agent because of adverse events occurred in 6.8% of the patients in the inavolisib group and in 0.6% of those in the placebo group.

CONCLUSIONS

In patients with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer, inavolisib plus palbociclib–fulvestrant led to significantly longer progression-free survival than placebo plus palbociclib–fulvestrant, with a greater incidence of toxic effects. The percentage of patients who discontinued any trial agent because of adverse events was low. (Funded by F. Hoffmann–La Roche; INAVO120 ClinicalTrials.gov number, NCT04191499.)

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A list of the investigators in the INAVO120 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Activating mutations in *PIK3CA* occur in approximately 35 to 40% of hormone receptor–positive breast cancers.[1-4] The presence of such mutations is a poor prognostic factor in patients with advanced breast cancer and is a predictive biomarker of response to phosphatidylinositol 3-kinase (PI3K) inhibitors.[1,3,5-7] Clinical trials have shown the benefit of regimens that target the key oncogenic drivers of hormone receptor–positive breast cancer, including endocrine therapy combined with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors[8-10] or with inhibitors of nodes in the PI3K–protein kinase B–mammalian target of rapamycin (PI3K–AKT–mTOR) signaling pathway[11-13]; however, treatment resistance remains a major challenge in clinical practice.[11-13]

The three key oncogenic pathways (estrogen receptor, CDK4/6, and PI3K) that drive hormone receptor–positive locally advanced or metastatic breast cancer are highly interconnected, with complex feedback mechanisms that may drive adaptation and resistance to treatment.[14] An effective treatment regimen with an acceptable level of safety that targets all three signaling pathways is needed. Preclinical research showed that substantial synergy can be achieved with simultaneous blockade of the estrogen receptor, CDK4/6, and PI3K pathways in *PIK3CA*-mutated xenograft models by further reducing the tumor burden and preventing or delaying the emergence of resistance to treatment.[15-17] However, previous use of this approach in the clinic has been unsuccessful, largely because of treatment-related side effects.[18-20]

Inavolisib is a highly potent and selective inhibitor of the alpha isoform of the p110 catalytic subunit of the PI3K complex that also promotes the degradation of mutated p110α. Previous PI3K inhibitors have had toxic effects and an unacceptable side-effect profile when combined with standard-of-care agents.[11,21] The enhanced selective inhibition of p110α and degradation of mutated p110α with inavolisib may lead to a wider therapeutic window, enabling the use of inavolisib combined with standard-of-care therapies to achieve sustained pathway inhibition.[17,22,23] A first-in-human phase 1 study (ClinicalTrials.gov number, NCT03006172) showed that inavolisib can be combined with palbociclib plus fulvestrant at the maximum single-agent dose of each drug with no drug–drug interactions, an acceptable side-effect profile, and promising preliminary antitumor activity in *PIK3CA*-mutated, hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative locally advanced or metastatic breast cancer.[24] Preclinical and clinical data showed that tumors harboring a broad range of *PIK3CA* hotspot mutations occurring at major functional domains (e.g., helical, kinase, and C2) are sensitive to inavolisib alone or in combination with standard therapies for *PIK3CA*-mutated, hormone receptor–positive, HER2-negative breast cancer.[17,25,26]

INAVO120 is a phase 3, double-blind, randomized, placebo-controlled trial comparing first-line inavolisib plus palbociclib–fulvestrant (inavolisib group) with placebo plus palbociclib–fulvestrant (placebo group) in patients with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer who had had disease recurrence during or within 12 months after the completion of adjuvant endocrine therapy. The trial was enriched for patients with clinicopathologic characteristics associated with a poor prognosis.

A Quick Take is available at NEJM.org

Methods

Trial Oversight

The INAVO120 trial enrolled patients in 28 countries. The trial was designed and overseen by a steering committee, which included representatives of the trial sponsor (F. Hoffmann–La Roche), and an independent data monitoring committee; the trial was funded by the sponsor. The protocol (available with the full text of this article at NEJM.org) and its amendments were approved by the relevant ethics committee or institutional review board at each site. The trial was performed in accordance with the International Council for Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki.

Data collection and analysis were performed by the sponsor in collaboration with the authors. The authors had access to the trial data. The first draft of the manuscript was developed with the use of third-party medical writing support funded by the sponsor, in collaboration with the authors. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

PATIENTS

Premenopausal, perimenopausal, or postmenopausal women or men with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer were eligible for enrollment. Additional eligibility criteria included disease recurrence or progression during or within 12 months after the completion of adjuvant endocrine therapy (patients with de novo metastatic breast cancer were excluded), a fasting glucose level of less than 126 mg per deciliter, a glycated hemoglobin level of less than 6.0%, and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[27]

Positivity for mutated *PIK3CA* was determined by local testing of tumor tissue or circulating tumor DNA (ctDNA) at a laboratory certified according to the Clinical Laboratory Improvement Amendments or an equivalent standard or by central testing of ctDNA at a laboratory designated by the sponsor. Local testing was performed with an appropriately validated polymerase-chain-reaction test or next-generation sequencing test. Central testing was primarily conducted with the FoundationOne Liquid CDx next-generation sequencing assay (Foundation Medicine); in China, the PredicineCARE next-generation sequencing assay (Huidu) was used.

TRIAL DESIGN AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive inavolisib (at a dose of 9 mg, administered orally, once daily on days 1 to 28 of each 28-day cycle) or placebo (once daily), each given with palbociclib (at a dose of 125 mg, administered orally, once daily on days 1 to 21 of each 28-day cycle) and fulvestrant (at a dose of 500 mg, administered intramuscularly, on days 1 and 15 of cycle 1 and approximately every 28 days thereafter). Randomization was performed with the use of a permuted block method. Premenopausal or perimenopausal women and men received a luteinizing hormone–releasing hormone agonist for hormone suppression for the duration of the trial intervention. The administration of the trial agents continued until disease progression, unacceptable toxic effects, withdrawal of consent, or death. Dose modifications for inavolisib and palbociclib are described in the protocol; dose reductions for fulvestrant were not allowed. Patients who discontinued any trial agent because of unacceptable side effects could continue to receive the other trial agents in their assigned regimen.

Randomization was stratified according to visceral disease (yes or no), resistance to endocrine therapy (primary or secondary), and region (North America and western Europe, Asia, or other). Primary resistance to endocrine therapy was defined as relapse during the first 2 years of adjuvant endocrine therapy, and secondary resistance to endocrine therapy was defined as relapse after the start of year 2 of adjuvant endocrine therapy or relapse within 12 months after the completion of adjuvant endocrine therapy.[28]

END POINTS

The primary end point was progression-free survival, defined as the time from randomization to the first occurrence of disease progression (as assessed by the investigator according to RECIST, version 1.1) or death from any cause, whichever occurred first. Data for patients without disease progression or death from any cause were censored at the time of the last tumor assessment (or at the time of randomization if no tumor assessment was performed after the baseline visit). Secondary end points included overall survival; confirmed objective response, best overall response, clinical benefit, and response duration, as assessed by the investigator according to RECIST, version 1.1; and patient-reported outcomes. Safety, unacceptable side effects, and pharmacokinetics were also assessed.

The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[29] Selected adverse events were evaluated on the basis of the known safety profile of inavolisib, and adverse events of special interest were defined as described in the protocol. We assessed adverse events using grouped terms.

STATISTICAL ANALYSIS

We planned to analyze the primary end point after approximately 194 events had occurred, which would provide the trial with 85% power to detect a hazard ratio for disease progression or death of 0.65 (inavolisib vs. placebo), which corresponds to an increase of 5.9 months in median progression-free survival, using a two-sided log-rank test with a significance level of 5%. Hazard ratios and corresponding 95% confidence inter-

vals were estimated with the use of a stratified Cox proportional hazards model. The Kaplan–Meier approach was used to estimate the median progression-free survival for each group, and the Brookmeyer–Crowley method was used to construct the corresponding 95% confidence intervals. The subgroup analysis of progression-free survival according to baseline characteristics was prespecified. Overall survival was to be tested in a hierarchical fashion if the between-group difference in progression-free survival was significant. An interim analysis was planned at the time of the primary analysis of progression-free survival (prespecified boundary for significance, P<0.0098), and the final analysis is planned after approximately 153 deaths have occurred.

Efficacy end points were analyzed in the full analysis population, which included all the patients who had undergone randomization. The duration of response was assessed in the patients who had undergone randomization and had an objective response. Safety analyses were conducted in all the patients who had received at least one dose of any trial agent (safety analysis population); the patients were analyzed according to the actual trial agents received. The analyses of secondary efficacy end points were controlled for type I error.

RESULTS

PATIENTS

Between January 29, 2020, and September 14, 2023, we enrolled 325 patients. Details regarding patient disposition are provided in Figure S1 in the Supplementary Appendix (available at NEJM.org). The tumor *PIK3CA* mutation status in most of the patients was assessed with ctDNA-based testing (Table S1). The median follow-up was 21.3 months in the inavolisib group and 21.5 months in the placebo group (data cutoff, September 29, 2023).

Baseline characteristics were well balanced between the two trial groups (Table 1); the median age was 54.0 years, and 60.0% of the patients were postmenopausal. The disease burden was high overall: 51.4% of the patients had metastases in at least 3 organs, 80.0% had visceral metastases, and 51.7% had liver metastases. Most of the patients had previously received neoadjuvant or adjuvant chemotherapy (82.8%) and had not previously received a CDK4/6 inhibitor (98.8%), and 47.7% of the patients had previously received neoadjuvant or adjuvant tamoxifen only. The distribution of relevant risk factors was well balanced between the trial groups. Black or African American patients were underrepresented.

TREATMENT

In the safety analysis population (162 patients in each trial group), patients in the inavolisib group received inavolisib for a median of 9.2 months; palbociclib, for 9.1 months; and fulvestrant, for 8.6 months. The median relative dose intensities were 95.8%, 87.3%, and 100.0%, respectively.

Patients in the placebo group received placebo for a median of 5.6 months; palbociclib, for 5.6 months; and fulvestrant, for 5.6 months. The median relative dose intensities were 88.4% for palbociclib and 100.0% for fulvestrant.

EFFICACY

In the full analysis population, which included 161 patients in the inavolisib group and 164 patients in the placebo group, the median progression-free survival was 15.0 months and 7.3 months, respectively (stratified hazard ratio for disease progression or death, 0.43; 95% confidence interval [CI], 0.32 to 0.59; P<0.001) (Fig. 1A). In the landmark survival analysis, the probability of progression-free survival was 82.9% at 6 months, 55.9% at 12 months, and 46.2% at 18 months in the inavolisib group and 55.9%, 32.6%, and 21.1%, respectively, in the placebo group. The analysis of progression-free survival showed a generally consistent treatment effect across key subgroups, including those defined according to the presence or absence of visceral metastases and the presence or absence of liver metastases, although the number of patients in some subgroups was small (Fig. 1B). Inavolisib plus palbociclib–fulvestrant appeared to have led to little improvement as compared with placebo plus palbociclib–fulvestrant in patients older than 65 years of age and patients who had previously received both an aromatase inhibitor and tamoxifen, but the number of patients in these subgroups was small. Progression-free survival was also assessed by blinded independent central review as a sensitivity analysis; results were consistent with those for progression-free survival as assessed by the investigator (stratified hazard ratio for disease progression or death, 0.50; 95% CI, 0.36 to 0.68; P<0.001) (Fig. S2).

At the time of the interim analysis of overall survival, the landmark survival analysis showed that the survival probability at 6, 12, and 18 months was 97.3%, 85.9%, and 73.7%, respectively, in the inavolisib group and 89.9%, 74.9%, and 67.5%, respectively, in the placebo group. The stratified hazard ratio for death (inavolisib vs. placebo) was 0.64 (95% CI, 0.43 to 0.97; P=0.03, which did not cross the predefined boundary for significance of <0.0098) (Fig. 2).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Inavolisib (N=161)	Placebo (N=164)	All Patients (N=325)
Median age (range) — yr	53.0 (27–77)	54.5 (29–79)	54.0 (27–79)
Female sex — no. (%)	156 (96.9)	163 (99.4)	319 (98.2)
Race — no. (%)†			
Asian	61 (37.9)	63 (38.4)	124 (38.2)
Black or African American	1 (0.6)	1 (0.6)	2 (0.6)
White	94 (58.4)	97 (59.1)	191 (58.8)
ECOG performance-status score — no. (%)‡			
0	100 (62.1)	106 (64.6)	206 (63.4)
1	60 (37.3)	58 (35.4)	118 (36.3)
Menopausal status at randomization — no. (%)			
Premenopausal	65 (40.4)	59 (36.0)	124 (38.2)
Postmenopausal	91 (56.5)	104 (63.4)	195 (60.0)
Median weight (range) — kg	62.5 (39–124)	64.0 (38–111)	63.0 (38–124)
Body-mass index — no. (%)§			
<18.5	8 (5.0)	10 (6.1)	18 (5.5)
≥18.5 to <25.0	78 (48.4)	75 (45.7)	153 (47.1)
≥25.0 to <30.0	44 (27.3)	50 (30.5)	94 (28.9)
≥30.0	29 (18.0)	28 (17.1)	57 (17.5)
Missing data	2 (1.2)	1 (0.6)	3 (0.9)
No. of organs with metastases — no. (%)			
1	21 (13.0)	32 (19.5)	53 (16.3)
2	59 (36.6)	46 (28.0)	105 (32.3)
≥3	81 (50.3)	86 (52.4)	167 (51.4)
Site of metastases — no. (%)			
Viscera¶	132 (82.0)	128 (78.0)	260 (80.0)
Liver	77 (47.8)	91 (55.5)	168 (51.7)
Lung	66 (41.0)	66 (40.2)	132 (40.6)
Bone only‖	5 (3.1)	6 (3.7)	11 (3.4)
Hormone-receptor status — no. (%)**			
ER-positive, PR-positive	113 (70.2)	113 (68.9)	226 (69.5)
ER-positive, PR-negative	45 (28.0)	45 (27.4)	90 (27.7)
Other	3 (1.9)	6 (3.7)	9 (2.8)
Resistance to endocrine therapy — no. (%)††			
Primary resistance	53 (32.9)	58 (35.4)	111 (34.2)
Secondary resistance	108 (67.1)	105 (64.0)	213 (65.5)
Missing data	0	1 (0.6)	1 (0.3)

Table 1. (Continued.)

Characteristic	Inavolisib (N=161)	Placebo (N=164)	All Patients (N=325)
Previous neoadjuvant or adjuvant chemotherapy — no. (%)	132 (82.0)	137 (83.5)	269 (82.8)
Previous neoadjuvant or adjuvant endocrine therapy — no. (%)			
Overall	160 (99.4)	163 (99.4)	323 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)	131 (40.3)
Tamoxifen only	82 (50.9)	73 (44.5)	155 (47.7)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)	37 (11.4)
Previous neoadjuvant or adjuvant CDK4/6 inhibitor — no. (%)	3 (1.9)	1 (0.6)	4 (1.2)

* The data are for patients in the full analysis population, which included all the patients who had undergone randomization. Palbociclib–fulvestrant was included in the inavolisib and placebo regimens. Percentages may not sum to 100 because of rounding. CDK4/6 denotes cyclin-dependent kinase 4 and 6.
† Race was reported by the patient..
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 (no disability) to 5 (death).
§ Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.
¶ Visceral disease is defined as lung, liver, brain, pleural, or peritoneal involvement.
‖ Patients with evaluable bone-only disease were not eligible; patients with disease that was limited to bone but had lytic lesions or both lytic lesions and blastic lesions and at least one measurable soft-tissue component (as defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1[27]) were eligible.
** Tumors were considered to be positive if at least 1% of tumor cells expressed estrogen receptor (ER) or progesterone receptor (PR), according to guidelines of the American Society of Clinical Oncology and the College of American Pathologists.[30]
†† Resistance to endocrine therapy was defined as primary resistance (relapse during the first 2 years of adjuvant endocrine therapy) or secondary resistance (relapse after the start of year 2 of adjuvant endocrine therapy or relapse within 12 months after the completion of adjuvant endocrine therapy) according to the 4th European School of Oncology–European Society of Medical Oncology International Consensus Guidelines for Advanced Breast Cancer.[28]

An objective response occurred in 58.4% of the patients in the inavolisib group and in 25.0% of those in the placebo group (difference, 33.4 percentage points; 95% CI, 23.3 to 43.5). The median response duration was 18.4 months and 9.6 months, respectively (hazard ratio, 0.57; 95% CI, 0.33 to 0.99) (Fig. 3).

SAFETY

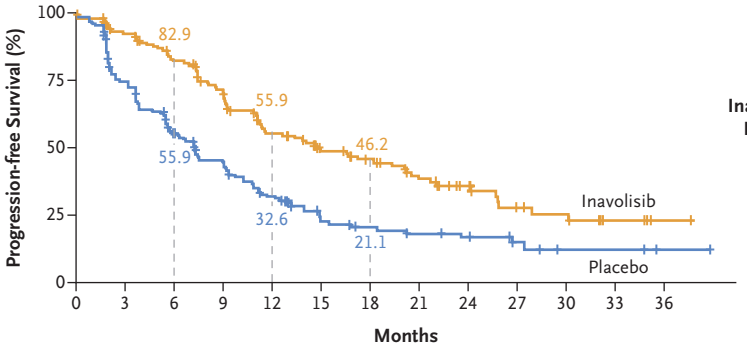
In the safety analysis population, at least 1 adverse event occurred in 98.8% of the patients in the inavolisib group and in 100% of those in the placebo group. Selected adverse events of any grade that occurred in at least 20% of the patients in either trial group included neutropenia (in 88.9% of the patients in the inavolisib group and in 90.7% of those in the placebo group), stomatitis or mucosal inflammation (in 51.2% and 26.5%, respectively), hyperglycemia (in 58.6% and 8.6%), diarrhea (in 48.1% and 16.0%), and rash (in 25.3% and 17.3%) (Table 2). Febrile neutropenia occurred in 2.5% of the patients in the inavolisib group and in 0.6% of those in the placebo group. The incidence of hyperglycemia was 65.5% among patients in the inavolisib group with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 30.0 and 56.8% among those with a BMI of less than 30.0.

Grade 3 or 4 adverse events were reported in 88.3% of the patients who received inavolisib and in 82.1% of those who received placebo. Neutropenia of grade 3 or 4 in severity occurred in 80.2% and 78.4% of patients, respectively; stomatitis or mucosal inflammation, in 5.6% and 0%; hyperglycemia, in 5.6% and 0%; and diarrhea, in 3.7% and 0%. No grade 3 or 4 rash was reported.

Serious adverse events occurred in 24.1% of the patients in the inavolisib group and in 10.5% of those in the placebo group. The most common serious adverse events among the patients are shown in Table S2.

Grade 5 (fatal) adverse events were reported in 3.7% of the patients who received inavolisib and in 1.2% of those who received placebo. In the inavolisib group, grade 5 adverse events were acute coronary syndrome, coronavirus disease 2019 (Covid-19), cerebral hemorrhage, cerebrovascular accident, and gastrointestinal hemorrhage

A Progression-free Survival in the Full Analysis Population



No. at Risk													
Inavolisib	161	134	111	92	66	48	41	31	22	13	11	5	1
Placebo	164	113	77	59	40	23	19	16	12	6	3	3	1

	No. of Events (%)	Median Progression-free Survival (95% CI)
		mo
Inavolisib (N=161)	82 (50.9)	15.0 (11.3–20.5)
Placebo (N=164)	113 (68.9)	7.3 (5.6–9.3)

Stratified hazard ratio for disease progression or death, 0.43 (95% CI, 0.32–0.59)
P<0.001

B Analysis of Progression-free Survival in Key Subgroups

Subgroup	No. of Patients		Median Progression-free Survival		Hazard Ratio for Disease Progression or Death (95% CI)
	Inavolisib	Placebo	Inavolisib	Placebo	
			mo		
All patients	161	164	15.0	7.3	0.50 (0.38–0.67)
Age					
<65 yr	136	130	16.6	7.2	0.44 (0.32–0.60)
≥65 yr	25	34	9.3	10.7	0.96 (0.50–1.83)
Geographic region					
Asia	56	58	14.6	5.8	0.40 (0.24–0.64)
North America or Western Europe	63	64	13.8	9.3	0.73 (0.47–1.15)
Other	42	42	21.0	5.6	0.40 (0.22–0.72)
ECOG performance-status score at baseline					
0	100	106	16.6	7.4	0.46 (0.32–0.66)
1	60	58	11.4	5.6	0.58 (0.36–0.92)
Menopausal status at randomization					
Premenopausal	65	59	20.1	6.5	0.35 (0.22–0.56)
Postmenopausal	91	104	13.4	7.5	0.64 (0.44–0.92)
Visceral disease					
No	29	36	25.8	7.4	0.43 (0.19–0.97)
Yes	132	128	13.8	7.2	0.51 (0.38–0.69)
Liver metastasis at enrollment					
No	84	73	24.2	11.3	0.56 (0.35–0.90)
Yes	77	91	11.0	5.6	0.48 (0.33–0.69)
No. of organs with metastases at enrollment					
1	21	32	20.2	7.4	0.35 (0.14–0.87)
2	59	46	18.2	7.4	0.47 (0.29–0.77)
≥3	81	86	14.1	7.3	0.55 (0.37–0.80)
Resistance to endocrine therapy					
Primary	53	58	11.4	3.7	0.39 (0.24–0.61)
Secondary	108	105	18.2	9.7	0.55 (0.38–0.80)
Hormone receptor status					
ER-positive, PR-negative	45	45	11.1	5.6	0.45 (0.27–0.76)
ER-positive, PR-positive	113	113	18.2	7.4	0.48 (0.34–0.68)
Previous endocrine therapy					
Aromatase inhibitor and tamoxifen	18	19	11.0	12.9	1.17 (0.42–3.24)
Aromatase inhibitor only	60	71	10.9	5.8	0.62 (0.41–0.94)
Tamoxifen only	82	73	21.0	7.4	0.38 (0.25–0.59)

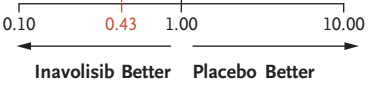


Figure 1 (facing page). Progression-free Survival.
Panel A shows progression-free survival (primary end point) in the full analysis population, which included all the patients who had undergone randomization. Progression-free survival was defined as the time from randomization to the first occurrence of disease progression (as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1[27]) or death from any cause, whichever occurred first. Palbociclib–fulvestrant was included in the inavolisib and placebo regimens. Tick marks indicate censored data. Panel B shows a forest plot of hazard ratios for progression-free survival in key subgroups in the full analysis population. Because the sample size of many subgroups was relatively small, the analysis, including that for all patients included in the full analysis set, was unstratified. Thus, the hazard ratios are shown relative to that for the stratified analysis of the full analysis population (dashed line). Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 (no disability) to 5 (death). Resistance to endocrine therapy was defined as primary resistance (relapse during the first 2 years of adjuvant endocrine therapy) or secondary resistance (relapse after the start of year 2 of adjuvant endocrine therapy or relapse within 12 months after the completion of adjuvant endocrine therapy) according to the 4th European School of Oncology–European Society of Medical Oncology International Consensus Guidelines for Advanced Breast Cancer.[28] Previous endocrine therapy includes neoadjuvant and adjuvant therapy. ER denotes estrogen receptor, and PR progesterone receptor.

in one patient each; no information was available for the sixth patient who died. In the placebo group, grade 5 adverse events included cardiac arrest and Covid-19 pneumonia in one patient each. None of the deaths were considered by the investigator to be related to the trial agents.

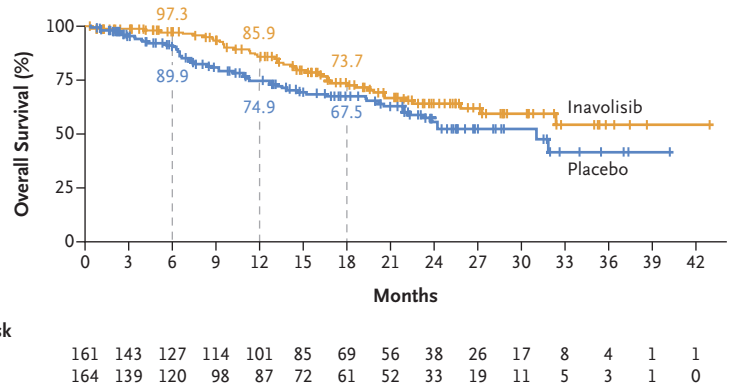
Adverse events led to the discontinuation of any trial agent in 6.8% of the patients in the inavolisib group (6.2% of the patients discontinued inavolisib; 4.9%, palbociclib; and 3.1%, fulvestrant) and in 0.6% of those in the placebo group (no patients discontinued palbociclib or fulvestrant because of adverse events) (Table S3). Adverse events led to a reduction in the dose of inavolisib and placebo in 14.2% and 3.1% of the patients, respectively. Hyperglycemia led to a reduction in the inavolisib dose in 2.5% of the patients; this was the only adverse event that led to a reduction in the inavolisib dose in at least 2% of the patients.

DISCUSSION

Our trial met the primary end point, showing that the addition of inavolisib to palbociclib–fulvestrant resulted in substantially longer progression-free survival than placebo plus palbociclib–fulvestrant in patients with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer whose disease had recurred during or within 12 months after the completion of adjuvant endocrine therapy. The benefit of inavolisib was generally observed across all key prespecified clinical subgroups and sensitivity analyses and was supported by the analysis of secondary end points, with meaningful improvements in the percentage of patients with a response and the response duration. Overall survival analysis showed a numerical trend in favor of the inavolisib regimen at the interim analysis; follow-up is ongoing. Inavolisib plus palbociclib–fulvestrant had a safety profile consistent with the safety profiles of the individual drugs in the regimen,[11,24-26,31-35] and the percentage of patients who discontinued any agent in the inavolisib regimen because of adverse events was low.

The trial population was enriched for patients with poor prognostic factors. We enrolled patients with resistance to endocrine therapy and measurable disease, which resulted in a large percentage of patients with a high disease burden, including metastases in at least 3 organs (in 51.4% of the patients), visceral disease (in 80.0%), and liver metastases (in 51.7%). In addition, a unique aspect of the current trial is that the tumor *PIK3CA* mutation status in more than 90% of the patients was determined with the use of ctDNA-based testing. These poor prognostic factors in the trial population are reflected in the significantly shorter progression-free survival in the placebo group as compared with the inavolisib group and underscore the improvement due to the addition of inavolisib to palbociclib–fulvestrant.

The criteria used to define resistance to endocrine therapy are internationally established on the basis of consensus.[28] Resistance to endocrine therapy includes a continuum of manifestations, which can be attributed to and described by multiple, complex contributing mechanisms. Robust preclinical data and early-phase clinical data suggest that the inavolisib-based combination regi-



No. at Risk															
Inavolisib	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Placebo	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

	No. of Deaths (%)	Median Overall Survival (95% CI)
		mo
Inavolisib (N=161)	42 (26.1)	NR (27.3–NR)
Placebo (N=164)	55 (33.5)	31.1 (22.3–NR)

Stratified hazard ratio for death, 0.64 (95% CI, 0.43–0.97)
P=0.03

Figure 2. Overall Survival.
Shown is overall survival in the full analysis population. NR denotes not reached.

men that was assessed in the current trial may be effective in a population of patients that is broader than the population with endocrine therapy–resistant disease.[17,22-24]

The substantial clinical benefit observed in our trial can be attributed to the simultaneous blockade of the three critical signaling pathways that drive *PIK3CA*-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer (the PI3K, estrogen receptor, and CDK4/6 pathways), which delayed and prevented the emergence of treatment resistance directed mainly by cross-talk among these pathways. Moreover, the clinical benefit of the inavolisib regimen occurred early after the start of treatment and was durable, as shown by the separation of Kaplan–Meier curves for progression-free survival at the time of the first tumor assessment and throughout the follow-up period. The landmark survival analysis showed that the probability of death by 6 months was 10.1% in the placebo group and 2.7% in the inavolisib group, which emphasizes the importance of administering inavolisib plus palbociclib–fulvestrant to this patient population as a first-line therapy.

Our trial showed that inavolisib can be combined with a CDK4/6 inhibitor and endocrine therapy at the full dose of each drug with an acceptable safety level and side-effect profile. The percentage of patients with hyperglycemia was higher in the inavolisib group than in the placebo group, and the incidence of hyperglycemia was slightly higher among patients with a BMI of at least 30.0 than among those with a BMI of less than 30.0; both findings can be attributed to the fact that hyperglycemia is an on-target toxic effect associated with PI3K pathway inhibitors. The incidence of other adverse events commonly associated with PI3K inhibitors — namely, diarrhea, stomatitis, and rash — was also higher in the inavolisib group. However, hyperglycemia, diarrhea, stomatitis, and rash were controlled with supportive care and dose modifications, which is reflected in the high dose intensity of each trial drug. The protocol allowed prophylactic use of metformin in patients with a high risk of hyperglycemia and recommended early use of dexamethasone mouthwash as treatment or prophylaxis for stomatitis on the basis of results of the SWISH study.[36] The use of dexamethasone mouthwash as prophylaxis beginning at the start of treatment may be appropriate in routine practice and should be investigated in future studies. No grade 3 or 4 rash, grade 3 or 4 pneumonitis, or colitis was reported. The incidence of neutropenia, including grade 3 or 4 events, was similar in the inavolisib and placebo groups, with febrile neutropenia occurring in a small percentage of patients in each group.

Although the treatment algorithm for hormone receptor–positive locally advanced or metastatic breast cancer has evolved with approved combination regimens that target the PI3K–AKT–mTOR pathway, none of these regimens are currently preferred as first-line options for patients with *PIK3CA*-mutated tumors. Alpelisib, a PI3Kα

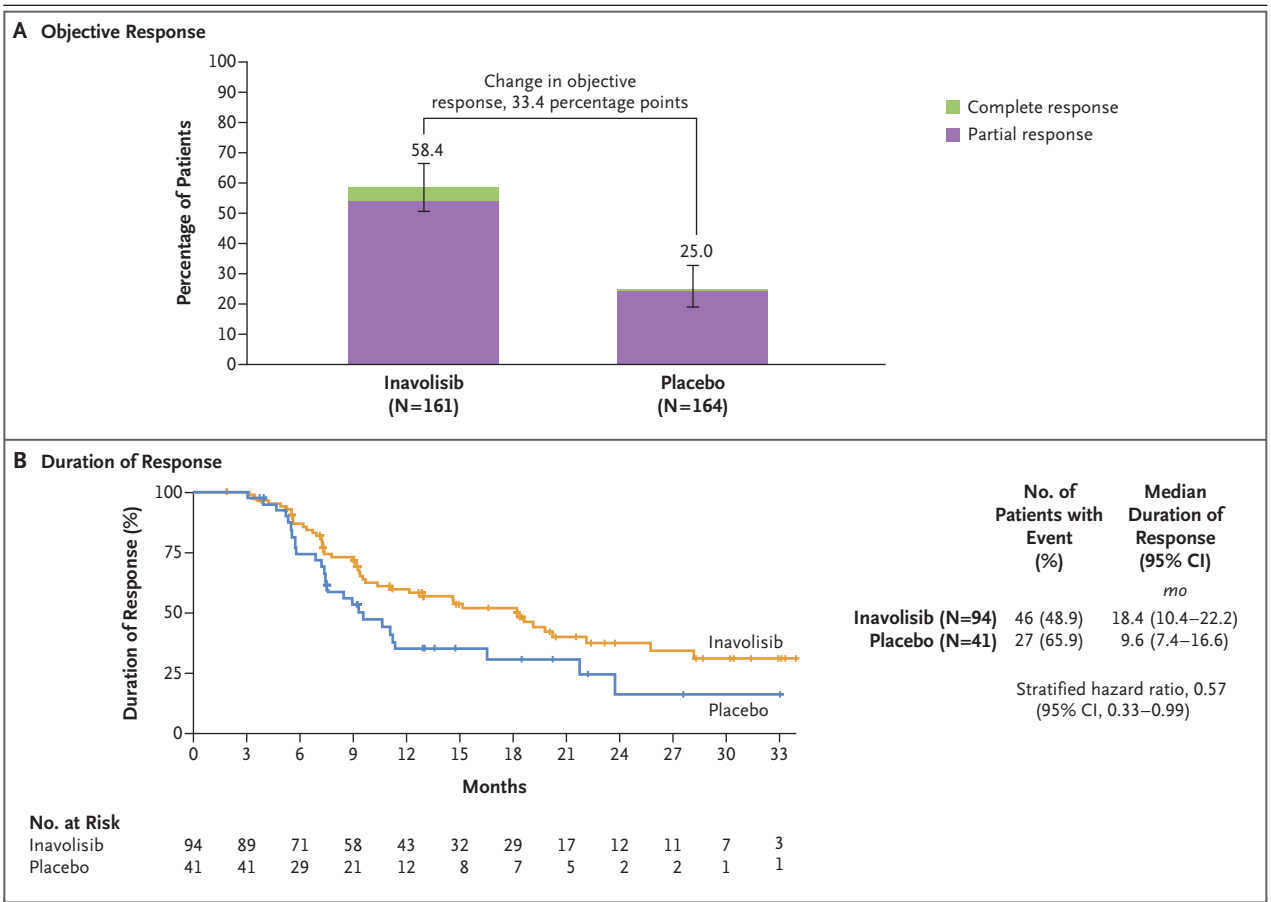


Figure 3. Objective Response and Response Duration.

Panel A shows the percentage of patients with an objective response as assessed by the investigator according to RECIST, version 1.1.[27] In the inavolisib group, 7 patients had a complete response, 87 had a partial response, 46 had stable disease, 7 had progressive disease, and 14 had missing data. In the placebo group, 1 patient had a complete response, 40 had a partial response, 79 had stable disease, 34 had progressive disease, and 10 had missing data. Data are for the full analysis population. Panel B shows the duration of response as assessed by the investigator according to RECIST, version 1.1.

inhibitor, and everolimus, an mTOR inhibitor, are recommended as second-line and later treatment options, in part because of their frequent and difficult-to-treat side effects. For example, treatment discontinuation because of adverse events occurred in 25.0% of the patients who received combination therapy with alpelisib and in 19% of those who received combination therapy with everolimus,[11,13] whereas treatment discontinuation because of adverse events occurred in 6.8% of the patients in the inavolisib group in our trial. Cross-trial comparisons should be made with caution owing to differences in trial design, patient populations, and analysis and reporting methods. Attempts to combine alpelisib or everolimus with a CDK4/6 inhibitor and endocrine therapy have been unsuccessful, mainly because of toxicity.[19,37] Recently, capivasertib, an AKT inhibitor, was approved for use in combination with fulvestrant for the treatment of patients with hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer harboring at least one alteration in *PIK3CA*, *AKT1*, or *PTEN* who had disease progression or recurrence during endocrine-based therapy.[12] In that trial (CAPItello-291), 13.0% of the patients discontinued capivasertib–fulvestrant therapy because of adverse events.[12]

Our trial has several limitations. First, the trial was designed to assess the use of only one of the three CDK4/6 inhibitors (palbociclib) currently approved for the treatment of hormone receptor–positive, HER2-negative advanced or metastatic breast cancer. However, medical community preferences and international guideline recommendations on the use of a specific CDK4/6 inhibitor or inhibitors shifted during the conduct of the

Table 2. Adverse Events.*

Adverse Event	Inavolisib (N=162)		Placebo (N=162)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Neutropenia	144 (88.9)	130 (80.2)	147 (90.7)	127 (78.4)
Thrombocytopenia	78 (48.1)	23 (14.2)	73 (45.1)	7 (4.3)
Stomatitis and mucosal inflammation	83 (51.2)	9 (5.6)	43 (26.5)	0
Anemia	60 (37.0)	10 (6.2)	59 (36.4)	3 (1.9)
Hyperglycemia	95 (58.6)	9 (5.6)	14 (8.6)	0
Diarrhea	78 (48.1)	6 (3.7)	26 (16.0)	0
Nausea	45 (27.8)	1 (0.6)	27 (16.7)	0
Rash	41 (25.3)	0	28 (17.3)	0
Decreased appetite	38 (23.5)	0	14 (8.6)	0
Fatigue	38 (23.5)	0	21 (13.0)	2 (1.2)
Covid-19	37 (22.8)	3 (1.9)	17 (10.5)	1 (0.6)
Headache	34 (21.0)	0	22 (13.6)	0
Leukopenia	28 (17.3)	11 (6.8)	40 (24.7)	17 (10.5)
Ocular toxic effects	36 (22.2)	0	21 (13.0)	0

* Shown are adverse events of any grade that occurred in at least 20% of the patients in either trial group. Data are for the safety analysis population, which included all the patients who had received at least one dose of any trial agent, with patients assessed according to the trial agents they received. Neutropenia, thrombocytopenia, stomatitis and mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea, rash, and ocular toxic effects were assessed as grouped terms. Covid-19 denotes coronavirus disease 2019.

trial. A study evaluating the efficacy and safety of combination treatment with ribociclib or abemaciclib plus inavolisib–fulvestrant in patients with metastatic or locally advanced breast cancer is ongoing (ClinicalTrials.gov number, NCT03424005). Second, few patients had previously received adjuvant CDK4/6 inhibitors, given that recruitment primarily occurred before adjuvant CDK4/6 inhibitors were available. It remains to be seen whether previous exposure to CDK4/6 inhibitors as adjuvant therapy compromises the efficacy of a CDK4/6 inhibitor as a component of therapy for advanced disease. Third, patients with type 1 or type 2 diabetes that required ongoing treatment were excluded; thus, future studies that evaluate the benefit–risk profile in this population will be useful. Fourth, diversity among the patients was limited, particularly with regard to the percentage of Black or African American patients. The majority of the patients were enrolled during the Covid-19 pandemic, which affected overall recruitment and likely contributed to the limited diversity.

This phase 3 trial showed that combination treatment with a PI3Kα inhibitor (inavolisib), a CDK4/6 inhibitor (palbociclib), and endocrine therapy (fulvestrant), all at full doses, in patients with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer resulted in substantially longer median progression-free survival than placebo plus palbociclib–fulvestrant, with a low percentage of patients discontinuing treatment because of adverse events (although the incidence of some toxic effects was somewhat higher in the inavolisib group than in the placebo group). Inavolisib plus palbociclib–fulvestrant may represent a new treatment option for these patients.

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APPENDIX

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