VIKTORIA-1 Trial of Gedatolisib Plus Fulvestrant With or Without Palbociclib in Hormone Receptor–Positive/HER2–/PIK3CA Wild-Type Advanced Breast Cancer

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ABSTRACT

PURPOSE Gedatolisib potently targets all four class I PI3K isoforms and mTORC1 and mTORC2 to comprehensively block the PI3K/AKT/mTOR pathway and has shown compelling activity in early clinical trials with palbociclib and fulvestrant.

METHODS This phase III randomized trial (VIKTORIA-1; ClinicalTrials.gov identifier: NCT05501886) evaluated the efficacy of gedatolisib-based therapy, comparing gedatolisib, palbociclib, and fulvestrant (gedatolisib triplet) and gedatolisib plus fulvestrant (gedatolisib doublet) with fulvestrant monotherapy in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative (HER2–), *PIK3CA* wild-type (WT) advanced breast cancer. Eligible patients had disease progression during or after CDK4/6 inhibitor and aromatase inhibitor treatment. Comparison of progression-free survival as assessed by blinded independent central review for gedatolisib triplet versus fulvestrant and gedatolisib doublet versus fulvestrant was the primary objective.

RESULTS A total of 392 patients were randomly assigned 1:1:1. The median study follow-up was 10.1 months. The median progression-free survival was 9.3 months in the gedatolisib-triplet group, 2.0 months in the fulvestrant group (hazard ratio [HR] for progression or death, 0.24 [95% CI, 0.17 to 0.35]; $P < .001$), and 7.4 months in the gedatolisib-doublet group (HR, 0.33 [95% CI, 0.24 to 0.48]; $P < .001$ *v* fulvestrant). Grade ≥3 treatment-related adverse events (TRAEs) reported in the gedatolisib-triplet and gedatolisib-doublet groups, respectively, included neutropenia (62.3%, 0.8%), stomatitis (19.2%, 12.3%), rash (4.6%, 5.4%), hyperglycemia (2.3%, 2.3%), and diarrhea (1.5%, 0.8%). Study treatment discontinuation because of TRAEs was reported in 2.3% (triplet) and 3.1% (doublet) of patients.

CONCLUSION The addition of gedatolisib to fulvestrant, with or without palbociclib, significantly reduced the risk of disease progression or death in patients with hormone receptor–positive/HER2–, *PIK3CA* WT advanced breast cancer.

ACCOMPANYING CONTENT

Appendix
Data Sharing Statement
Data Supplement
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INTRODUCTION

For most treatment-naïve patients with hormone receptor–positive, human epidermal growth factor 2 (HER2)–negative advanced breast cancer (ABC), combination therapy with an endocrine agent and a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is recommended.[1-3] The majority of patients, however, eventually develop resistant disease, and the optimal sequencing of subsequent therapies remains undefined.[4]

The PI3K/AKT/mTOR (PAM) pathway is a complex, multicomponent signaling pathway that drives breast cancer growth and contributes to endocrine and CDK4/6i resistance through a compensatory mechanism in which the estrogen receptor and/or cyclin D1-CDK4/6 pathways are inhibited.[5,6]

CONTEXT

Key Objective

Does the addition of the multitarget PI3K/Akt/mTOR inhibitor gedatolisib to fulvestrant, with or without palbociclib, improve clinical outcomes in patients with hormone receptor–positive/HER2−/*PIK3CA* wild-type advanced breast cancer that progressed on or after a CDK4/6i and nonsteroidal aromatase inhibitor?

Knowledge Generated

Both the gedatolisib triplet and gedatolisib doublet produced statistically significant and clinically meaningful improvements in progression-free survival relative to fulvestrant monotherapy, with benefit maintained across clinically relevant subgroups. The safety profile of each regimen was generally consistent with that of the individual agents. Gedatolisib-based therapy was associated with manageable stomatitis and low rates of hyperglycemia.

Relevance *(K.D. Miller)*

The gedatolisib-based combinations expand the population that may benefit from PI3K/AKT/mTOR inhibitors to those without defined mutations in the pathways. Future studies should compare these regimens to other second-line options to define the optimal agents and sequence.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

Preclinical data demonstrate that PAM inhibition can restore sensitivity to endocrine therapy (ET) and CDK4/6is, supporting evaluation of triple-drug regimens that block all three relevant, interconnected pathways: PAM, estrogen, and cyclin D1-CDK4/6.[7,8] Therapeutic attempts to completely block the PAM pathway, however, have been limited by toxicity, leading to the development of agents targeting only single components of the pathway that have relatively modest efficacy limited to biomarker-selected patient subsets.[9-13] The development of a PAM inhibitor with clinical activity independent of PAM-related gene alterations and a manageable safety profile would be an important therapeutic advance.

Gedatolisib is a highly potent, multitarget inhibitor of all class I PI3K isoforms and both mTOR complexes, mTORC1 and mTORC2, that comprehensively block the PAM pathway.[14] Gedatolisib has superior preclinical potency and cytotoxicity to alpelisib, capivasertib, and everolimus in PI3K pathway–mutant and wild-type (WT) breast cancer cell lines, and gedatolisib with fulvestrant, with and without palbociclib, was active in treatment-naïve and treatment-resistant lines.[6,14] In a phase Ib trial in hormone receptor–positive/HER2− ABC, gedatolisib plus ET and palbociclib demonstrated clinical activity in both *PIK3CA*-mutated and *PIK3CA*-WT disease, with acceptable safety and no drug-drug interactions or cross-toxicity with palbociclib.[15] The median progression-free survival (PFS) and median overall survival (OS) were 12.9 months and 33.9 months, respectively, for patients with *PIK3CA*-mutated and *PIK3CA*-WT disease who received gedatolisib once weekly for 3 weeks (days 1, 8, and 15) with 1 week off in combination with palbociclib and fulvestrant as second- or third-line treatment after previous CDK4/6i therapy.[15,16] We report the primary analysis of VIKTORIA-1, Study 1, a phase III trial evaluating the efficacy and safety of gedatolisib-based therapy in patients with hormone receptor–positive/HER2−/*PIK3CA*-WT advanced breast cancer after progression on a CDK4/6i and a nonsteroidal aromatase inhibitor (NSAI).

METHODS

Trial Design and Treatment

VIKTORIA-1 is a phase III, global, open-label, randomized, two-part clinical trial. Eligible patients were assigned to Study 1 or Study 2 based on tumor *PIK3CA* status, as determined by the *therascreen* PIK3CA RGQ PCR screening test (Qiagen GmbH, Hilden, Germany) assessed centrally using archival or fresh tissue or a blood sample if tissue was not available (Data Supplement, Appendix, online only). *PTEN*, *AKT1*, and other PAM pathway alterations were not used to determine eligibility and were not exclusionary. Study 1 (*PIK3CA*-WT disease) completed enrollment ahead of Study 2 (*PIK3CA*-mutated disease) and is reported herein.

Study 1 patients were randomly assigned 1:1:1 to receive 28-day cycles consisting of gedatolisib, palbociclib, and fulvestrant (gedatolisib triplet), gedatolisib and fulvestrant (gedatolisib doublet), or fulvestrant alone. Drugs were administered as follows: gedatolisib 180 mg intravenously weekly for 3 weeks (days 1, 8, 15) with 1 week off; palbociclib 125 mg orally once daily for 3 weeks (21 days), with 1 week off; and fulvestrant 500 mg intramuscularly (2 × 5-mL injections) once every 2 weeks during cycle 1 (days 1 and 15) and then once every 4 weeks beginning with cycle 2.

Patients in the fulvestrant group could cross over to the gedatolisib-triplet or gedatolisib-doublet regimen on radiographically confirmed, investigator-assessed disease progression.

Prophylactic use of a steroid-containing swish-and-spit regimen[17] was mandated, and oral nonsedating antihistamine therapy was recommended for patients in the gedatolisib groups. Dose modifications for gedatolisib and palbociclib were allowed. Fulvestrant was administered in accordance with product labeling.

Random assignment was performed using interactive response technology, stratified by the presence of visceral metastasis (yes/no), time to radiologic disease progression on immediate previous therapy (≤ or >6 months), and region (United States/Canada or rest of the world).

Patients

Adults 18 years and older with hormone receptor–positive/HER2– metastatic or locally advanced breast cancer, including pre- and perimenopausal patients with medically induced menopause, were eligible for enrollment. Additional eligibility criteria included disease progression during or after combined CDK4/6i and NSAI treatment, measurable disease per RECIST version 1.1, and Eastern Cooperative Oncology Group performance status 0-1. Exclusion criteria included type 1 diabetes or uncontrolled type 2 diabetes (HbA1c >6.4%); advanced, symptomatic, potentially life-threatening visceral spread; previous treatment with a PI3K, AKT, or mTOR inhibitor; or, in the advanced setting, previous chemotherapy, antibody-drug conjugate therapy, or more than two lines of ET.

End Points

Progression-free survival was the primary end point of Study 1, defined as time from random assignment to the first occurrence of disease progression (as assessed by blinded independent central review [BICR], in accordance with RECIST version 1.1) or death from any cause. Comparisons of PFS for the gedatolisib triplet versus fulvestrant and the gedatolisib doublet versus fulvestrant were conducted hierarchically in the intent-to-treat (ITT) population. Data for patients without disease progression or death from any cause were censored at the time of the last tumor assessment (or at time of random assignment if no tumor assessment was performed after random assignment). Secondary end points included OS for the gedatolisib triplet versus fulvestrant (first key secondary end point) and the gedatolisib doublet versus fulvestrant (key secondary end point), objective response (confirmed complete response or partial response), duration of response (DOR), safety, quality of life, and pharmacokinetics.

The severity of adverse events was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and assessed using grouped terms. Selected adverse events were evaluated based on the known safety profile of gedatolisib.

Assessments

Tumors were assessed by computed tomography or magnetic resonance imaging and by whole-body bone scan at screening, then every 8 weeks for 12 months, and every 12 weeks thereafter. Hematologic and biochemical laboratory tests were performed at screening, day 1 of each cycle, and end of therapy. Patients receiving palbociclib had additional hematology testing, and before each infusion, patients receiving gedatolisib had additional glucose monitoring. Adverse events were monitored until 30 days after the last dose or treatment discontinuation and before the initiation of new anticancer therapy, if possible.

Trial Oversight

The trial was designed and overseen by a steering committee of medical oncology experts, including representatives from the sponsor (Celcuity Inc) and an independent data-monitoring committee (IDMC) funded by the sponsor. The protocol and its amendments were approved by the institutional review board or an independent ethics committee at each site. The trial was conducted in accordance with principles derived from international guidelines, including the International Ethical Guidelines for Biomedical Research Involving Human Subjects, International Council for Harmonisation E6 Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

All patients provided written informed consent. Data were collected by trial investigators, and the IDMC reviewed safety and tolerability data for futility to ensure patient safety. Data were analyzed by the sponsor in collaboration with the authors, who had access to the trial data. The manuscript was developed by the sponsor in collaboration with the authors, with sponsor-funded, third-party medical writing assistance. All authors participated in data interpretation, contributed to manuscript development, and approved the final version for submission. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Statistical Analysis

Study 1 was powered to assess the effects of gedatolisib plus fulvestrant, with or without palbociclib, versus fulvestrant alone on PFS. We planned to enroll 351 patients (117 per arm). For the first primary analysis in hierarchical order, we calculated that 145 PFS events would provide a 98% power to detect a hazard ratio (HR) of 0.5, assuming a median PFS of 7.5 months for the gedatolisib triplet versus 3.75 months for fulvestrant, with a one-sided alpha of 0.025. For the second primary analysis in hierarchical order, we calculated that an estimated 155 PFS events would provide a 75% power to detect an HR of 0.652, assuming a median PFS of

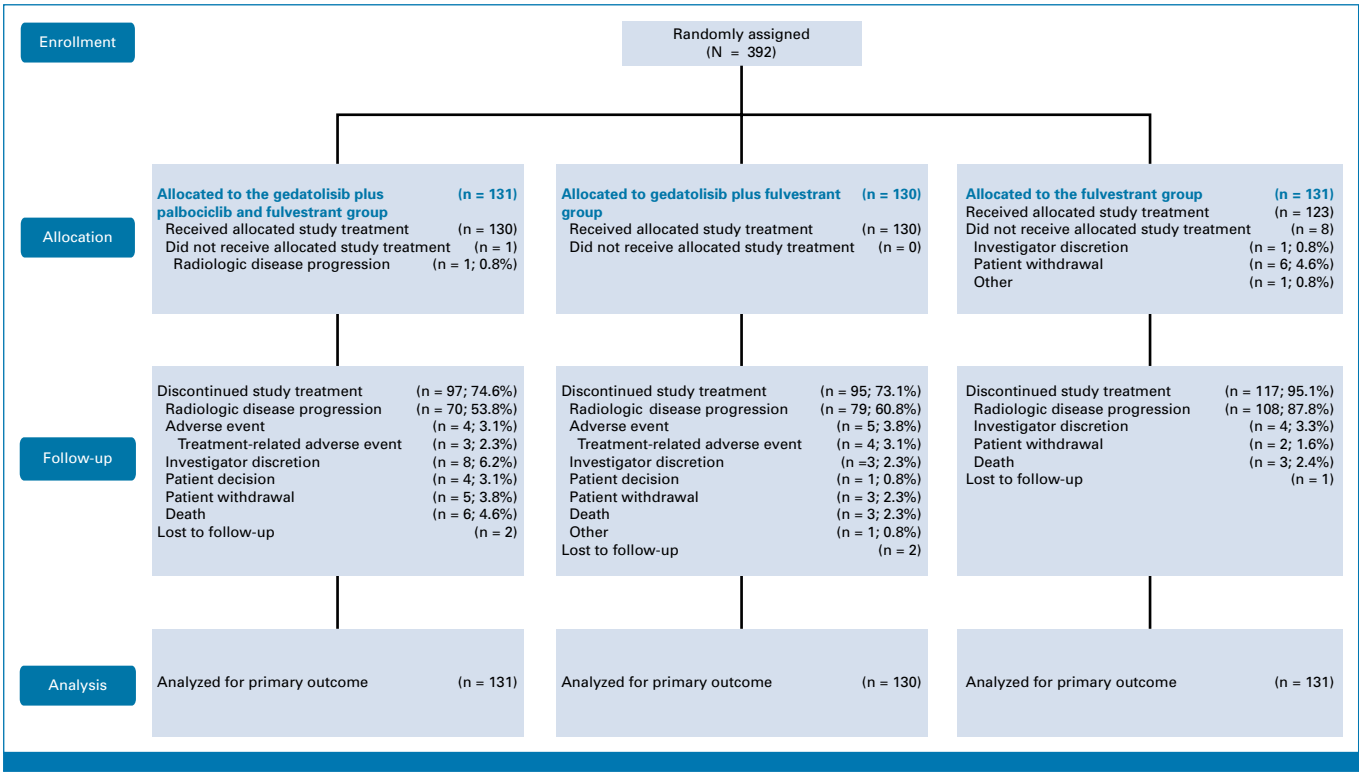

FIG 1. Patient disposition. The sample size planned for the study was 351 patients (117 in each treatment arm). An additional 41 patients who had given consent and were in active screening at the time the number of events necessary to conduct the primary analysis occurred were allowed to enroll, for a total sample size of 392 patients.

5.75 months for the gedatolisib doublet versus 3.75 months for fulvestrant, with a one-sided alpha of 0.025. Interim analysis for OS was planned to coincide with the primary PFS analysis, with a one-sided alpha assigned independently of 0.000174 and 0.000173 for the gedatolisib triplet and gedatolisib doublet versus fulvestrant, respectively, as the interim boundary to maintain the overall type I error rate of ≤0.025 in the primary OS analysis. The study will continue to follow patients for OS, with the target number of events estimated to occur approximately 48 months after first random assignment.

Primary and key secondary end points were evaluated using the Kaplan-Meier method and tested by a stratified log-rank test. Hazard ratios and associated 95% CI were estimated from a stratified Cox proportional-hazards model. Primary efficacy analyses included all randomly assigned patients (ITT population) and were conducted in hierarchical order such that if an end point failed to reject the null hypothesis, all subsequent end points in the primary analysis and their *P* values would be considered descriptive.

Safety and exposure analyses included all patients who received at least one dose of one or more of the study drugs and were performed in accordance with the treatment received, regardless of random assignment. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 27.1, severity was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, and safety data were summarized with descriptive statistics.

RESULTS

Patients

From December 5, 2022, to January 23, 2025, Study 1 enrolled 392 patients at 147 sites in 23 countries (131 patients assigned to the gedatolisib-triplet group, 130 to the gedatolisib-doublet group, and 131 to the fulvestrant group; Fig 1). Because screening in Study 1 and Study 2 was ongoing simultaneously and occurring more quickly than expected when the enrollment goal for Study 1 was met, the decision was made to allow 41 patients who had already signed consent, entered screening, and met criteria for Study 1 (e.g., *PIK3CA*-WT) to enroll. Tumor *PIK3CA* status had been assessed by tumor tissue–based testing for 84.7% of patients and by blood-based testing for 15.3%.

Demographics and baseline characteristics of the patients were well-balanced across treatment arms (Table 1). The median age was 56 years (range, 28-83 years), and 73% of patients were postmenopausal. Visceral metastases were present in 80.4% of patients, and 58.2% had liver metastases. All patients received at least one previous CDK4/6i, and 98% of patients received such therapy in the advanced

TABLE 1. Demographic and Clinical Characteristics at Baseline

Characteristic	Gedatolisib Plus Palbociclib and Fulvestrant Group (n = 131)	Gedatolisib Plus Fulvestrant Group (n = 130)	Fulvestrant Group (n = 131)
Age, years, median (range)	57 (33-83)	57 (32-81)	54 (28-83)
Female sex, No. (%)	129 (98.5)	130 (100)	128 (97.7)
Postmenopausal, No. (%)	101 (77.1)	93 (71.5)	92 (70.2)
Race/ethnic group, No. (%)			
White	85 (64.9)	95 (73.1)	95 (72.5)
Black or African American	5 (3.8)	3 (2.3)	1 (0.8)
Asian	18 (13.7)	19 (14.6)	25 (19.1)
American Indian/Alaska Native	2 (1.5)	2 (1.5)	1 (0.8)
Native Hawaiian/Other Pacific Islander	1 (0.8)	0 (0.0)	0 (0.0)
Other/Multiracial	4 (3.1)	5 (3.8)	2 (1.5)
Unknown or not reported	16 (12.2)	6 (4.6)	7 (5.3)
Geographic region, No. (%)			
United States/Canada	21 (16.0)	21 (16.2)	22 (16.8)
Asia-Pacific	18 (13.7)	18 (13.8)	26 (19.8)
Latin America	35 (26.7)	36 (27.7)	35 (26.7)
Western Europe	34 (26.0)	30 (23.1)	30 (22.9)
Central/Eastern Europe	23 (17.6)	25 (19.2)	18 (13.7)
ECOG performance status score, No. (%)			
0	70 (53.4)	85 (65.4)	77 (58.8)
1	61 (46.6)	45 (34.6)	54 (41.2)
Advanced breast cancer at initial diagnosis, No. (%)	63 (48.1)	51 (39.2)	45 (34.4)
Breast cancer stage IV at study entry, No. (%)	131 (100)	130 (100)	131 (100)
Visceral disease,[a] No. (%)	102 (77.9)	104 (80.0)	109 (83.2)
Previous (neo)adjuvant therapy, No. (%)			
Chemotherapy	33 (25.2)	39 (30.0)	38 (29.0)
ET	46 (35.1)	57 (43.8)	64 (48.9)
No. of previous lines of ET for ABC, No. (%)			
0	3 (2.3)	2 (1.5)	4 (3.1)
1	113 (86.3)	113 (86.9)	115 (87.8)
2	15 (11.5)	15 (11.5)	12 (9.2)
Time to disease progression on immediate previous therapy,[a] No (%)			
≤6 months	21 (16.0)	19 (14.6)	20 (15.3)
>6 months	109 (83.2)	111 (85.4)	111 (84.7)
Previous adjuvant CDK4/6 inhibitor, No. (%)			
Palbociclib	1 (0.8)	2 (1.5)	1 (0.8)
Ribociclib	0	2 (1.5)	1 (0.8)
Abemaciclib	2 (1.5)	2 (1.5)	2 (1.5)
Previous CDK4/6 inhibitor for ABC,[b] No. (%)			
Palbociclib	56 (42.7)	47 (36.2)	52 (39.7)
Ribociclib	59 (45.0)	62 (47.7)	70 (53.4)
Abemaciclib	23 (17.6)	26 (20.0)	16 (12.2)
Median duration of previous CDK4/6 inhibitor for ABC, months (IQR)	21.7 (13.7-35.0)	18.1 (10.8-30.0)	20.0 (12.0, 34.2)

Abbreviations: ABC, advanced breast cancer; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy.
[a]Data per Electronic Data Capture.
[b]Nineteen patients received more than one previous CDK4/6 inhibitor for advanced breast cancer.

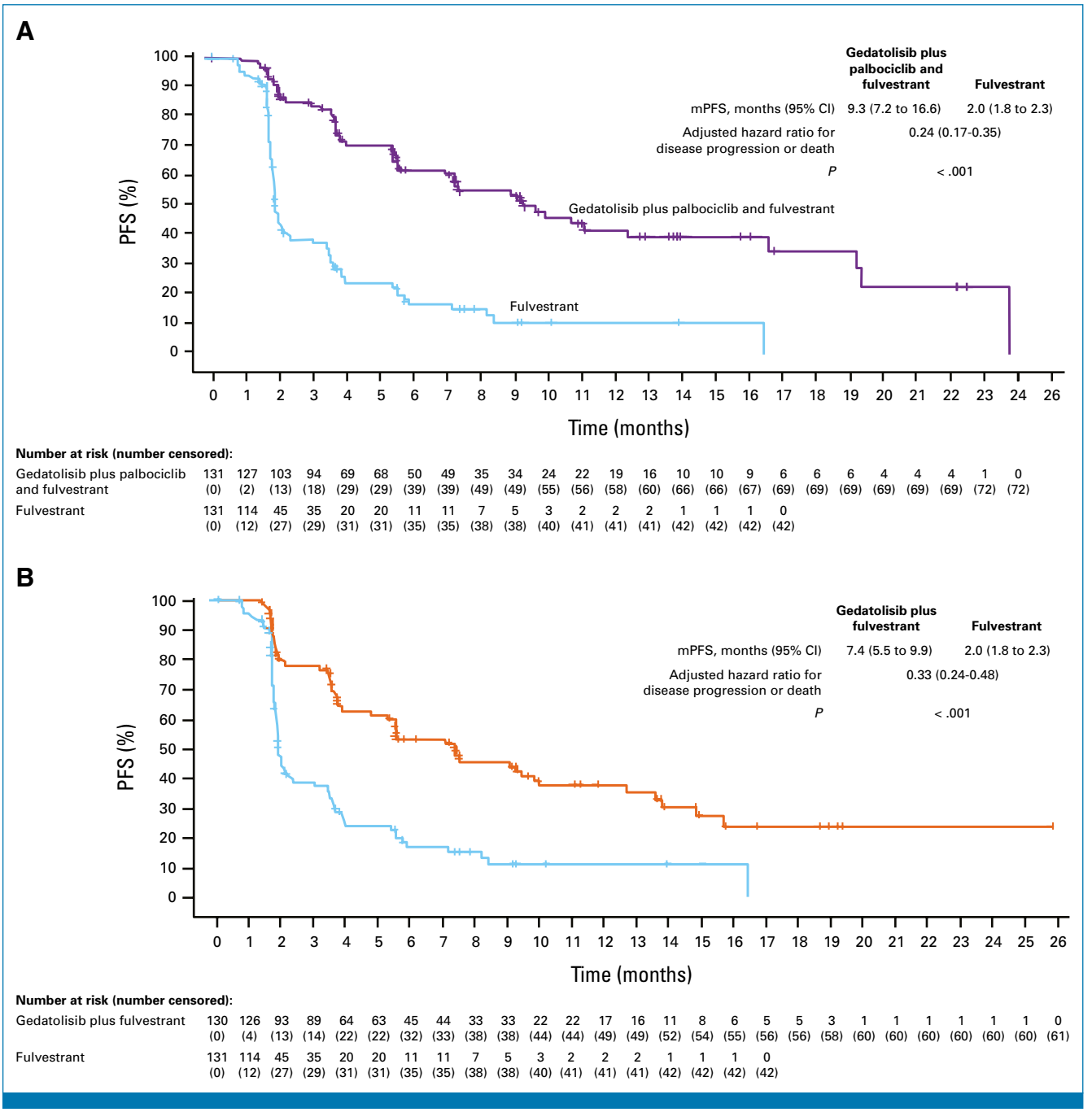

FIG 2. PFS. Kaplan-Meier estimates of progression-free survival are shown for patients randomly assigned to (A) gedatolisib plus palbociclib and fulvestrant versus fulvestrant alone and (B) gedatolisib plus fulvestrant versus fulvestrant alone. mPFS, median progression-free survival; PFS, progression-free survival.

disease setting (ribociclib, 48.7%; palbociclib, 39.5%; abemaciclib, 16.6%). The median duration of previous CDK4/6i therapy was 20.4 months (range, 1.7-108.4 months).

Treatment

At the data cutoff (May 30, 2025), the median follow-up was 10.1 months (IQR, 6.6-15.1). Thirty-three patients (25.4%) from the gedatolisib-triplet group and 35 (26.9%) from the gedatolisib-doublet group were continuing to receive treatment, compared with 6 (4.9%) from the fulvestrant group. Median treatment durations were 6.2 months, 5.7 months, and 1.8 months, respectively. Median relative dose intensities of gedatolisib were 92.1% and 100% in the triplet and doublet groups, respectively.

Efficacy

The median PFS per BICR was 9.3 months in the gedatolisib-triplet group and 2.0 months in the fulvestrant

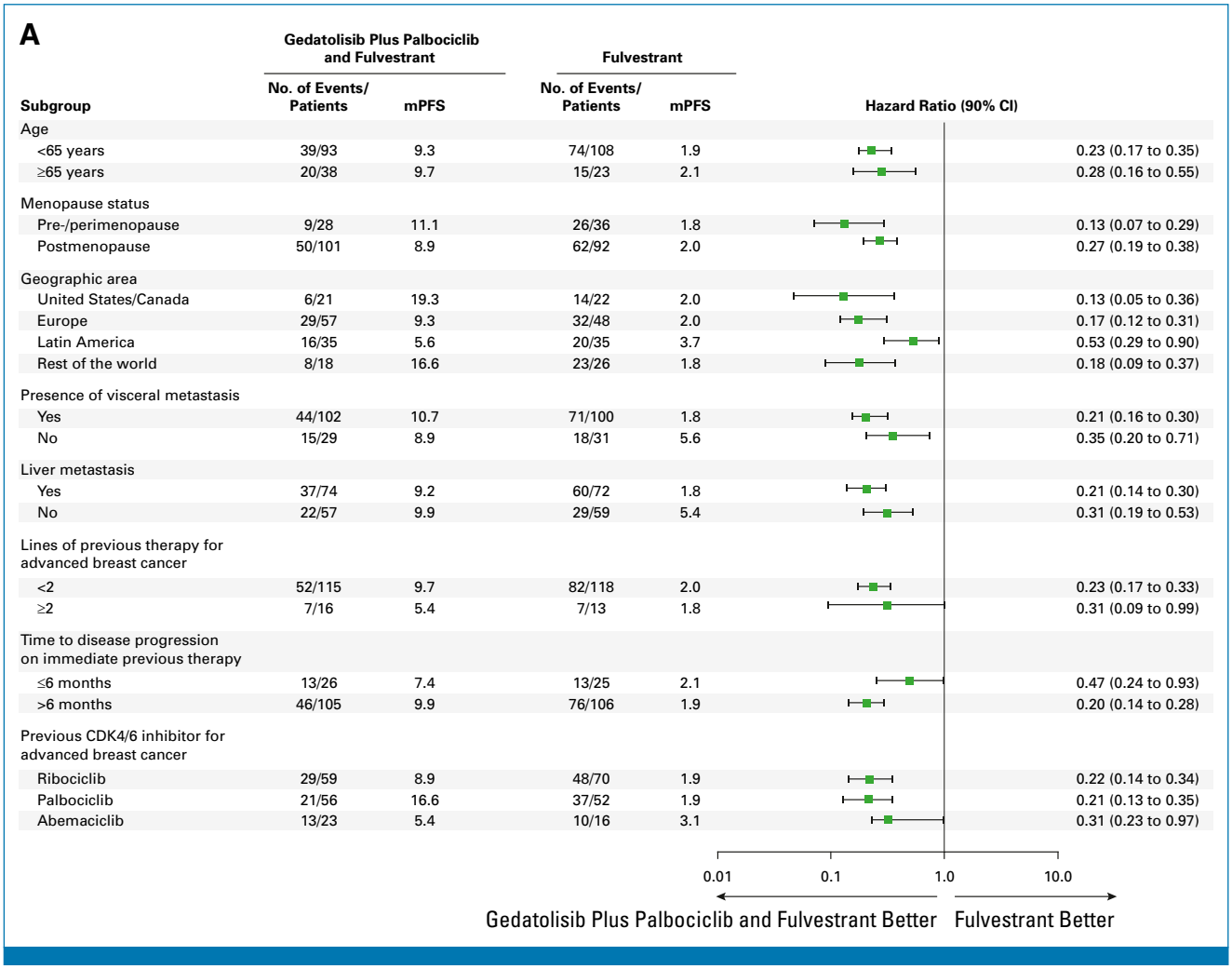

FIG 3. Subgroup analysis of PFS. Analyses of PFS across prespecified patient subgroups are shown for patients randomly assigned to (A) gedatolisib plus palbociclib and fulvestrant versus fulvestrant alone and (B) gedatolisib plus fulvestrant versus fulvestrant alone. mPFS, median progression-free survival; PFS, progression-free survival. (continued on following page)

group (stratified HR, 0.24 [95% CI, 0.17 to 0.35]; $P < .001$; Fig 2A). The median PFS in the gedatolisib-doublet group was 7.4 months (stratified HR, 0.33 [95% CI, 0.24 to 0.48]; $P < .001$ for the comparison with fulvestrant; Fig 2B). The analysis of PFS across prespecified patient subgroups showed a generally consistent treatment effect (Fig 3).

The objective response rate, which required confirmation by a subsequent scan, was 31.5% in the gedatolisib-triplet group, including one complete response, 28.3% in the gedatolisib-doublet group, and 1.0% in the fulvestrant group (Data Supplement, Table S1). The median DOR was 17.5 months and 12.0 months for the triplet and doublet groups, respectively (Data Supplement, Fig S1). Median DOR could not be calculated with only one responder in the fulvestrant group.

At the time of primary analysis, the stratified HR for death was 0.69 (95% CI, 0.43 to 1.12) for the planned interim comparison of the gedatolisib-triplet and fulvestrant groups and 0.74 (95% CI, 0.46 to 1.19) for the comparison of the gedatolisib-doublet and fulvestrant groups, neither crossing the prespecified boundary for statistical significance (Fig 4). The planned sensitivity analysis censoring patients who crossed over to gedatolisib-based treatment at disease progression is shown in the Data Supplement (Fig S2).

Safety

Treatment-related adverse events (TRAEs) of any grade that occurred in at least 20% of patients and events of clinical interest in any treatment group are shown in Table 2. Of these, grade 3 TRAEs for the gedatolisib-triplet, gedatolisib-doublet, and fulvestrant groups included neutropenia (52.3%, 0%, and 0.8% of patients, respectively), stomatitis (19.2%, 12.3%, and 0%), rash (4.6%, 5.4%, and 0%), nausea (3.8%, 0.8%, and 0%), hyperglycemia (2.3%, 2.3%, and 0%), diarrhea (1.5%, 0.8%, and 0%), and vomiting (1.5%, 0%, and 0%); grade 4 TRAEs for the gedatolisib-triplet and gedatolisib-doublet groups were neutropenia (10.0%, 0.8%), leukopenia (0.8% in the triplet group), and

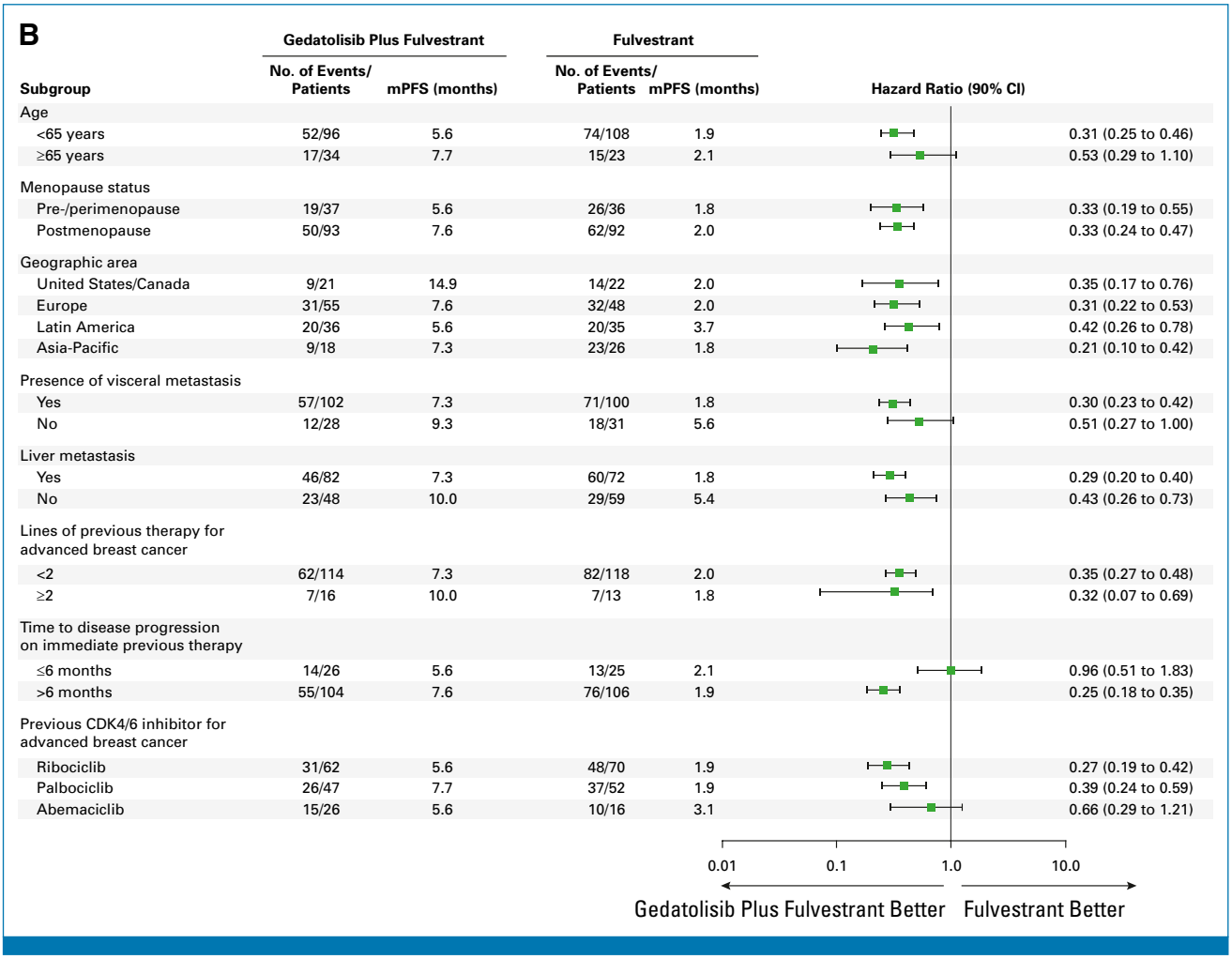

FIG 3. (Continued).

pneumonitis (0.8% in the doublet group). Additional analysis indicated that the majority of the first treatment-related stomatitis events experienced by patients was grade 1 (57 of 90 for the triplet and 48 of 74 for the doublet), with fewer patients experiencing grade 2 or grade 3 as their first event. Most patients experienced improvement to a lower grade of stomatitis within the first 2 weeks on treatment (Data Supplement, Table S3).

TRAEs led to the discontinuation of study treatment in 2.3% of patients in the triplet group, 3.1% in the doublet group, and 0% in the fulvestrant group. There were two grade 5 adverse events assessed by the investigator as treatment-related, both in the gedatolisib-triplet group: one event of pneumonia attributed to palbociclib and one event of hepatic failure assessed as related to all three study drugs (Data Supplement, Appendix).

Serious TRAEs occurred in 10.8% of patients in the gedatolisib-triplet group, in 9.2% of those in the gedatolisib-doublet group, and in 0.8% of those in the fulvestrant group (Data Supplement, Table S2).

DISCUSSION

VIKTORIA-1 met its primary end point, showing that the addition of gedatolisib to fulvestrant, with or without palbociclib, achieved clinically meaningful improvements in PFS relative to fulvestrant in patients with hormone receptor–positive/HER2– *PIK3CA*-WT advanced breast cancer that progressed on or after a CDK4/6i and NSAI. To our knowledge, the magnitude of difference between the gedatolisib triplet and fulvestrant is the largest reported in a contemporary phase III trial in this patient population, underlying the importance of combination treatment in this setting and, importantly, validating the PAM pathway as a molecular driver even in *PIK3CA*-WT disease. Our findings support evaluation of triplet therapy in earlier treatment lines. The benefits of gedatolisib combination therapy were observed across all prespecified clinical subgroups. Interim OS results are immature but show numerical trends favoring the investigational arms despite using all OS data without any adjustments for the crossover design; follow-up is ongoing. Safety profiles were generally consistent with the individual agents, with a low rate of treatment discontinuation because

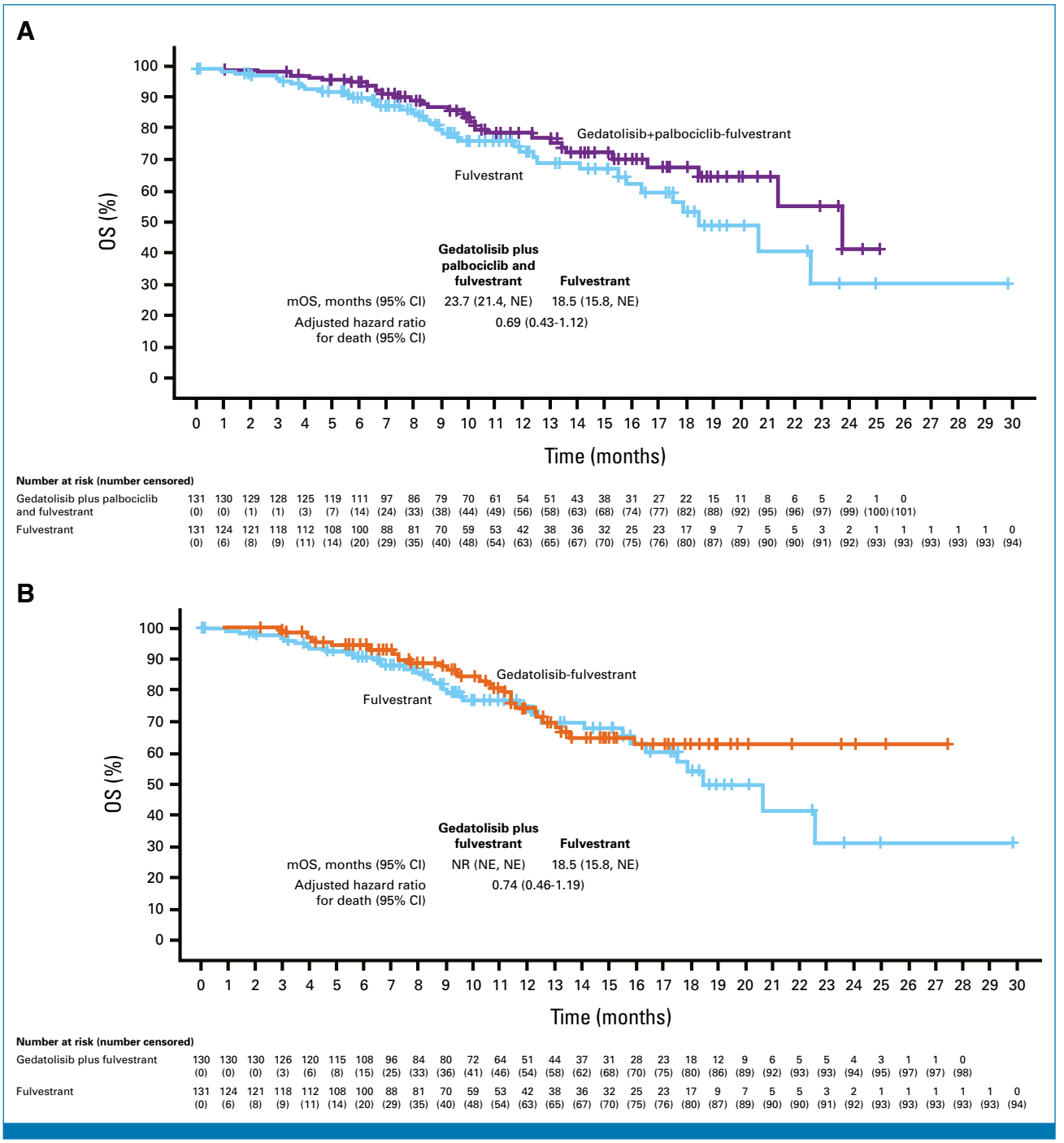

FIG 4. OS (interim analysis). Kaplan-Meier estimates of OS are shown for patients randomly assigned to (A) gedatolisib plus palbociclib and fulvestrant versus fulvestrant alone and (B) gedatolisib plus fulvestrant versus fulvestrant alone. At the time of this interim analysis, 99 patients (25.3%) had died (30 in the gedatolisib-triplet group, 32 in the gedatolisib-doublet group, and 37 in the fulvestrant group). Sixty-three patients assigned to fulvestrant crossed over to gedatolisib plus palbociclib and fulvestrant (n = 52) or gedatolisib plus fulvestrant (n = 11). Analysis was performed on the intent-to-treat population. The interim boundary for each comparison in this interim analysis was a one-sided alpha of ≤0.00017 to maintain the overall type I error rate of ≤0.025 in the final analysis. Tick marks indicate censored data. mOS, median overall survival; NE, not estimable; NR, not reached; OS, overall survival.

of adverse events. The addition of gedatolisib did not result in an increased number of neutropenic adverse events relative to historical data for the combination of fulvestrant plus palbociclib alone.[18]

Notably, all patients in the trial had disease progression on previous CDK4/6i, suggesting that the addition of gedatolisib to fulvestrant, with or without palbociclib, may help overcome resistance to both CDK4/6i and ET. Moreover, in

TABLE 2. TRAEs (safety population)

	Gedatolisib Plus Palbociclib and Fulvestrant Group (n = 130)			Gedatolisib Plus Fulvestrant Group (n = 130)			Fulvestrant Group (n = 123)		
Adverse Event, No. (%)	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Stomatitis[a]	90 (69.2)	25 (19.2)	0	74 (56.9)	16 (12.3)	0	0	0	0
Neutropenia[b]	85 (65.4)	68 (52.3)	13 (10.0)	2 (1.5)	0	1 (0.8)	1 (0.8)	1 (0.8)	0
Nausea	57 (43.8)	5 (3.8)	0	56 (43.1)	1 (0.8)	0	4 (3.3)	0	0
Rash[c]	36 (27.7)	6 (4.6)	0	42 (32.3)	7 (5.4)	0	0	0	0
Vomiting	36 (27.7)	2 (1.5)	0	30 (23.1)	0	0	1 (0.8)	0	0
Fatigue	29 (22.3)	2 (1.5)	0	27 (20.8)	1 (0.8)	0	5 (4.1)	0	0
Diarrhea[d]	22 (16.9)	2 (1.5)	0	16 (12.3)	1 (0.8)	0	0	0	0
Hyperglycemia[d]	12 (9.2)	3 (2.3)	0	15 (11.5)	3 (2.3)	0	0	0	0
Leukopenia[d]	14 (10.8)	8 (6.2)	1 (0.8)	0	0	0	0	0	0
Thrombocytopenia[d]	5 (3.8)	1 (0.8)	0	1 (0.8)	0	0	1 (0.8)	0	1 (0.8)
Pneumonitis[d]	4 (3.1)	0	0	5 (3.8)	1 (0.8)	1 (0.8)	0	0	0

NOTE. Shown are adverse events of any grade that occurred in at least 20% of the patients in any trial group unless otherwise noted. 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 in accordance with the trial agents they received. If a patient experienced more than one occurrence of an event, it was counted once for the highest grade.

Abbreviation: TRAEs, treatment-related adverse events.

[a]Includes stomatitis, oral mucosal inflammation, mouth ulceration, aphthous ulcer, glossitis, lip ulceration, gingivitis, and gingival pain.

[b]Includes neutropenia and neutrophil count decreased.

[c]Includes rash, rash erythematous, rash macular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash vesicular, and rash maculopapular.

[d]Additional events of clinical importance.

studies of second- to third-line ET, many patients experienced rapid disease progression, seen as early steep drops in the survival curves.[4] In our trial, this effect was attenuated in both gedatolisib groups, especially in the triplet group where the drop is less pronounced, demonstrating the important role the PAM pathway plays as a disease driver in this population.

Adverse events that were associated with gedatolisib in VIKTORIA-1 were mainly grade 1 or 2 in severity. The most commonly reported TRAE was stomatitis (69.2% and 56.9% with the gedatolisib-triplet and gedatolisib-doublet regimens, respectively, including 19.2% and 12.3% rates of grade 3 severity). The introduction of the swish-and-spit prophylactic regimen[17] in VIKTORIA-1 led to a reduction in the incidence and severity of stomatitis relative to the phase Ib study of gedatolisib.[15] Moreover, the majority of patients experienced a reduction to lower-grade stomatitis within the first 2 weeks of treatment. The safety profile of gedatolisib combination therapy in VIKTORIA-1 also compares favorably with other drug combinations evaluated in this patient population, including single-target PAM pathway inhibitors, such as the PI3Kα inhibitor alpelisib, the AKT inhibitor capivasertib, and the mTORC1 inhibitor everolimus. In VIKTORIA-1, 10.8% and 9.2% of patients receiving the gedatolisib triplet or gedatolisib doublet, respectively, experienced a serious adverse event. While this is higher than that with fulvestrant (<1%), it compares favorably with SAE rates from other clinical trials evaluating PAM inhibitors, such as everolimus (23% in BOLERO-2), alpelisib (35% in SOLAR-1), and capivasertib (16% in CAPItello-291).[11,19,20] Hyperglycemia, an on-target effect of PAM inhibition, was uncommon in VIKTORIA-1, observed in 9.2% and 12.3% of patients in the gedatolisib-triplet and gedatolisib-doublet arms, respectively, with three grade 3 events (2.3%) in each arm. By contrast, hyperglycemia was reported in 63.7% of patients (36.6% grade 3/4) treated with alpelisib plus fulvestrant in SOLAR-1.[11] The improved tolerability of gedatolisib is likely multifactorial, related to the intravenous administration route that avoids first-pass metabolism, the low nanomolar potency that achieves PAM blockade at relatively low drug concentrations, and the pharmacokinetic profile that supports three times a month (days 1, 8, and 15 in 28-day cycles) rather than daily dosing.

Our study has limitations. Although *PIK3CA* status was determined for all patients in VIKTORIA-1, there were insufficient samples to assess for *ESR1* mutations, which only emerged after trial initiation as a predictive biomarker for other agents.[21,22] Specifically, *PIK3CA* status was determined by PCR. Although leftover nucleic acid from tissue samples was used for exploratory *ESR1* next-generation sequencing, there were insufficient samples for assessment. Furthermore, the preferred sample type for *ESR1* mutation testing is plasma and dedicated exploratory plasma samples were not collected in this trial.

VIKTORIA-1 was designed to assess only one CDK4/6i, palbociclib, in combination with gedatolisib. A previous

study suggests that palbociclib retreatment has limited efficacy in patients who received it previously.[23] Our results, however, suggest that adding gedatolisib restored sensitivity to any previous CDK4/6i therapy. In addition, several patient subgroups reported greater median PFS with the gedatolisib triplet than the gedatolisib doublet, including pre-/perimenopausal patients (mPFS of 11.1 *v* 5.6, respectively), those who progressed on previous therapy <6 months (mPFS of 7.4 *v* 5.6), and those who received previous palbociclib (mPFS of 16.6 *v* 7.6). While definitive conclusions cannot be drawn, these results suggest enhanced involvement of the CDK4/6 pathway in the tumors of these patient subgroups and the corresponding need for continuous treatment with a CDK4/6i. The clinical impact and safety of adding gedatolisib to fulvestrant with either abemaciclib or ribociclib remain to be determined.

Fulvestrant monotherapy was selected as the control arm to meet regulatory requirements, and the results were consistent with those from six other recent randomized studies in patients who have received previous CDK4/6i therapy.[20,21,24-27] Although fulvestrant is no longer the standard of care in the second-line setting in all countries,[1-3,28] the median PFS of 9.3 months in the gedatolisib-triplet group is clinically meaningful independent of the control arm's performance and is among the longest reported for a chemotherapy-free second- to third-line regimen in a phase III trial in patients with hormone receptor–positive/HER2– advanced breast cancer.

In conclusion, gedatolisib, a highly potent multitarget inhibitor of the PAM pathway, significantly improved PFS when added to fulvestrant, with or without palbociclib, in patients with *PIK3CA*-WT advanced breast cancer whose disease progressed during or after treatment with a CDK4/6i and NSAI. These findings support the use of gedatolisib combination therapy as a potential new standard of care in the second-line setting. Analyses from Study 2 (*PIK3CA*-mutated) will be forthcoming and will further define the role of gedatolisib-based therapy in a broader population. In addition, the randomized phase III VIKTORIA-2 trial (ClinicalTrials.gov identifier: NCT06757634) is evaluating gedatolisib in combination with palbociclib plus fulvestrant as first-line therapy for patients with endocrine-resistant, hormone receptor–positive/HER2– ABC.

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A complete list of the VIKTORIA-1 investigators is provided in the Appendix.

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VIKTORIA-1 Trial of Gedatolisib Plus Fulvestrant With or Without Palbociclib in Hormone Receptor–Positive/HER2–/PIK3CA Wild-Type Advanced Breast Cancer

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Site and Investigator List

Country	Site	Site Name	Name
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	1010	Bon Secours St Francis Medical Oncology Center	Irvin, William
	1012	CARTI Cancer Center	Makhoul, Issam
	1014	Seattle Cancer Care Alliance	Specht, Jennifer
	1022	Weill Cornell Medical College—New York Presbyterian Hospital	Cristofanilli, Massimo
	1024	Henry Ford Health System	Jabbour-Aida, Hiba
	1027	Torrance Memorial Physician Network—Cancer Care	Chan, David
	1030	Dana-Farber Cancer Institute	Giordano, Antonio
	1031	University of California Irvine—Chao Family Comprehensive Cancer Center	Parajuli, Ritesh
	1034	Yale University, Yale Cancer Center	Silber, Andrea
	1035	Cancer Specialists of North Florida	Vankayala, Hema
	1036	Breast Cancer Center at Memorial Regional Hospital	Guaqueta, Delia
	1039	Queens Hospital Center	Bashir, Tayyaba
	1040	Beth Israel Deaconess Medical Center	Wulf, Gerburg
	1042	Oncology Consultants, PA	Alvarez, Ricardo
	1047	Northwest Medical Specialties, PLLC	Blau, Sibel
	1056	Kaiser Permanente	Suga, Jennifer
	1058	Fort Wayne Medical Oncology and Hematology, Inc	Babu, Sunil
	1064	Oncology & Hematology Associates of Southwest Virginia, Inc, DBA Blue Ridge Cancer Care	Gillespie-Twardy, Amanda
	1068	Texas Oncology—Austin	Hudson, Kathryn
	1070	Illinois Cancer Specialists	Sobol, Urszula
	1075	Mercy Health—Paducah Medical Oncology and Hematology	Claudino, Wederson
	1082	Texas Oncology—Baylor Charles A. Sammons Cancer Center	Osborne, Cynthia
Canada	1201	Centre Integre Universitaire de Sante et de Services Sociaux du Saguenay-Lac-Saint-Jean	Guimaraes, Jose
	1204	Centre Hospitalier de l'Universite de Montreal (CHUM)	Charpentier, Danielle
	1206	BC Cancer—Vancouver, Medical Oncology	Sulpher, Jeffrey
	1209	Walker Family Cancer Center	Phillips, Cameron
Austria	2002	University Hospital Innsbruck—Tyrolean Hospital, Department of Gynecology and Obstetrics	Egle, Daniel
	2004	University Hospital St Poelten, Department of Internal Medicine I	Wiesholzer, Martin
	2006	Order Hospital Linz Ltd.—Hospital of Sisters of Mercy, Department of Internal Medicine I	Pusch, Renate
	2008	Hospital Wels—Grieskirchen, Department of Internal Medicine IV	Heibl, Sonja
Belgium	2103	AZ Groeninge	Nuytemans, Laure
	2104	Saint Luc University Hospital	Duhoux, Francois
	2106	University Hospitals Leuven, Campus Gasthuisberg	Neven, Patrick
	2107	University Hospital Antwerp (UZA)	Altintas, Sevilay

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TABLE A1. Site and Investigator List (continued)

Country	Site	Site Name	Name
France	2201	University Hospital Center of Poitiers	Isambert, Nicolas
	2202	Gustave Roussy	Pistilli, Barbara
	2203	Hopital de la Timone—La Timone's Hospital	Meurer, Marie
	2204	Bergonie Institute	Arnedos, Monica
	2205	Saint Anne Clinic	Tazi, Youssef
	2206	La Roche-sur-Yon Hospital	Priou, Frank
	2207	Francois Baclesse Center	Emile, George
Germany	2301	Klinikum Bayreuth GmbH	Mundhenke, Christoph
	2304	Universitaetsmedizin der Johannes Gutenberg-Universitaet Mainz	Schmidt, Marcus
	2305	Vivantes Klinikum am Urban	Hackenthal, Matthias
	2306	Klinikum Suedstadt Rostock	Reimer, Toralf
	2307	Caritasklinikum St Theresia	Deryal, Mustafa
	2310	Universitaetsklinikum Muenster	Tio, Joke
Italy	2501	San Gerardo of Tintori IRCCS Foundation	Cazzaniga, Marina
	2502	University Hospital Campus Bio-Medico	Tonini, Giuseppe
	2504	European Institute of Oncology (IEO), IRCCS	Colleoni, Marco Angelo
	2505	University Polyclinic Foundation "Agostino Gemelli"—IRCCS	Tortora, Giampaolo
	2506	USL Company Toscana Center—New Hospital of Prato	Biganzoli, Laura
	2508	University Hospital of Parma	Boggiani, Daniela
Spain	2601	University Hospital Foundation Jimenez Diaz	Izarzugaza Peron, Yann
	2602	Infanta Cristina Hospital	Gonzalez-Haba Martinez, Alba
	2603	University Hospital Ramon y Cajal	Martinez Janez, Noelia
	2604	University Hospital Complex of Santiago (CHUS)	Rodriguez Lopez, Carmela
	2605	University Clinical Hospital Virgen de la Arrixaca	Alonso Romero, Jose Luis
	2606	Caceres Hospital Complex—San Pedro de Alcantara General Hospital	Gonzalez Santiago, Santiago
	2607	Catalan Institute of Oncology, Hospital Duran i Reynals	Stradella Trucco, Agostina
	2608	Hospital Ruber Internacional	Saavedra Serrano, Cristina
United Kingdom	2801	Nottingham City Hospital	Khan, Sarah
	2802	The Royal Marsden Hospital—London	Ring, Alistair
	2805	The Christie NHS Foundation Trust	O'Brien, Ciara
	2806	Velindre Cancer Centre	Waters, Simon
	2807	The Royal Marsden Hospital—Sutton	Ring, Alistair
Greece	2902	University General Hospital of Ioannina	Mauri, Davide
	2903	Theageneio Anticancer Hospital of Thessaloniki	Rallis, Grigorios
	2904	EUROMEDICA General Clinic of Thessaloniki	Papazisis, Kostantinos
	2905	Alexandra General Hospital of Athens	Zagouri, Flora
Bulgaria	4001	Multiprofile Hospital for Active Treatment—Uni Hospital, Panagyurishte	Krasteva, Rossitza
	4002	University Specialized Hospital for Active Treatment in Oncology	Konsoulova-Kirova, Assia
	4004	Multiprofile Hospital for Active Treatment for Women's Health—Nadezhda	Donev, Ivan Shterev
	4005	Multiprofile Hospital for Active Treatment "Serdika", Sofia	Miteva-Yovcheva, Nadezhda
Czech Republic	4101	University Hospital Motol, Clinic of Oncology	Buchler, Tomas
	4102	University Hospital Olomouc, Clinic of Oncology	Melichar, Bohuslav
	4103	Thomayer University Hospital, Clinic of Oncology	Kubala, Eugen
Hungary	4202	University of Debrecen Clinical Center, Institute of Oncology	Arkosy, Peter
	4203	Bacs-Kiskun County Teaching Hospital, Center for Oncoradiology	Kocsis, Judit

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TABLE A1. Site and Investigator List (continued)

Country	Site	Site Name	Name
Poland	4301	St John Paul 2nd Mazovian Provincial Hospital in Siedlce Limited Liability Company, Siedlce Oncology Centre	Bodnar, Lubomir
	4302	Polish Mother's Memorial Hospital-Research Institute; Department of Oncology	Kalinka, Ewa
	4303	Przychodnia Lekarska "KOMED"	Karaszewska, Boguslawa
	4304	Maria Sklodowska-Curie—National Research Institute of Oncology	Nowecki, Zbigniew
	4305	West Pomeranian Oncology Center	Hetman, Katarzyna
	4306	Maria Sklodowska-Curie—National Research Institute of Oncology—Krakow	Grela-Wojewoda, Aleksandra
	4308	LUX MED Oncology LLC, Szamocka Hospital	Studzinski, Maciej
	4309	Prof. Tadeusz Koszarowski Opole Oncology Center	Radecka, Barbara
Romania	4401	Onco Clinic Consult S.A., Dept of Medical Oncology	Visan, Patricia
	4402	"Sf. Nectarie" Oncology Center, Department of Medical Oncology	Schenker, Michael
	4404	"Prof. Dr. Alexandru Trestioreanu" Institute of Oncology, Bucharest, Medical Oncology Department II	Alexandru, Aurelia
	4406	S.C. Oncopremium-Team SRL, Department of Medical Oncology	Herzal, Alina Amalia
	4407	"Prof. Dr. Ion Chiricuta" Institute of Oncology, Radiotherapy Department I	Antone, Nicoleta Zenovia
	4408	S.C. Radiotherapy Center Cluj SRL, Department of Medical Oncology	Ungureanu, Andrei
India	6004	HCG Cancer Center	Babu, Govind
	6007	Sri Ram Cancer and Superspeciality Centre, Mahatma Gandhi Medical College & Hospital	Malhotra, Hemant
Australia	7001	Perth Breast Cancer Institute, Breast Cancer Research Center—WA	Lo, Louisa
	7005	Mater Hospital Brisbane, Mater Cancer Care Center	Shannon, Catherine
	7008	Icon Cancer Centre—Southport	Islam, Mohammed
South Korea	8001	Samsung Medical Center	Shin, Junghoon
	8002	Gangnam Severance Hospital, Yonsei University Health System	Kim, Jee Hung
	8003	Asan Medical Center	Kim, Sung-Bae
	8004	Ulsan University Hospital	Koh, Su-Jin
	8005	Severance Hospital, Yonsei University Health System	Kim, Gun Min
	8006	Korea University Anam Hospital	Park, Kyong Hwa
Singapore	8101	Tan Tock Seng Hospital	Heong, Valerie
	8103	Raffles Hospital	Tan, Terence Alk Huang
	8104	OncoCare Cancer Centre	Wong, Nan Soon
	8105	Curie Oncology	Ngo Su-Mien, Lynette
Taiwan	8201	China Medical University Hospital	Liu, Liang-Chih
	8202	Taipei Veterans General Hospital	Tseng, Ling-Ming
	8203	Kaohsiung Medical University Chung-Ho Memorial Hospital	Hou, Ming-Feng
	8204	Changhua Christian Hospital	Chen, Shou-Tung
	8205	National Taiwan University Hospital	Lu, Yen-Shen
	8208	National Cheng Kung University Hospital	Lee, Kuo-Ting
	8209	National Taiwan University Hospital—Yunlin Branch (Huwei District)	Chen, Jo-Pai

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TABLE A1. Site and Investigator List (continued)

Country	Site	Site Name	Name
Argentina	9001	Hospital Britanico de Buenos Aires	Korbenfeld, Ernesto
	9002	Centro Medico Austral	Streich, Guillermo
	9003	Fleischer Medical Center	Rosselli, Geronimo
	9004	CER San Juan	Puig, Juan Manuel
	9005	Pergamino Clinic	Kahl, Susana
	9006	9 of July Sanatorium	Rodriguez, Juan Jose
	9007	IONC—Cordoba Oncology Institute	Richardet, Martin
	9008	Instituto de Oncologia de Rosario	Micheri, Cristian
	9010	CEDIT	Salazar, Matias
	9011	Alexander Fleming Institute	Nadal, Jorge Carlos
	9012	Fundacion Centro de Medicina Nuclear y Molecular Entre Rios (CEMENER)	Bader, Maria Marta
	9013	Fundación CENIT para la Investigation en Neurosciencias	Casalnuovo, Monica Lis
Brazil	9101	Instituto D'or de Pesquisa e Ensino—ONCO STAR	Testa, Laura
	9102	Clinica de Neoplasias Litoral (Catarina Pesquisa Clinica)	Santos Borges, Giuliano
	9103	Fundação Antonio Prudente	Goldner Cesca, Marcelle
	9105	ONCOSITE—CENTRO DE PESQUISA CLINICA EM ONCOLOGIA	Franke, Fabio Andre
	9107	A Beneficenda Portuguesa de Sao Paulo Mirante	Zibetti Dal Molin, Graziela
	9108	Suporte Nutricional e Quimioterapia LTDA—Pronutrir	Braga, Virginia
	9110	CTO—Cancer Treatment Center	Fernandes, Bruno Melo
Mexico	9301	ProcliniQ Clinical Research	Cruz, Marlid
	9302	Sociedad Administradora de Servicios de Salud S.C.	Martinez Alvarez, Ivan
	9303	Cryptex Investigacion Clinica, S.A. de C.V.	Motola, Daniel
	9305	Centro Medico Zambrano Hellion	Villarreal, Cynthia
	9306	Avix Clinical Research	Sanchez, Mario
	9307	Fundação Antonio Prudente	Willars Inman, Eva
	9308	Clinical Research Center Chapultepec, S.A. de C.V.	Remolina-Bonilla, Yuly A.
	9309	Filios Alta Medicina S.A. de C.V.	Martinez Rodriguez, Jorge Luis