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ORIGINAL ARTICLE

Safety overview and management of inavolisib alone and in combination therapies in *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer (GO39374)

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Background: Inavolisib is a potent and selective PI3Kα inhibitor that promotes degradation of mutated p110α. We report safety from a phase I/Ib dose-escalation/-expansion study (GO39374; NCT03006172) of inavolisib alone or in combination therapies in *PIK3CA*-mutated, hormone receptor (HR)-positive, HER2-negative advanced breast cancer.

Patients and methods: Patients received inavolisib [oral once daily (od)] alone, with letrozole (2.5 mg od) or fulvestrant (500 mg intramuscularly 4 weekly) ± palbociclib (125 mg od for 21/28 days); metformin was included in one arm. Primary endpoint: safety and tolerability.

Results: At data cutoff (1 January 2024), 190 patients had been treated, of which 179 (94.2%) had discontinued study treatment, mainly due to progressive disease [146 (76.8%)]. Treatment-related any-grade and grade 3-5 adverse events (AEs) occurred in 181 (95.3%) and 107 (56.3%) patients, respectively. Inavolisib-related AEs led to inavolisib withdrawal in 5 (2.6%) and dose reductions/interruptions in 103 (54.2%) patients. Hyperglycemia, diarrhea, stomatitis (grouped terms), and rash (grouped terms) occurred in 129 (67.9%), 124 (65.3%), 93 (48.9%), and 47 (24.7%) patients, respectively. Hyperglycemia, diarrhea, and stomatitis mainly occurred early in treatment, and were manageable with supportive measures (including oral antihyperglycemic agents, common antidiarrheal medications, and dexamethasone mouthwash, respectively) and/or inavolisib dose modifications (dose interruptions with or without dose reductions). Hyperglycemia remained frequent in patients with risk factors, despite early metformin treatment. Rash was mostly grade 1 and required no treatment. Patients treated for ≥1 year [$n = 65$ (34.2%)] demonstrated encouraging long-term tolerability.

Conclusions: Inavolisib alone or in combination with HR-positive breast cancer therapies demonstrated a manageable safety and tolerability profile, which supports its ongoing development.

Key words: breast cancer, PI3K inhibitor, *PIK3CA*-mutated, safety, hormone receptor-positive

INTRODUCTION

Among breast cancers, hormone receptor (HR)-positive, HER2-negative is the most common subtype, accounting for ∼68% of cases globally.[1] Endocrine therapy combined with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors is the standard first-line treatment of locally advanced or metastatic disease.[2,3] However, some patients do not respond or have limited response to endocrine-based therapies, and ultimately, most patients develop endocrine resistance.[4,5]

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Thus, additional well-tolerated, highly efficacious therapies are needed.

Approximately 35%-40% of patients with HR-positive, HER2-negative breast cancer present with activating mutations in the *PIK3CA* gene.[6-8] *PIK3CA* encodes the p110α catalytic subunit of the phosphoinositide 3-kinase (PI3K) complex, which is involved in regulation of cell growth, proliferation, survival, and migration through the PI3K/AKT/mTOR signaling pathway. Activating *PIK3CA* mutations drive constitutive hyperactivation of the PI3K/AKT/mTOR signaling pathway, which is associated with intrinsic endocrine resistance.[9] However, despite the approval of the PI3Kα inhibitor alpelisib in combination with fulvestrant for patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer,[10] widespread implementation of this targeted therapy in clinical practice has been challenging due to high rates of adverse event (AE)-related dose reductions and treatment discontinuations.

Inavolisib is a potent and selective PI3Kα inhibitor that promotes mutated p110α degradation. In biochemical assays, inavolisib was >300-fold more selective for p110α over the p110 β, δ, and γ isoforms and demonstrated increased potency in tumor cells bearing mutated p110α over wildtype p110α.[11,12] These properties may limit toxicity[11,12] and enable combinations of inavolisib with a variety of therapies, including endocrine therapies and CDK4/6 inhibitors, to improve efficacy.

Inavolisib was evaluated in a first-in-human, open-label, multicenter, phase I/Ib dose-escalation and dose-expansion study (GO39374; NCT03006172) for safety and tolerability, pharmacokinetics, and preliminary antitumor activity, as a single agent and as part of combination therapies, in patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer. Data for inavolisib plus palbociclib and letrozole (arm B) and inavolisib plus palbociclib and fulvestrant (arm E) demonstrating the manageable safety profile, lack of drug—drug interactions, and promising preliminary antitumor activity of the combinations have recently been reported.[13] Here, we describe in detail the safety and tolerability of inavolisib alone and in combination with endocrine therapy (letrozole or fulvestrant) with and without palbociclib, and the management of selected AEs (hyperglycemia, diarrhea, stomatitis, rash) commonly associated with therapeutic inhibition of the PI3K pathway.

MATERIALS AND METHODS

Study design and procedures

Patients included in this analysis were enrolled in one of six treatment arms and received inavolisib [orally once daily (od)] alone (arm A), in combination with palbociclib (125 mg orally od for 21 days of a 28-day cycle) and letrozole (2.5 mg orally od) (arm B), with letrozole (arm C), with fulvestrant (500 mg via intramuscular injection on days 1 and 15 of cycle 1 and then every 4 weeks starting from cycle 2 day 1) (arm D), with palbociclib and fulvestrant (arm E), or with palbociclib, fulvestrant, and metformin (up to 2000 mg orally od starting on day 1, with inavolisib initiated on cycle 1 day 15) (arm F) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105303). The study also included an arm (arm G) for patients with HER2-positive breast cancer, who were treated with inavolisib in combination with trastuzumab and pertuzumab; results from this arm will be published separately.

Patients in the single-agent inavolisib arm (arm A) received inavolisib at 6 mg, 9 mg, or 12 mg od doses during the dose-escalation stage of the study using a standard 3 + 3 dose-escalation design. Patients in the inavolisib plus letrozole and palbociclib arm (arm B) received inavolisib at 3 mg, 6 mg, or 9 mg od doses in the dose-escalation stage and at 9 mg od in the dose-expansion stage of the study. Patients in the inavolisib plus letrozole arm (arm C) received inavolisib at 6 mg or 9 mg od doses in the dose-escalation stage and at 9 mg od in the dose-expansion stage of the study. Patients in the inavolisib plus fulvestrant without or with palbociclib arms (arm D, and arms E and F, respectively) received inavolisib at the 9 mg od dose in the dose-expansion stage of the study only; each of these arms included a safety run-in phase involving the first six patients enrolled (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105303).

Patients continued to be treated in the study until disease progression or unacceptable toxicity. Patients were followed for safety until 30 days after the last dose of study treatment.

PIK3CA tumor mutation status was determined from local site testing of tumor tissue or plasma-derived circulating tumor DNA [polymerase chain reaction (PCR) testing or next-generation sequencing] or from sponsor central testing of fresh or archival tumor tissue with the PCR-based Cobas® PIK3CA Mutation Test (F. Hoffmann-La Roche Ltd, Basel, Switzerland). HR status and HER2 status were assessed locally per institutional clinical guidelines.

GO39374 was carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Protocol approval was obtained from the independent ethics committee at each participating site. All patients provided written informed consent before any study-specific activities. An internal safety committee reviewed cumulative safety data during the dose-escalation phase and periodically throughout the conduct of the study.

Patient eligibility

Patients were ≥18 years old and had a *PIK3CA*-mutated tumor (H1047R/Y/L, E542K, E545K/D/G/A, Q546K/R/E/L, N345K, C420R, G1049R, R88Q, M1043I), evaluable or measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1,[14] an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of ≥12 weeks, adequate hematologic and organ function within 14 days before initiation of study treatment, fasting blood glucose levels ≤140 mg/dl, and glycosylated hemoglobin (HbA_{1c}) levels <7%.

Exclusion criteria included treatment of cancer with chemotherapy, cancer immunotherapy, or biologic therapy

within 3 weeks before initiation of study treatment, or with endocrine therapy within 2 weeks before initiation of study treatment; known and untreated, or active central nervous system metastases; and any prior treatment with a PI3K inhibitor in selected cohorts in the single-agent inavolisib arm and the inavolisib plus letrozole arm (arms A and C, respectively) in the dose-escalation stage, and in all arms in the dose-expansion stage.

Assessments

The primary endpoint was safety and tolerability (incidence, nature, and severity of AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0, and changes from baseline in vital signs and laboratory test results. It should be noted that under NCI CTCAE v4.0 used in this protocol, hyperglycemia was graded based on fasting blood glucose levels; hyperglycemia grading has more recently been changed in NCI CTCAE v5.0 to reflect the interventions required. Selected AEs investigated in this study included hyperglycemia, diarrhea, stomatitis, and rash. Stomatitis was a grouped term, which included: stomatitis, mucosal inflammation, mouth ulceration, glossitis, tongue ulceration, glossodynia, lip ulceration, and palatal ulcer. Rash was a grouped term, which included: rash, rash maculopapular, dermatitis acneiform, erythema, hand dermatitis, rash erythematous, and rash pruritic. For treatment exposure, the cumulative dose intensity was defined as the total dose administered relative to the total planned dose.

Statistical analysis

The planned enrollment for the study was up to ∼236 patients overall: up to 96 in the dose-escalation stage and ∼140 in the dose-expansion stage. This study was intended to obtain preliminary safety, pharmacokinetic, antitumor activity, and pharmacodynamic information in the safety-assessable population. The safety-assessable population included all patients who received one or more doses of study treatment. Safety analyses were descriptive. For categoric variables, count and percentage were provided. For continuous variables, median and range were provided.

RESULTS

Patients

At the data cutoff date (1 January 2024), 191 patients had been enrolled between December 2016 and August 2021, and 190 had been treated on the study across the six treatment arms included in this analysis (arms A-F), including 65 (34.2%) patients who had been treated for >1 year. Baseline demographics, disease characteristics, and dispositions for all patients enrolled are shown in Table 1. All patients but one were females with breast cancer [one male with colorectal cancer was enrolled in the single-agent inavolisib arm (arm A)]; median age was 59.0 years; 109 (57.1%) patients had an ECOG performance status of 0, and 139 (72.8%) self-reported as white (Table 1). The median number of prior therapies in the metastatic setting was 2 (range, 1-10) (Table 1). The most common prior cancer therapies were aromatase inhibitors [n = 172 (90.1%)], followed by chemotherapy [n = 153 (80.1%)] and CDK4/6 inhibitors [n = 126 (66.0%)] (Table 1). Eleven (5.8%) patients were still receiving study treatment at the time of data cutoff [two patients in the inavolisib plus palbociclib and letrozole arm (arm B), two patients in the inavolisib plus fulvestrant arm (arm D), six patients in the inavolisib plus palbociclib and fulvestrant arm (arm E), and one patient in the inavolisib plus palbociclib, fulvestrant, and metformin arm (arm F)]. A total of 179 (94.2%) patients had discontinued study treatment, mainly due to progression of the disease under investigation [progressive disease per RECIST v1.1: n = 146 (76.8%); symptomatic deterioration (due to underlying cancer): n = 17 (8.9%)]. Overall, seven (3.7%) patients discontinued study treatment due to AEs, and one (0.5%) patient died while on study treatment due to an unrelated event of grade 5 hypertrophic cardiomyopathy, related to a pre-existing underlying cardiac disorder (Table 1). In addition, six patients died during the safety follow-up [four patients due to disease progression and two patients due to AEs unrelated to study treatment (pleural effusion and peritonitis)].

The median treatment duration for inavolisib across all arms was 7.2 months (range, 0.2-70.7 months) and the median inavolisib cumulative dose intensity was 96.0% (range, 22.7%-238.6%; intra-patient dose escalation was allowed in the dose-escalation phase of the study). The median letrozole treatment duration was 6.4 months (range, 0.3-72.0 months) and the median cumulative dose intensity was 99.4% (range, 62.5%-100.2%). The median fulvestrant treatment duration was 7.9 months (range, 0.0-55.9 months) and the median cumulative dose intensity was 97.9% (range, 30.6%-398.0%; upper range impacted by a data entry error). The median palbociclib treatment duration was 13.0 months (range, 1.4-70.6 months) and the median cumulative dose intensity was 85.1% (range, 43.0%-101.0%). The median metformin treatment duration (calculated for arm F only, as part of the study treatment) was 3.7 months (range, 0.8-45.1 months) with a median cumulative dose intensity of 90.5% (range, 4.9%-100.0%).

Safety overview

A safety summary by treatment arm is provided in Table 2. Any-grade treatment-related AEs and grade 3-4 treatment-related AEs occurred in 181 (95.3%) patients and 107 (56.3%) patients, respectively (Table 2). The most common any-grade AE related to any treatment across the six arms included in this analysis was hyperglycemia [n = 127 (66.8%)], followed by stomatitis [n = 93 (48.9%); grouped terms], diarrhea [n = 84 (44.2%)], and nausea [n = 70 (36.8%)] (Table 3). The most common grade ≥3 AEs related to any treatment across all arms were hyperglycemia [n = 46 (24.2%)] and neutropenia [n = 45 (23.7%)] (Table 3).

Table 1. Baseline demographics, disease characteristics, and patient disposition (full analysis set)

	Arm A: inavolisib (n = 20)	Arm B: inavolisib + palbociclib + letrozole (n = 33)	Arm C: inavolisib + letrozole (n = 37)	Arm D: inavolisib + fulvestrant (n = 60)	Arm E: inavolisib + palbociclib + fulvestrant (n = 20)	Arm F: inavolisib + palbociclib + fulvestrant + metformin (n = 21)	All patients (N = 191)
Median age, years (range)	65.0 (41-77)	57.0 (37-80)[a]	58.0 (43-79)	59.5 (31-85)	55.0 (33-73)[a]	65.0 (33-77)	59.0 (31-85)
Female, n (%)	19 (95.0)	33 (100)[a]	37 (100)	60 (100)	20 (100)[a]	21 (100)	190 (99.5)
Race, n (%)							
Asian	0	1 (3.0)[a]	0	3 (5.0)	0[a]	1 (4.8)	5 (2.6)
Black or African American	1 (5.0)	1 (3.0)[a]	0	1 (1.7)	0[a]	0	3 (1.6)
White	14 (70.0)	26 (78.8)[a]	28 (75.7)	45 (75.0)	10 (50.0)[a]	16 (76.2)	139 (72.8)
Multiple	0	0	0	1 (1.7)	0	0	1 (0.5)
Unknown	5 (25.0)	5 (15.2)[a]	9 (24.3)	10 (16.7)	10 (50.0)[a]	4 (19.0)	42 (22.5)
Ethnicity, n (%)							
Hispanic or Latino	1 (5.0)	1 (3.0)[a]	1 (2.7)	2 (3.3)	1 (5.0)[a]	0	6 (3.1)
Not Hispanic or Latino	13 (65.0)	29 (87.9)[a]	28 (75.7)	45 (75.0)	8 (40.0)[a]	17 (81.0)	140 (73.3)
Not reported	0	1 (3.0)[a]	2 (5.4)	7 (11.7)	4 (20.0)[a]	1 (4.80)	15 (7.9)
Unknown	6 (30.0)	2 (6.1)[a]	6 (16.2)	6 (10.0)	7 (35.0)[a]	3 (14.3)	30 (15.7)
ECOG PS, n (%)							
0	11 (55.0)	20 (60.6)[a]	26 (70.3)	34 (56.7)	10 (50.0)[a]	8 (38.1)	109 (57.1)
1	9 (45.0)	13 (39.4)[a]	11 (29.7)	26 (43.3)	10 (50.0)[a]	13 (61.9)	82 (42.9)
BMI, n (%)	n = 20	n = 32	n = 37	n = 60	n = 20	n = 20	n = 189
<18.5 kg/m^2	0	1 (3.1)	1 (2.7)	4 (6.7)	0	0	6 (3.2)
≥18.5 to <25.0 kg/m^2	9 (45.0)	11 (34.4)	17 (45.9)	27 (45.0)	11 (55.0)	1 (5.0)	76 (40.2)
≥25.0 to <30.0 kg/m^2	6 (30.0)	10 (31.3)	11 (29.7)	20 (33.3)	7 (35.0)	4 (20.0)	58 (30.7)
≥30.0 kg/m^2	5 (25.0)	10 (31.3)	8 (21.6)	9 (15.0)	2 (10.0)	15 (75.0)	49 (25.9)
HbA_{1c}, n (%)	n = 20	n = 32	n = 37	n = 60	n = 20	n = 20	n = 189
<5.7%	14 (70.0)	20 (62.5)	28 (75.7)	41 (68.3)	15 (75.0)	10 (50.0)	128 (67.7)
≥5.7 to <6.5%	6 (30.0)	11 (34.4)	6 (16.2)	19 (31.7)	5 (25.0)	7 (35.0)	54 (28.6)
≥6.5%	0	1 (3.1)	3 (8.1)	0	0	3 (15.0)	7 (3.7)
Fasting blood glucose, n (%)	n = 20	n = 33	n = 37	n = 52	n = 19	n = 19	n = 180
<100 mg/dl	14 (70.0)	22 (66.7)	19 (51.4)	39 (75.0)	14 (73.7)	7 (36.8)	115 (63.9)
≥100 to <126 mg/dl	6 (30.0)	10 (30.3)	18 (48.6)	12 (23.1)	5 (26.3)	9 (47.4)	60 (33.3)
≥126 mg/dl	0	1 (3.0)	0	1 (1.9)	0	3 (15.8)	5 (2.8)
Median number of prior therapies in the metastatic setting (range)	3 (1-10)	2 (1-4)[a]	3 (1-10)	2 (1-7)	1 (1-4)[a]	3 (1-9)	2 (1-10)
Prior therapies, n (%)							
Chemotherapy	19 (95.0)	26 (78.8)[a]	32 (86.5)	43 (71.7)	15 (75.0)[a]	18 (85.7)	153 (80.1)
Chemotherapy in the metastatic setting	15 (75.0)	13 (39.4)[a]	18 (48.6)	21 (35.0)	4 (20.0)[a]	13 (61.9)	84 (44.0)
CDK4/6 inhibitor	18 (90.0)	24 (80.0)[a]	29 (78.4)	58 (96.7)	0[a]	14 (66.7)	126 (66.0)
Aromatase inhibitor	19 (95.0)	28 (93.3)[a]	35 (94.6)	58 (96.7)	16 (80.0)[a]	20 (95.2)	172 (90.1)
SERD	13 (65.0)	21 (70.0)[a]	27 (73.0)	29 (48.3)	3 (15.0)[a]	15 (71.4)	101 (52.9)
Fulvestrant	13 (65.0)	21 (70.0)[a]	26 (70.3)	29 (48.3)	3 (15.0)[a]	14 (66.7)	98 (51.3)
Discontinued study treatment, n (%)	n = 20	n = 33	n = 37	n = 60	n = 20	n = 20	n = 190
Any reason	20 (100)	31 (93.9)	37 (100)	58 (96.7)	14 (70.0)	19 (95.0)	179 (94.2)
AE	0	3 (9.1)	0	0	2 (10.0)	2 (10.0)	7 (3.7)
Death	0	0	0	1 (1.7)	0	0	1 (0.5)
Other	0	0	1 (2.7)	0	0	0	1 (0.5)
Physician decision	0	1 (3.0)	0	1 (1.7)	0	1 (5.0)	3 (1.6)
Progressive disease	16 (80.0)	25 (75.8)	31 (83.8)	51 (85.0)	10 (50.0)	13 (65.0)	146 (76.8)
Symptomatic deterioration	4 (20.0)	2 (6.1)	3 (8.1)	5 (8.3)	1 (5.0)	2 (10.0)	17 (8.9)
Withdrawal by subject	0	0	2 (5.4)	0	1 (5.0)	1 (5.0)	4 (2.1)

AE, adverse event; BMI, body mass index; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; HbA_{1c}, glycosylated hemoglobin A_{1c}; SERD, selective estrogen receptor antagonist and degrader.

[a]Arms B and E data previously presented in Jhaveri KL, Accordino MK, Bedard PL, et al. Phase I/Ib trial of inavolisib plus palbociclib and endocrine therapy for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer. *J Clin Oncol*. 2024;42:3947-3956.

All grade ≥3 events of neutropenia were reported in palbociclib-containing arms (arms B, E, and F).

Three (1.6%) patients had an AE with a fatal outcome (all unrelated to treatment; hypertrophic cardiomyopathy, pleural effusion, and peritonitis) and 13 (6.8%) had treatment-related serious AEs (Table 2). Five (2.6%) patients discontinued treatment due to inavolisib-related AEs and 103 (54.2%) had dose modifications (reductions and/or interruptions) of inavolisib due to inavolisib-related AEs (Table 2).

In the dose-escalation phase of the single-agent inavolisib arm (arm A), two dose-limiting toxicities (DLTs) were reported at the inavolisib 12 mg od dose level: one event of grade 4 hyperglycemia and one of grade 3 fatigue. Based on these two DLT events, the maximum tolerated dose was determined to be 9 mg od. No DLTs were reported in the

Table 2. Safety summary (safety-assessable population)

	Arm A: inavolisib (*n* = 20)	Arm B: inavolisib + palbociclib + letrozole (*n* = 33)	Arm C: inavolisib + letrozole (*n* = 37)	Arm D: inavolisib + fulvestrant (*n* = 60)	Arm E: inavolisib + palbociclib + fulvestrant (*n* = 20)	Arm F: inavolisib + palbociclib + fulvestrant + metformin (*n* = 20)	All patients (*N* = 190)
Any-grade AE, *n* (%)	20 (100)	33 (100)[a]	37 (100)	59 (98.3)	20 (100)[a]	19 (95.0)	188 (98.9)
Related to any treatment	19 (95.0)	33 (100)[a]	35 (94.6)	56 (93.3)	20 (100)[a]	18 (90.0)	181 (95.3)
Grade 3-4 AE, *n* (%)	11 (55.0)	30 (90.9)[a]	16 (43.2)	33 (55.0)	17 (85.0)[a]	17 (85.0)	124 (65.3)
Related to any treatment	8 (40.0)	29 (87.9)[a]	12 (32.4)	26 (43.3)	17 (85.0)[a]	15 (75.0)	107 (65.3)
AE with fatal outcome, *n* (%)	0	0[a]	0	3 (5.0)	0[a]	0	3 (1.6)
Serious AE, *n* (%)	7 (35.0)	14 (42.4)[a]	4 (10.8)	13 (21.7)	6 (30.0)[a]	8 (40.0)	52 (27.4)
Related to any treatment	1 (5.0)	4 (12.1)[a]	2 (5.4)	4 (6.7)	0[a]	2 (10.0)	13 (6.8)
AE leading to withdrawal from inavolisib, *n* (%)	0	3 (9.1)	0	1 (1.7)	2 (10.0)	2 (10.0)	8 (4.2)
Related to inavolisib	0	2 (6.1)	0	0	2 (10.0)	1 (5.0)	5 (2.6)
AE leading to dose reduction/ interruption of inavolisib, *n* (%)	11 (55.0)	25 (75.8)	17 (45.9)	39 (65.0)	17 (85.0)	16 (80.0)	125 (65.8)
Related to inavolisib	10 (50.0)	20 (60.6)	16 (43.2)	31 (51.7)	13 (65.0)	13 (65.0)	103 (54.2)
Summary of selected AEs							
Hyperglycemia[b]							
Any grade, *n* (%)	15 (75.0)	21 (63.6)	26 (70.3)	39 (65.0)	14 (70.0)	14 (70.0)	129 (67.9)
Grade 1	5 (25.0)	9 (37.3)	12 (32.4)	14 (23.3)	3 (15.0)	1 (5.0)	44 (23.2)
Grade 2	6 (30.0)	5 (15.2)	7 (18.9)	9 (15.0)	8 (40.0)	4 (20.0)	39 (20.5)
Grade 3	3 (15.0)	7 (21.2)	7 (18.9)	14 (23.3)	3 (15.0)	8 (40.0)	42 (22.1)
Grade 4	1 (5.0)	0	0	2 (3.3)	0	1 (5.0)	4 (2.1)
Median time to first occurrence, days (range)							
Any grade	15 (1-43)	14 (1-1674)	8 (2-148)	9 (2-911)	8 (6-764)	22.5 (17-274)[c]	14 (1-1674)
Grade ≥2	19.5 (12-480)	33 (2-1871)	8 (4-86)	9 (3-821)	55 (6-1366)	23 (19-85)[c]	19 (2-1871)
Grade ≥3	15 (15-41)	92 (2-1331)	8 (7-99)	17.5 (3-228)	55 (6-913)	23 (19-253)[c]	22 (2-1331)
Total number of AEs	43	28	9	27	22	48	308
Outcomes, number of AEs (%)							
Recovered/resolved	35 (81.4)	18 (64.3)	6 (66.7)	9 (33.3)	12 (54.5)	42 (87.5)	265 (86.0)
Not recovered/resolved	8 (18.6)	8 (28.6)	3 (33.3)	16 (59.3)	9 (40.9)	6 (12.5)	36 (11.7)
Recovering/resolving	0	2 (7.1)	0	2 (7.4)	1 (4.5)	0	2 (0.6)
Recovered/resolved with sequelae	0	0	0	4 (4.9)	1 (2.7)	0	5 (1.6)
Fatal	0	0	0	0	0	0	0
Diarrhea							
Any grade, *n* (%)	14 (70.0)	25 (75.8)	19 (51.4)	37 (61.7)	17 (85.0)	12 (60.0)	124 (65.3)
Grade 1	11 (55.0)	18 (54.5)	15 (40.5)	22 (36.7)	13 (65.0)	6 (30.0)	85 (44.7)
Grade 2	3 (15.0)	6 (18.2)	4 (10.8)	13 (21.7)	3 (15.0)	5 (25.0)	34 (17.9)
Grade 3	0	1 (3.0)	0	2 (3.3)	1 (5.0)	1 (5.0)	5 (2.6)
Grade 4	0	0	0	0	0	0	0
Median time to first occurrence, days (range)							
Any grade	30 (9-289)	17 (1-938)	11 (2-100)	17 (1-716)	31 (3-338)	15 (2-361)[c]	17 (1-938)
Grade ≥2	86 (33-276)	163 (17-1204)	42 (8-259)	54 (8-561)	436.5 (16-941)	53.5 (17-361)[c]	68 (8-2104)
Grade ≥3	NE	17 (17-17)	NE	294.5 (8-581)	212 (212-212)	80 (80-80)[c]	80 (8-581)
Total number of AEs	23	81	34	109	45	26	318
Outcomes, number of AEs (%)							
Recovered/resolved	19 (82.6)	75 (93.8)	30 (88.2)	91 (83.5)	41 (91.1)	20 (76.9)	277 (87.1)
Not recovered/resolved	4 (17.4)	5 (6.2)	4 (11.8)	11 (10.1)	4 (8.9)	6 (23.1)	34 (10.7)
Recovering/resolving	0	0	0	3 (2.8)	0	0	3 (0.9)
Recovered/resolved with sequelae	0	0	0	4 (3.7)	0	0	4 (1.3)
Fatal	0	0	0	0	0	0	0
Stomatitis (grouped terms)[d]							
Any grade, *n* (%)	4 (20.0)	23 (67.9)	12 (32.4)	25 (41.7)	18 (90.0)	11 (55.0)	93 (48.9)
Grade 1	4 (20.0)	14 (42.4)	11 (29.7)	20 (33.3)	11 (55.0)	8 (40.0)	68 (35.8)
Grade 2	0	8 (24.2)	1 (2.7)	4 (6.7)	5 (25.0)	2 (10.0)	20 (10.5)
Grade 3	0	1 (3.0)	0	1 (1.7)	2 (10.0)	1 (5.0)	5 (2.6)
Grade 4	0	0	0	0	0	0	0
Median time to first occurrence, days (range)							
Any grade	99.5 (8-418)	18 (2-298)	16.5 (5-52)	15 (1-194)	16.5 (4-274)	26 (2-63)[c]	18 (1-418)
Grade ≥2	NE	71 (6-390)	93 (93-93)	219 (108-300)	72 (5-615)	71 (22-1078)[c]	87.5 (5-1078)
Grade ≥3	NE	121 (121-121)	NE	203 (203-203)	230.5 (27-434)	78 (78-78)[c]	121 (27-434)
Total number of AEs	5	50	19	39	41	18	172

Continued

Table 2. Continued

	Arm A: inavolisib (n = 20)	Arm B: inavolisib + palbociclib + letrozole (n = 33)	Arm C: inavolisib + letrozole (n = 37)	Arm D: inavolisib + fulvestrant (n = 60)	Arm E: inavolisib + palbociclib + fulvestrant (n = 20)	Arm F: inavolisib + palbociclib + fulvestrant + metformin (n = 20)	All patients (N = 190)
Outcomes, number of AEs (%)							
Recovered/resolved	4 (80.0)	42 (84.0)	15 (78.9)	29 (74.4)	34 (82.9)	12 (66.7)	136 (79.1)
Not recovered/resolved	1 (20.0)	7 (14.0)	3 (15.8)	9 (23.1)	6 (14.6)	6 (33.3)	32 (18.6)
Recovering/resolving	0	1 (2.0)	1 (5.3)	1 (2.6)	1 (2.4)	0	4 (2.3)
Recovered/resolved with sequelae	0	0	0	0	0	0	0
Fatal	0	0	0	0	0	0	0
Rash (grouped terms)[e]							
Any grade, n (%)	3 (15.0)	14 (42.4)	4 (10.8)	15 (25.0)	6 (30.0)	5 (25.0)	47 (24.7)
Grade 1	2 (10.0)	12 (36.4)	3 (8.1)	15 (25.0)	6 (30.0)	5 (25.0)	43 (22.6)
Grade 2	1 (5.0)	2 (6.1)	0	0	0	0	3 (1.6)
Grade 3	0	0	1 (2.7)	0	0	0	1 (0.5)
Grade 4	0	0	0	0	0	0	0
Median time to first occurrence, days (range)							
Any grade	145 (16-178)	68.5 (2-1146)	109.5 (15-281)	29 (5-559)	71 (15-746)	57 (20-159)[c]	59 (2-1146)
Grade ≥2	178 (178-178)	614 (59-1169)	642 (642-642)	NE	NE	NE	410 (59-1169)
Grade ≥3	NE	NE	642 (642-642)	NE	NE	NE	642 (642-642)
Total number of AEs	3	24	6	24	8	6	71
Outcomes, number of AEs (%)							
Recovered/resolved	3 (100)	17 (70.8)	5 (83.3)	20 (83.3)	7 (87.5)	5 (83.3)	57 (80.3)
Not recovered/resolved	0	7 (29.2)	1 (16.7)	2 (8.3)	1 (12.5)	1 (16.7)	12 (16.9)
Recovering/resolving	0	0	0	1 (4.2)	0	0	1 (1.4)
Recovered/resolved with sequelae	0	0	0	0	0	0	0
Unknown	0	0	0	1 (4.2)	0	0	1 (1.4)
Fatal	0	0	0	0	0	0	0

AE, adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NE, not evaluable.
[a]Arms B and E data previously presented in Jhaveri KL, Accordino MK, Bedard PL, et al. Phase I/Ib trial of inavolisib plus palbociclib and endocrine therapy for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer. *J Clin Oncol.* 2024;42:3947-3956.
[b]Graded based on fasting blood glucose levels, per NCI CTCAE v4.0.
[c]In arm F (inavolisib in combination with palbociclib, fulvestrant, and metformin), inavolisib was not initiated until cycle 1 day 15, following treatment with metformin starting on cycle 1 day 1.
[d]Stomatitis grouped terms: stomatitis, mucosal inflammation, mouth ulceration, glossitis, tongue ulceration, glossodynia, lip ulceration, and palatal ulcer.
[e]Rash grouped terms: rash, rash maculopapular, dermatitis acneiform, erythema, hand dermatitis, rash erythematous, and rash pruritic.

dose-escalation phases in other arms [inavolisib plus letrozole and palbociclib (arm B) or plus letrozole alone (arm C)].

Selected AEs

Selected AEs were defined based on the known and evolving safety profile of inavolisib and protocol-defined AEs of special interest. Table 2 shows the incidence, severity, time to first onset, and outcomes of selected AEs (hyperglycemia, diarrhea, stomatitis, and rash; stomatitis and rash were grouped terms and results for the grouped terms are presented throughout). Grade 3-4 hyperglycemia occurred in 46 (24.2%) patients; incidence of grade 3-4 diarrhea, stomatitis, and rash was low, occurring in five (2.6%), five (2.6%), and one (0.5%) patients, respectively (Table 2). Hyperglycemia, diarrhea, and stomatitis tended to occur early in treatment, specifically in the first cycle; however, there was no clear trend for rash AEs, which occurred less frequently than the other selected events (Figure 1). The median time to onset for any grade selected events was 14 days for hyperglycemia, 17 days for diarrhea, 18 days for stomatitis, and 59 days for rash (Table 2). For all the selected AEs, most events had recovered to baseline or resolved at the time of the data cutoff: 86.0% of hyperglycemia AEs, 87.1% of diarrhea AEs, 79.1% of stomatitis AEs, and 80.3% of rash AEs (Table 2).

Management of selected AEs

Hyperglycemia was mainly managed with inavolisib dose interruptions [n = 60 (31.6%)] and oral antihyperglycemic medications: metformin [n = 77 (40.5%)], empagliflozin [n = 30 (15.8%)], sitagliptin [n = 29 (15.3%)], pioglitazone [n = 18 (9.5%)], and insulin [n = 12 (6.3%)]. A total of 89 (46.8%) patients required one or more antihyperglycemic medications in addition to or in place of metformin to adequately control hyperglycemia. Median time from onset to improvement by at least one grade (per NCI CTCAE v4.0) or resolution of grade ≥2 hyperglycemia was 8 days (range, 1-64 days). A total of 73 (38.6%) patients required a dose modification because of hyperglycemia, including a dose interruption in 60 (31.6%) patients, a dose reduction in 18 (9.5%) patients, and withdrawal in one (0.5%) patient. Baseline HbA_{1c} ≥5.7% and body mass index (BMI) ≥30.0 kg/m^2 were

Table 3. Most common AEs, occurring in ≥20% of patients at any grade (safety-assessable population)

Patients, *n* (%)	All patients (*N* = 190)			
	Any-grade AE	Any-grade treatment-related AE	Grade ≥3 AE	Grade ≥3 treatment-related AE
Hyperglycemia[a]	129 (67.9)	127 (66.8)	46 (24.2)	46 (24.2)
Diarrhea	124 (65.3)	84 (44.2)	5 (2.6)	2 (1.1)
Nausea	112 (58.9)	70 (36.8)	8 (4.2)	3 (1.6)
Stomatitis (grouped terms)[b]	93 (48.9)	90 (47.4)	5 (2.6)	5 (2.6)
Vomiting	78 (41.1)	33 (17.4)	4 (2.1)	1 (0.5)
Neutropenia	63 (33.2)	59 (31.1)	45 (23.7)	45 (23.7)
Decreased appetite	63 (33.2)	46 (24.2)	3 (1.6)	1 (0.5)
Headache	60 (31.6)	14 (7.4)	2 (1.1)	0
Fatigue	58 (30.5)	41 (21.6)	11 (5.8)	7 (3.7)
Anemia	55 (28.9)	38 (20.0)	13 (6.8)	6 (3.2)
Rash (grouped terms)[c]	47 (24.7)	28 (14.7)	1 (0.5)	1 (0.5)
Dysgeusia	46 (24.2)	37 (19.5)	0	0
Cough	44 (23.2)	7 (3.7)	0	0
Abdominal pain	42 (22.1)	16 (8.4)	3 (1.6)	0
Alopecia	40 (21.1)	36 (18.9)	0	0
Constipation	40 (21.2)	15 (7.9)	0	0
Arthralgia	40 (21.2)	14 (7.4)	1 (0.5)	0
Aspartate aminotransferase increased	38 (20.0)	10 (5.3)	10 (5.3)	0

AE, adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
[a]Graded based on fasting blood glucose levels, per NCI CTCAE v4.0.
[b]Stomatitis grouped terms: stomatitis, mucosal inflammation, mouth ulceration, glossitis, tongue ulceration, glossodynia, lip ulceration, and palatal ulcer.
[c]Rash grouped terms: rash, rash maculo-papular, dermatitis acneiform, erythema, hand dermatitis, rash erythematous, and rash pruritic.

risk factors for hyperglycemia (Figure 2). In arm F, grade 3 hyperglycemia was most frequently observed in patients with at least one risk factor for hyperglycemia treated with inavolisib plus palbociclib and fulvestrant, despite early metformin treatment from day 1 through day 15 [$n = 8$ (40.0%)] (Table 2). No diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic syndrome events were reported.

Diarrhea was managed with common antidiarrheal medications, e.g. loperamide [$n = 51$ (26.8%)]. Median time from onset to improvement by at least one grade (per NCI CTCAE v4.0) or resolution of any-grade diarrhea was 3.5 days [range, 2-1627 days (censored value)].

Stomatitis was manageable with inavolisib dose interruptions [$n = 9$ (4.7%)] and treatment with dexamethasone mouthwash [$n = 56$ (29.5%); administered per institutional guidelines]. Median time from onset to improvement by at least one grade (per NCI CTCAE v4.0) or resolution of any-grade stomatitis was 18 days [range, 2-1926 days (censored value; patients with no improvement or resolution were censored at the earliest date of completion or discontinuation, end of the AE reporting period, or clinical cutoff)].

Rash was mainly grade 1 and most rash events required no medication. Overall, 28 (14.7%) patients received treatment of rash, the most common of which was topical hydrocortisone in 12 (6.3%) patients. Median time from onset to improvement by at least one grade (per NCI CTCAE v4.0) or resolution of any-grade rash was 17 days [range, 1-957 days (censored value)].

Other AEs of special interest

Across the six arms included in this analysis, a total of 64 (33.7%) patients experienced any-grade neutropenia; grade 3-4 neutropenia occurred in 46 (24.2%) patients. In the palbociclib-containing arms, any-grade and grade 3-4 neutropenia occurred in 27 (81.8%) and 23 (69.7%) patients, respectively, in the inavolisib plus palbociclib and letrozole arm (arm B); 17 (85.0%) and 14 (70.0%) patients, respectively, in the inavolisib plus palbociclib and fulvestrant arm (arm E); and 11 (55.0%) and 9 (45.0%) patients, respectively, in the inavolisib plus palbociclib, fulvestrant, and metformin arm (arm F). Colitis occurred in only one (0.5%) patient across the six arms [in the inavolisib plus fulvestrant arm (arm D)]; the AE was grade 3 and was managed with inavolisib interruption and steroids. Pneumonitis (a known risk with palbociclib) occurred in two patients and was low grade; both patients received palbociclib-containing regimens [one in the inavolisib plus palbociclib and letrozole arm (arm B) and one in the inavolisib plus palbociclib, fulvestrant, and metformin arm (arm F)].

Long-term safety

Among patients who had been treated for >1 year, baseline demographics were similar to the full analysis set. Two (3.1%) patients in the inavolisib plus palbociclib and letrozole arm (arm B) received inavolisib at the 3 mg od dose; all other patients received inavolisib at the 9 mg od dose. Median treatment duration in all patients treated for >1 year was 24.5 months (range, 11.9-70.7 months) and the median total cumulative dose intensity was 95.8%. Treatment-related AEs of any grade occurred in all patients treated for >1 year; the most common of which were hyperglycemia [$n = 48$ (73.8%)], stomatitis [$n = 48$ (73.8%)], diarrhea [$n = 36$ (55.5%)], neutropenia [$n = 34$ (52.3%)], nausea [$n = 27$ (41.5%)], alopecia [$n = 22$ (33.8%)], and rash [$n = 16$ (24.8%)]. Grade 3-4 treatment-related AEs occurred in 46 (70.8%) patients. The most frequent was neutropenia [$n = 28$ (43.1%)], which was mainly reported in the palbociclib-containing arms (arms B, E, and F). Other frequently occurring grade 3-4 treatment-related AEs were hyperglycemia [$n = 12$ (18.5%)], leukopenia [$n = 6$ (9.2%)], and thrombocytopenia [$n = 5$ (7.7%)]. Inavolisib-related AEs leading to inavolisib withdrawal and dose reduction and/or interruption occurred in two (3.1%) patients and 43 (66.2%) patients, respectively.

DISCUSSION

Despite advances in the treatment of HR-positive, HER2-negative advanced breast cancer, including those cancers that harbor *PIK3CA* mutations, there remains a critical need for highly efficacious therapies that are well tolerated such that they can be administered over long treatment durations.[15] This first-in-human study demonstrated that inavolisib alone or in combination with letrozole or fulvestrant

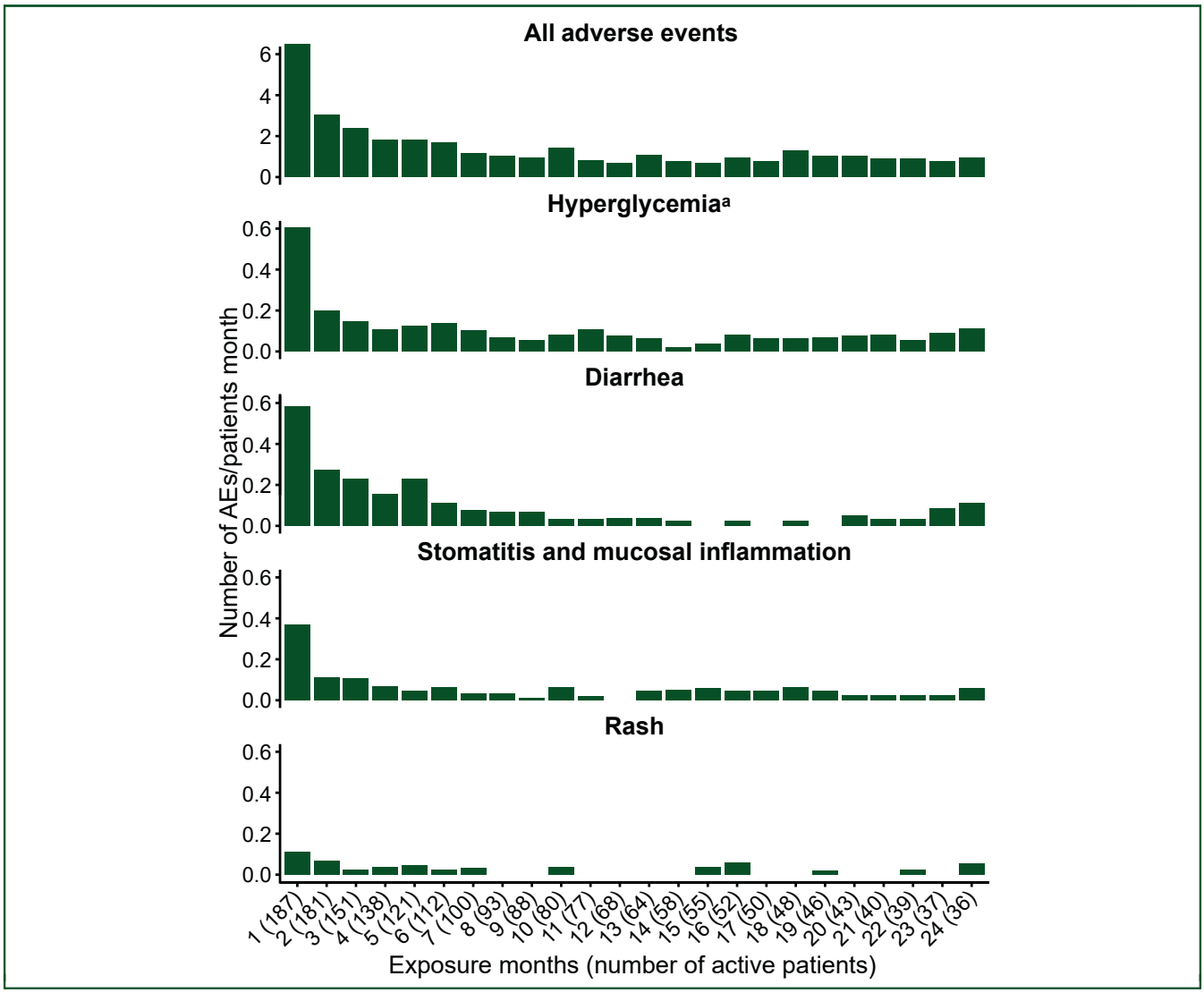

Figure 1. Rate of AEs and selected AEs over time (safety-assessable population).
AE, adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
[a]Graded based on fasting blood glucose levels, per NCI CTCAE v4.0.

with and without palbociclib can be administered at a high dose intensity and for a long treatment duration to patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer. Although some AEs such as hyperglycemia, diarrhea, and stomatitis were common, these were manageable with standard supportive measures, dose interruption, or dose reduction to enable patients to remain on study treatment, including those patients who remained on study treatment >1 year.

Agents targeting the PI3K pathway have demonstrated clinical activity; however, tolerability has remained a challenge. For example, in the phase III trial that established alpelisib plus fulvestrant as a standard of care in *PIK3CA*-mutated, HR-positive, HER2-negative breast cancer, the rate of permanent discontinuation of alpelisib due to AEs was 25.0%, with the most common AEs leading to discontinuation of alpelisib being hyperglycemia (6.3%) and rash (3.2%).[16] In clinical practice, AEs such as rash, hyperglycemia, and diarrhea have limited the broad implementation of this regimen. A phase III trial of capivasertib (a pan-AKT inhibitor) plus fulvestrant demonstrated clinical benefit; however, an intermittent capivasertib administration schedule (4 days off; 3 days on) was required to mitigate toxicities.[17] Additional clinical experience with agents targeting the PI3K pathway has resulted in strategies to further improve management and reduce the rate and severity of on-target AEs, such as the use of dexamethasone-based mouthwash for the prevention of stomatitis.[18]

Results from this inavolisib phase I/Ib study demonstrate the manageable and tolerable safety profile of inavolisib as a single agent and in combination with endocrine therapy with or without palbociclib. The reported AEs were in line with the anticipated safety profile of inavolisib, the known safety profiles of the other individual components of combination therapies, and the underlying disease. Overall, the majority of AEs related to any study treatment were grade 1 or 2. Importantly, the low number of inavolisib-related AEs

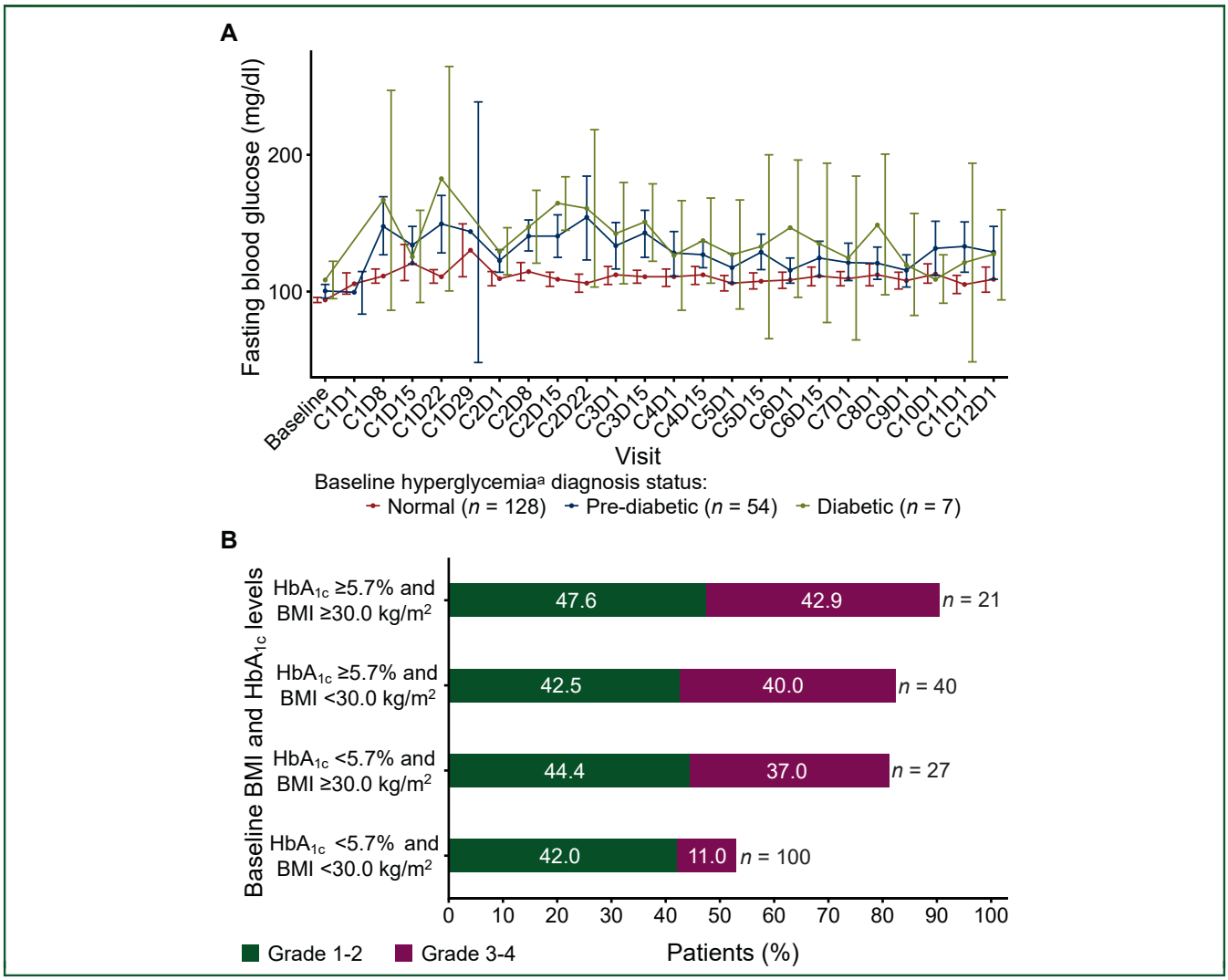

Figure 2. (A) Fasting blood glucose over time, based on HbA_{1c} status at baseline (safety-assessable population). (B) Hyperglycemia AEs by baseline BMI and HbA_{1c} levels (safety-assessable population). Baseline hyperglycemia diagnosis status was categorized as normal (HbA_{1c} <5.7%); pre-diabetic (HbA_{1c} ≥5.7 to <6.5%); or diabetic (HbA_{1c} ≥6.5%).

AE, adverse event; BMI, body mass index; CxDx, cycle x day x; HbA_{1c}, glycosylated hemoglobin A_{1c}; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

[a]Graded based on fasting blood glucose levels, per NCI CTCAE v4.0.

leading to inavolisib withdrawal and the high median cumulative inavolisib dose intensity across treatment arms indicates that inavolisib is generally well tolerated, including at its selected dose of 9 mg od, not only as a single agent but also as part of a variety of combination regimens administered at their labeled doses and schedules for the treatment of HR-positive, HER2-negative breast cancer. Furthermore, data for patients treated for >1 year (including five patients treated for >5 years in palbociclib-containing arms) indicated encouraging long-term safety and tolerability of inavolisib, with no new or unexpected safety signals.

Importantly for the implementation of inavolisib in clinical trials and clinical practice, this study also identified supportive measures to manage selected AEs. These AEs were those commonly reported with inhibitors of the PI3K pathway and included hyperglycemia, diarrhea, stomatitis, and rash. Except for rash, which showed no clear trend and was mainly low grade, other selected AEs mainly occurred early in treatment (within the first treatment cycle) and could be managed with appropriate supportive medications, such as metformin for hyperglycemia, loperamide for diarrhea, and dexamethasone mouthwash premedication (not mandated per protocol) and treatment of stomatitis, or with inavolisib dose modifications (dose interruptions with or without dose reductions).

The management of hyperglycemia included anti-hyperglycemic medications from different classes, most commonly metformin (a biguanide), empagliflozin (a sodium-glucose cotransporter inhibitor), sitagliptin (a dipeptidyl peptidase 4 inhibitor), and pioglitazone (a thiazolidinedione). Notably, the use of insulin was limited and mainly in the setting of hospitalization (either for hyperglycemia or for other serious AEs). In addition, a subset of patients required one or more antihyperglycemic medications in addition to or in place of metformin to adequately control hyperglycemia. In a small cohort of this study [in the inavolisib plus palbociclib, fulvestrant, and metformin arm (arm F)], the

occurrence of grade 3 hyperglycemia among patients with at least one risk factor (BMI $\geq$30.0 kg/m^2 and/or HbA_{1c} $\geq$5.7%) remained high, despite the use of metformin treatment before initiating inavolisib, but was manageable. In contrast, the METALLICA study reported a reduction in the incidence and severity of alpelisib-induced events of hyperglycemia among patients at high risk of hyperglycemia (those with fasting blood glucose 100-140 mg/dl and/or HbA_{1c} 5.7%-6.4%).[19] Potential reasons for the distinct findings in these two studies could be due to differences in the patient populations (for example, METALLICA included only patients in Spain whereas this study included patients predominantly in the United States), the specific criteria used to define patients at high risk for hyperglycemia, and the speed with which the metformin dose was up-titrated.

In practice, patients should be advised to maintain an active lifestyle and initiate a low carbohydrate diet upon starting treatment with a PI3Kα inhibitor. Studies have suggested a ketogenic diet may also limit hyperglycemia in these patients.[20,21] Metformin is a first-line treatment for the management of hyperglycemia, enabling glucose control and continued PI3Kα inhibitor treatment. Of note, gastrointestinal side effects with metformin are well known and can be mitigated with up-titration strategies that balance tolerability and reaching an effective metformin dose to enable reinitiation or continuation of PI3Kα inhibitor treatment. In addition, the use of home glucose monitors enables additional monitoring and is an important component to support the management of hyperglycemia, particularly in patients with risk factors. Further research is warranted to identify the optimal preventive and management strategies for hyperglycemia with PI3Kα inhibitors.

Overall, our results support the ongoing clinical development of inavolisib for patients with endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative breast cancer, particularly the phase III, placebo-controlled INAVO120 study (NCT04191499) of inavolisib plus palbociclib and inavolisib plus fulvestrant, which recently reported substantially longer progression-free survival compared with palbociclib and fulvestrant alone.[22] These results were the basis for the recent United States Food and Drug Administration approval of inavolisib in combination with palbociclib plus fulvestrant in this population. Other phase III trials are also ongoing [e.g. NCT05646862 (inavolisib plus fulvestrant versus alpelisib plus fulvestrant in patients with *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received previous treatment with a combination of CDK4/6 inhibitors and endocrine therapy) and NCT05894239 (inavolisib plus the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with *PIK3CA*-mutated, HER2-positive locally advanced or metastatic breast cancer)]. A phase II umbrella study is currently underway, which will assess inavolisib plus fulvestrant in combination with other CDK4/6 inhibitors (abemaciclib and ribociclib; NCT03424005). These studies will continue to inform the development and safety management of inavolisib-based treatment regimens.

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DISCLOSURE

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DATA SHARING

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli: https://vivli.org/ourmember/roche/. For up-to-date 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://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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