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ITOVEBI® (inavolisib) EXPLAIN THE LABEL

This is a medical resource for scientific information and is intended for healthcare providers practicing in the United States

Veeva Document Number: M-US-00028036(v4.0)

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DISCLAIMER

Please Note: The information we provide may include references to a Genentech product or use of a Genentech product that the FDA has not approved; because the FDA has not approved such product(s) or use, no conclusions regarding safety or efficacy may be made. Providing this information should not be construed as recommendation for use of a Genentech product for unapproved uses. For FDA-approved products, please consult the product's full prescribing information for a complete discussion of risks and benefits of the product(s) for its approved indication(s).

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FDA=Food and Drug Administration.

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INDICATION

ITOVEBI® (inavolisib) is a kinase inhibitor indicated in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

Please see the full Prescribing Information for Itovebi (inavolisib).

Please note: For other FDA-approved products, please consult the products' full prescribing information for a complete discussion of the risks and benefits of the products for their approved indications.

FDA=Food and Drug Administration; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025.

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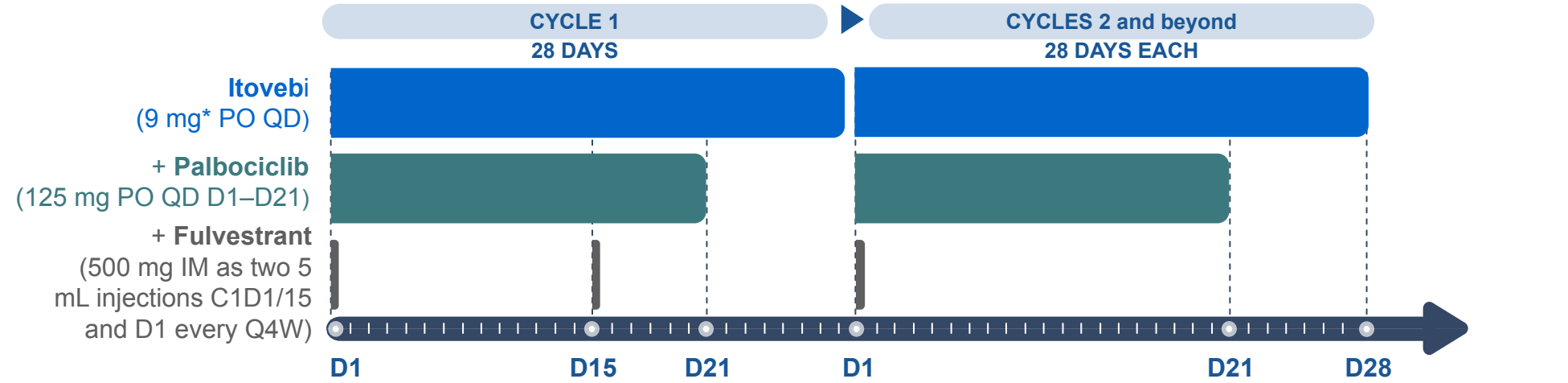
DOSING REGIMEN OVERVIEW



IMPORTANT DOSING INFORMATION

- *The recommended dosage of Itovebi is 9 mg taken orally once daily, with or without food, until disease progression or unacceptable toxicity *[see Prescribing Information, Recommended Dosage (2.3)].*
- *The recommended starting dosage of Itovebi for patients with moderate renal impairment (eGFR 30 to <60 mL/min based on CKD-EPI) is 6 mg orally once daily *[see Prescribing Information, Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*
- Before initiating Itovebi, evaluate renal function, evaluate fasting plasma glucose (FPG)/blood glucose (FBG) and hemoglobin A1C (HbA1c) and optimize blood glucose prior to starting Itovebi and at regular intervals during treatment [see Prescribing Information, Warnings and Precautions (5.1)].

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; C=cycle; D=day; eGFR=estimated glomerular filtration rate; IM=intramuscular; PO=by mouth; QD=daily; Q4W=every 4 weeks.

1. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025.

Please see the full Prescribing Information for Itovebi (inavolisib).

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INAVO120 OVERVIEW

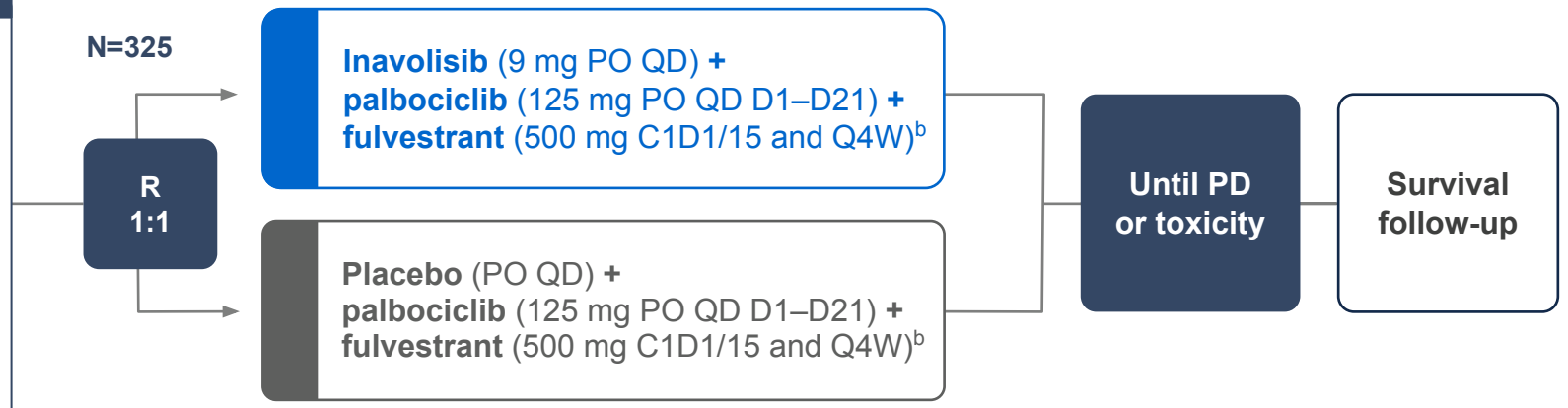
INAVO120 STUDY DESIGN[1]

Phase 3 Inavolisib + Palbociclib + Fulvestrant vs Palbociclib + Fulvestrant in *PIK3CA*mut HR+/HER2− Locally Advanced or mBC

Key eligibility criteria

***PIK3CA*mut, HR+/HER2− advanced BC confirmed by central ctDNA[a] or local tissue/ctDNA test**

- Measurable disease
- Progression during/within 12 months of adjuvant endocrine therapy completion
- No prior therapy for advanced BC
- **Fasting glucose <126 mg/dL and HbA1c <6.0%**
- The study *excluded* patients with any history of T1 diabetes mellitus or T2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment at study entry



Stratification factors

Visceral disease (Yes vs no)

Region (North America/Western Europe vs Asia vs other)

Endocrine resistance

- **Primary:** relapse while on the first 2 years of adjuvant ET
- **Secondary[c]:** relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET

Endpoints

Primary

PFS by investigator

Select secondary

OS[d], ORR, DOR, PROs

Enrollment period: December 2019 to September 2023.

[a] *PIK3CA* mutation status was prospectively determined in a central laboratory using the FoundationOne® Liquid CDx assay on plasma-derived ctDNA or in local laboratories using various validated PCR or NGS assays on tumor tissue or plasma. [b] Premenopausal women received ovarian suppression. [c] Defined per 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer in the early setting.[2] [d] OS testing only if PFS is positive; interim OS analysis at primary PFS analysis. AE=adverse event; BC=breast cancer; C=cycle; CDx=companion diagnostic test; ctDNA=circulating tumor DNA; D=day; DOR=duration of response; ESMO=European Society for Medical Oncology; ESO=European School of Oncology; ET=endocrine therapy; HbA1c=hemoglobin A1c; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; mut=mutated; NGS=next-generation sequencing; ORR=overall response rate; OS=overall survival; PCR=polymerase chain reaction; PD=progressive disease; PFS=progression-free survival; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO=by mouth; PRO=patient-reported outcome; Q#W=every # weeks; QD=daily; R=randomized; T=Type.

1. Turner NC, et al. *N Engl J Med* 2024;391:1584-1596. 2. Cardoso F, et al. *Ann Oncol*. 2018;29:1634–1657. 3. https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

DEMOGRAPHICS AND BASELINE PATIENT CHARACTERISTICS*

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Median age, years (range)	53 (27-77)	54.5 (29-79)
Female sex, n (%)	156 (96.9)	163 (99.4)
Race, n (%)†		
Asian	61 (37.9)	63 (38.4)
Black or African American	1 (0.6)	1 (0.6)
White	94 (58.4)	97 (59.1)
ECOG performance-status score, n (%)‡		
0	100 (62.1)	106 (64.6)
1	60 (37.3)	58 (35.4)
Menopausal status at randomization, n (%)		
Premenopausal	65 (40.4)	59 (36.0)
Postmenopausal	91 (56.5)	104 (63.4)
Median weight, kg (range)	62.5 (39-124)	64.0 (38-111)
No. of organs with metastases, n (%)		
1	21 (13.0)	32 (19.5)
2	59 (36.6)	46 (28.0)
≥3	81 (50.3)	86 (52.4)

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Site of metastases, n (%)		
Viscera§	132 (82.0)	128 (78.0)
Liver	77 (47.8)	91 (55.5)
Lung	66 (41.0)	66 (40.2)
Bone only¶	5 (3.1)	6 (3.7)
Hormone-receptor status, n (%)**		
ER+/PR+	113 (70.2)	113 (68.9)
ER+/PR-	45 (28.0)	45 (27.4)
Other	3 (1.9)	6 (3.7)
Resistance to endocrine therapy, n (%)††		
Primary	53 (32.9)	58 (35.4)
Secondary	108 (67.1)	105 (64.0)
Missing data	0	1 (0.3)

301 (92.6%) patients were enrolled per ctDNA testing (284 [94.4%] central, 17 [5.6%] local), and 24 (7.4%) patients were enrolled per local tissue testing.

* 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. † Race was reported by the patient. ‡ Performance-status scores range from 0 (no disability) to 5 (death). § 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 RECIST, v1.127) were eligible. ** Tumors were considered to be positive if ≥1% of tumor cells expressed ER or PR, according to ASCO CAP guidelines. †† Primary resistance: relapse during the first 2 years of adjuvant ET. Secondary resistance: relapse after the start of year 2 of adjuvant ET or relapse within 12 months after the completion of adjuvant ET. AE=adverse event; ASCO=American Society of Clinical Oncology; CAP=College of American Pathologists; ctDNA=circulating tumor DNA; ECOG PS=Eastern Cooperative Oncology Group performance status; ER=estrogen receptor; ET=endocrine therapy; Fulv=fulvestrant; Inavo=inavolisib; Palbo=palbociclib; Pbo=placebo; PR=progesterone receptor; RECIST=Response Evaluation Criteria In Solid Tumors.

Turner NC, et al. *N Engl J Med* 2024;391:1584-1596.

PRIOR THERAPY

Characteristic, n (%)	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Prior (neo)adjuvant chemotherapy	132 (82)	137 (83.5)
Prior (neo)adjuvant endocrine therapy	160 (99.4)	163 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)
Tamoxifen only	82 (50.9)	73 (44.5)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)
Prior (neo)adjuvant CDK4/6 inhibitor	3 (1.9)	1 (0.6)

AE=adverse event; CDK4/6=cyclin-dependent kinase 4 and 6; Fulv=fulvestrant; Inavo=inavolisib; Palbo=palbociclib; Pbo=placebo.

Turner NC, et al. *N Engl J Med* 2024;391:1584-1596.

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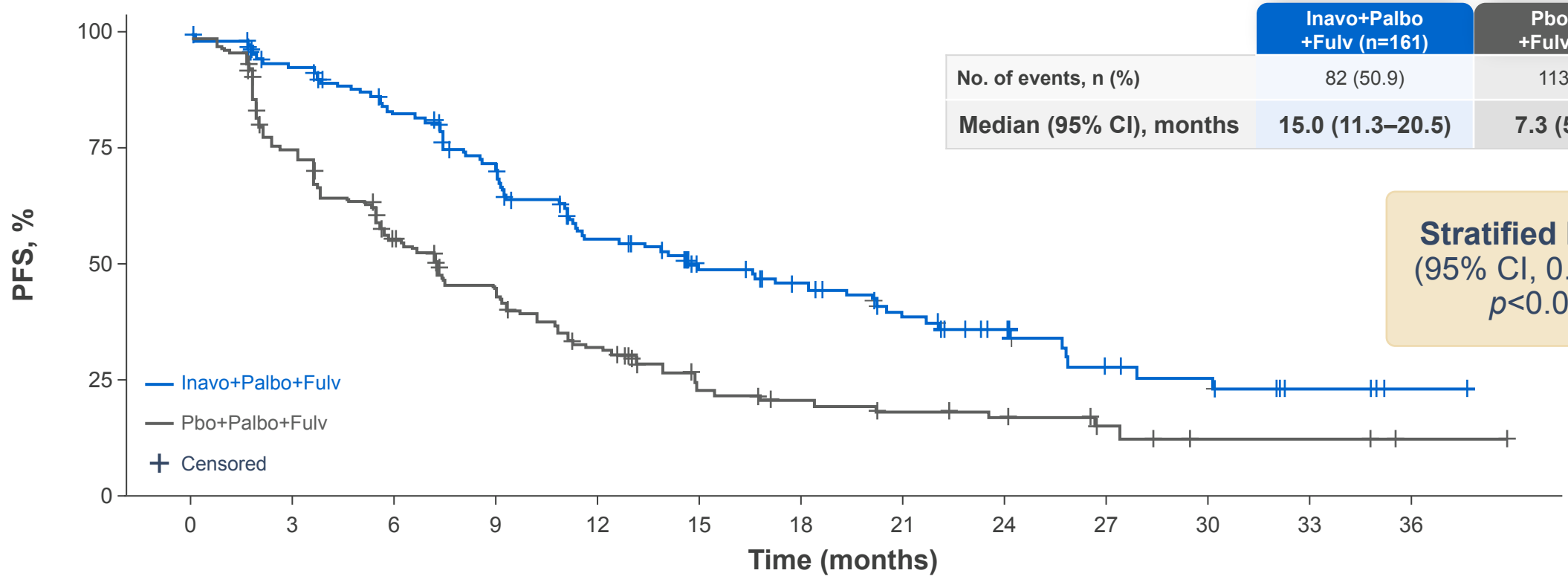
INAVO120 EFFICACY & SAFETY

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (INVESTIGATOR ASSESSED)



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), months	**15.0 (11.3–20.5)**	**7.3 (5.6–9.3)**

Stratified HR=0.43
(95% CI, 0.32–0.59)
p<0.0001

Patients at risk:													
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up: **21.3 months**

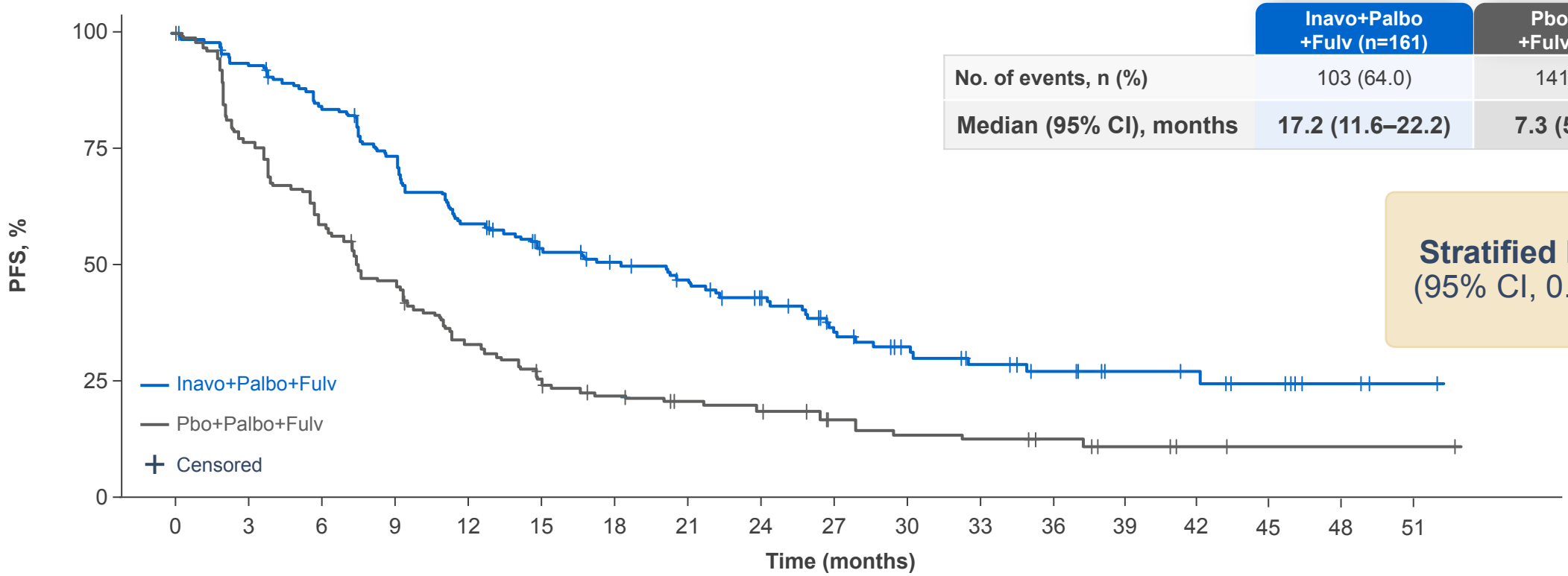
Data cutoff: September 29, 2023.

AE=adverse event; CI=confidence interval; Fulv=fulvestrant; HR=hazard ratio; Inavo=inavolisib; Palbo=palbociclib; Pbo=placebo; PFS=progression-free survival.

Turner NC, et al. *N Engl J Med* 2024;391:1584-1596.

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL* (UPDATED ANALYSIS)

Descriptive analysis; no conclusions can be made



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	103 (64.0)	141 (86.0)
Median (95% CI), months	17.2 (11.6–22.2)	7.3 (5.9–9.2)

Stratified HR=0.42
(95% CI, 0.32–0.55)

Patients at risk:																		
Inavo+Palbo+Fulv	161	146	129	112	89	73	65	57	46	32	25	19	15	11	10	7	3	1
Pbo+Palbo+Fulv	164	125	95	74	50	34	30	24	21	14	11	10	8	4	2	1	1	1

Median follow-up: **34.2 months**

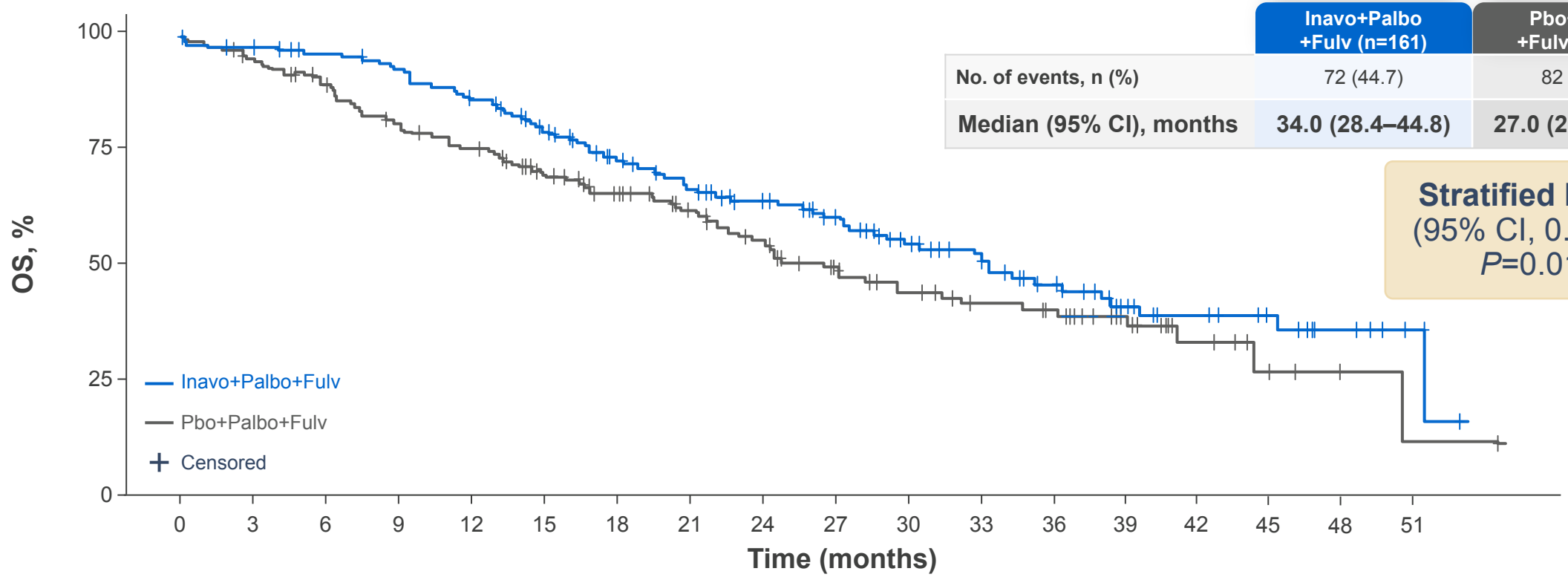
Data cutoff: November 15, 2024.

* Investigator assessed.

HR=hazard ratio; Inavo=inavolisib; Palbo=palbociclib; Pbo=placebo.

Jhaveri, KL, et al. N Engl J Med. Published online May 31, 2025.

SECONDARY ENDPOINT: OVERALL SURVIVAL (FINAL ANALYSIS)[1]



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	72 (44.7)	82 (50.0)
Median (95% CI), months	**34.0 (28.4–44.8)**	**27.0 (22.8–38.7)**

Stratified HR=0.67
(95% CI, 0.48–0.94)
P=0.0190*

Patients at risk:																		
Inavo+Palbo+Fulv	161	155	149	142	131	114	99	88	78	67	54	43	34	22	19	13	7	1
Pbo+Palbo+Fulv	164	155	142	127	119	104	90	77	63	48	42	36	32	18	10	4	2	1

Median follow-up: **34.2 months**

Data cutoff: November 15, 2024.

*** The prespecified boundary for statistical significance ($p < 0.0469$) was crossed.** At the previous primary analysis of PFS (data cutoff September 29, 2023; median follow-up of 21.3 months), the data from the interim analysis of overall survival were not mature, with 30% deaths in the overall population.[2,3]

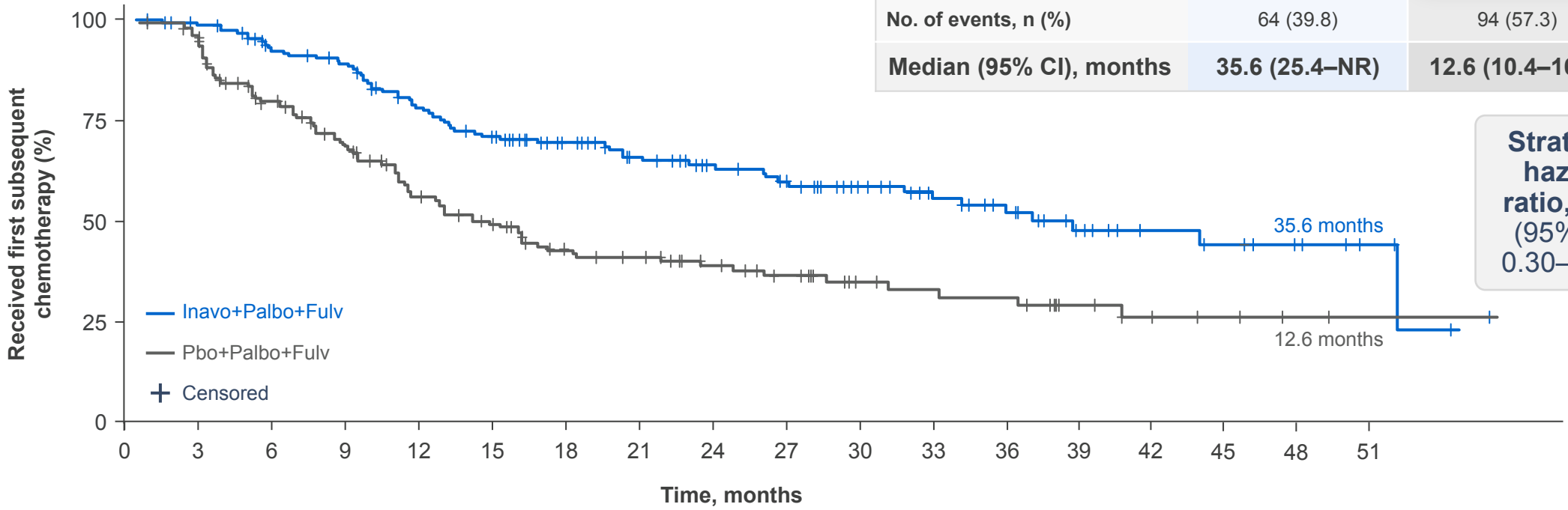
AE=adverse event; CI=confidence interval; Fulv=fulvestrant; HR=hazard ratio; Inavo=inavolisib; Palbo=palbociclib; Pbo=placebo; OS=overall survival.

1. Jhaveri, KL, et al. N Engl J Med. Published online May 31, 2025. 2. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025. 3. Turner NC, et al. *N Engl J Med* 2024; 391:1584-1596.

TIME FROM RANDOMIZATION TO FIRST SUBSEQUENT CHEMOTHERAPY AFTER TREATMENT DISCONTINUATION (UPDATED ANALYSIS)

Descriptive post hoc analysis; no conclusions can be made.

	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	64 (39.8)	94 (57.3)
Median (95% CI), months	**35.6 (25.4–NR)**	**12.6 (10.4–16.1)**



Stratified hazard ratio, 0.43 (95% CI, 0.30–0.60)

Patients at risk:

Inavo+Palbo+Fulv	161	153	136	122	104	89	77	67	57	47	39	31	23	14	13	9	5	1
Pbo+Palbo+Fulv	164	134	111	89	68	58	45	40	31	22	16	15	13	9	5	3	1	1

Median follow-up: **34.2 months**

Data cutoff: November 15, 2024

Addl=additional; AE=adverse event; CI=confidence interval; Fulv=fulvestrant; HR=hazard ratio; Inavo=inavolisib; mgmt.=management; NE=not estimable; OS=overall survival; Palbo=palbociclib; Pbo=placebo.

Jhaveri, KL, et al. N Engl J Med. Published online May 31, 2025.

KEY POST-PROGRESSION THERAPIES (UPDATED ANALYSIS)

Patients, n (%)	Inavolisib		Placebo	
	Second line	Third line or more	Second line	Third line or more
Discontinued treatment	**111/161 (68.9)**		**144/164 (87.8)**	
No subsequent therapy - death	**17/161 (10.6)**		**22/164 (13.4)**	
Received subsequent therapy*	**83/111 (74.8)**	**48/111 (43.2)**	**109/144 (75.7)†**	**56/144 (38.9)**
Chemotherapy (any)	**46/83 (55.4)**	**41/48 (85.4)**	**79/109 (72.5)**	**49/56 (87.5)**
Capecitabine	26/83 (31.3)	14/48 (29.2)	37/109 (33.9)	24/56 (42.9)
Paclitaxel	12/83 (14.5)	17/48 (35.4)	20/109 (18.3)	16/56 (28.6)
Epiribulin	1/83 (1.2)	11/48 (22.9)	6/109 (5.5)	17/56 (30.4)
Antibody-drug conjugate (any)	**1/83 (1.2)**	**8/48 (16.7)**	**1/109 (0.9)**	**20/56 (35.7)**
Trastuzumab deruxtecan	0	6/48 (12.5)	1/109 (0.9)	16/56 (28.6)
Sacituzumab govitecan	0	2/48 (4.2)	0	8/56 (14.3)
PI3K inhibitor (any)	**5/83 (6.0)**	**2/48 (4.2)**	**11/109 (10.1)**	**3/56 (5.4)**
Alpelisib	5/83 (6.0)	2/48 (4.2)	9/109 (8.3)	2/56 (3.6)
mTOR kinase inhibitor (everolimus)	**8/83 (9.6)**	**4/48 (8.3)**	**10/109 (9.2)**	**9/56 (16.1)**
CDK4/6 inhibitor (any)	**8/83 (9.6)**	**3/48 (6.2)**	**5/109 (4.6)**	**3/56 (5.4)**
Ribociclib	1/83 (1.2)	1/48 (2.1)	5/109 (4.6)	0
Abemaciclib	2/83 (2.4)	2/48 (4.2)	0	2/56 (3.6)
Other (any)	**6/83 (7.2)**	**0**	**3/109 (2.8)**	**5/56 (8.9)**

Following treatment discontinuation, fewer patients in the inavolisib group than in the placebo group received chemotherapy in the second line, antibody–drug conjugates in the third line or later, or a PI3K inhibitor in the second line or later

Data cutoff: November 15, 2024

* Twenty-eight of 111 patients (25.2%) did not receive subsequent therapy in the inavolisib arm due to PD (12 patients), death/censored (7), AEs (2), loss to follow-up (1), non-compliance with study drug (1), physician decision (1), symptomatic deterioration (1), or withdrawal by subject (3). Eleven patients in the inavolisib group had not received subsequent treatment but were documented being alive as of the clinical cutoff date. Thirty-four of 144 patients (23.6%) did not receive subsequent therapy in the placebo group due to PD (24 patients), death/censored (4), withdrawal by subject (3), symptomatic deterioration (2), or AEs (1). Twelve patients in the placebo arm had not received subsequent treatment but were documented as being alive as of the clinical cutoff date; † One-hundred-and-ten patients in this group received post-progression therapies but one patient was excluded as they were listed as “not applicable” in the database.

AE, adverse event; CDK4/6, cyclin-dependent kinase 4/6; mTOR, mammalian target of rapamycin; PD, progressive disease; PI3K, phosphatidylinositol 3-kinase.

Jhaveri, KL, et al. N Engl J Med. Published online May 31, 2025.

ADVERSE REACTIONS (≥10% WITH ≥5% [ALL GRADES] OR ≥2% [GRADE 3–4] HIGHER INCIDENCE IN THE INAVOLISIB ARM) – TABLE 3 FROM THE USPI

Adverse Reaction	Inavo+Palbo+Fulv (n=162)		Pbo+Palbo+Fulv (n=162)	
	All grades, %	Grade 3–4, %	All grades, %	Grade 3–4, %
Gastrointestinal Disorders				
Stomatitis[a]	51	6*	27	0
Diarrhea	48	3.7*	16	0
Nausea	28	0.6*	17	0
Vomiting	15	0.6*	5	1.2*
General Disorders and Administration Site Conditions				
Fatigue	38	1.9*	25	1.2*
Skin and Subcutaneous Tissue Disorders				
Rash[b]	26	0	19	0
Alopecia	19	0	6	0
Dry skin[c]	13	0	4.3	0
Metabolism and Nutrition Disorders				
Decreased appetite	24	0	9	0
Infections and Infestations				
COVID-19 infection	23	1.9	10	0.6
Urinary tract infection[b]	15	1.2*	9	0
Nervous System Disorders				
Headache[b]	22	0	14	0
Investigations				
Decreased weight	17	3.7*	0.6	0

* No Grade 4 adverse reactions were observed. [a] Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis. [b] Includes other related terms. [c] Includes dry skin, skin fissures, xerosis, and xeroderma. Fulv=fulvestrant; Inavo=inavolisib; Palbo=palbociclib; Pbo=placebo. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025.

Please see the full Prescribing Information for Itovebi (inavolisib).

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SELECT LAB ABNORMALITIES (≥10% WITH A ≥2% [ALL GRADES OR GRADE 3–4] HIGHER INCIDENCE IN THE INAVOLISIB ARM) – TABLE 4 FROM THE USPI

Laboratory abnormality*	Inavo+Palbo+Fulv[a]		Pbo+Palbo+Fulv[b]	
	All grades, %	Grade 3–4, %	All grades, %	Grade 3–4, %
Hematology				
Neutrophils (total, absolute) decreased	95	82	97	79
Hemoglobin decreased	88	8 †	85	2.5 †
Platelets decreased	84	16	71	3.7
Lymphocytes (absolute) decreased	72	9	68	14
Chemistry				
Glucose (fasting) increased[c]	**85**	**12**	**43**	**0**
Calcium decreased	42	3.1	32	3.7
Potassium decreased	38	6	21	0.6 †
Creatinine increased	38	1.9 †	30	1.2 †
ALT increased	34	3.1 †	29	1.2 †
Sodium decreased	28	2.5 †	19	2.5
Magnesium decreased	27	0.6	21	0
Lipase (fasting) increased	16	1.4 †	7	0

* In the INAVO120 study, per the INAVO120 study protocol, not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets certain criteria defined in the study protocol. It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. † No Grade 4 laboratory abnormalities were observed. [a] The denominator used to calculate the rate varied from 122 to 160 on the basis of the number of patients with a baseline value and at least one posttreatment value. [b] The denominator used to calculate the rate varied from 131 to 161 based on the number of patients with a baseline value and at least one post-treatment value. [c] **Grading according to CTCAE version 4.03**. ALT=alanine aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; Fulv=fulvestrant; Inavo=inavolisib; Palbo=palbociclib; Pbo=placebo. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

CTCAE GRADING CRITERIA FOR HYPERGLYCEMIA IN INAVO120[1,2]

- *Hyperglycemia* was graded according to CTCAE **v5.0** in INAVO120 and **as assessed by the investigator.**[a]
- *Glucose (fasting) increased* was graded according CTCAE **v4.03** in INAVO120.[a]

CTCAE version[3]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Version 5 (released November 27, 2017)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Version 4 (released June 14, 2010)	Fasting glucose >ULN–160 mg/dL (>ULN–8.9 mmol/L)	Fasting glucose >160–250 mg/dL (>8.9–13.9 mmol/L)	Fasting glucose >250–500 mg/dL (>13.9–27.8 mmol/L); hospitalization indicated	Fasting glucose >500 mg/dL (>27.8 mmol/L); life-threatening consequences	Death

The INAVO120 study start date was January 29, 2020.[4]

[a] Per the INAVO120 study protocol, not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets certain criteria defined in the study protocol. It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

CTCAE=Common Terminology Criteria for Adverse Events.

1. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025. 2. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025. 3. NIH. Division of Cancer Treatment and Diagnosis. Cancer Therapy Evaluation Program. Available at https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events. 4. INAVO120 study information. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

HYPERGLYCEMIA AND FASTING GLUCOSE RATES IN INAVO120

Adverse event[1]	Inavo+Palbo+Fulv (n=162)		Pbo+Palbo+Fulv (n=162)	
	All grades, n (%)	Grade 3–4, n (%)	All grades, n (%)	Grade 3–4, n (%)
Hyperglycemia	95 **(58.6)**	9 **(5.6)**	14 **(8.6)**	**0**

- Hyperglycemia was graded according to CTCAE **v5.0** in INAVO120 and **as assessed by the investigator.**[a]

Lab Abnormality[2]	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)
Glucose (fasting) increased[b]	**85**	**12**	**43**	**0**

- Fasting glucose was graded according to CTCAE **v4.03** in INAVO120.
- Increased fasting glucose occurred in 85% of patients treated with ITOVEBI, including 22% of patients with Grade 2 (FPG > 160 to 250 mg/dL), 12% with Grade 3 (FPG > 250 to 500 mg/dL), and 0.6% with Grade 4 (FPG > 500 mg/dL) events.[b]

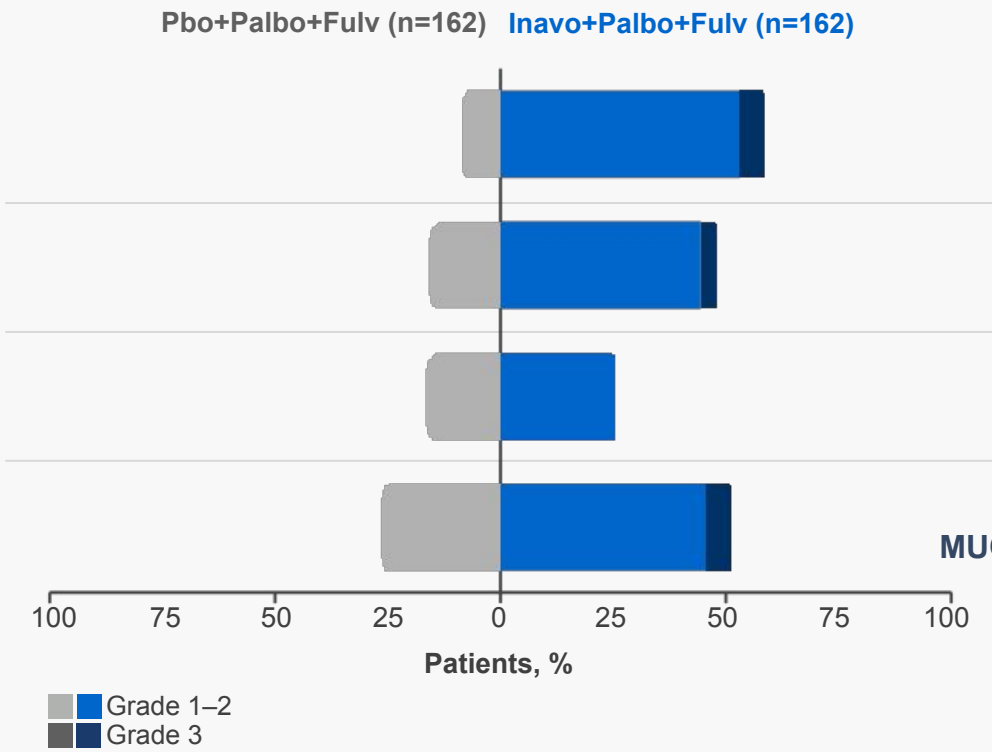
[a] Per the INAVO120 study protocol[3], not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets certain criteria defined in the study protocol. It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. [b] Section 5.1 of the Itovebi® US Prescribing Information has important Warnings & Precautions information about hyperglycemia.

CTCAE=Common Terminology Criteria for Adverse Events; Fulv=fulvestrant; Inavo=inavolisib; Palbo=palbociclib; Pbo=placebo.

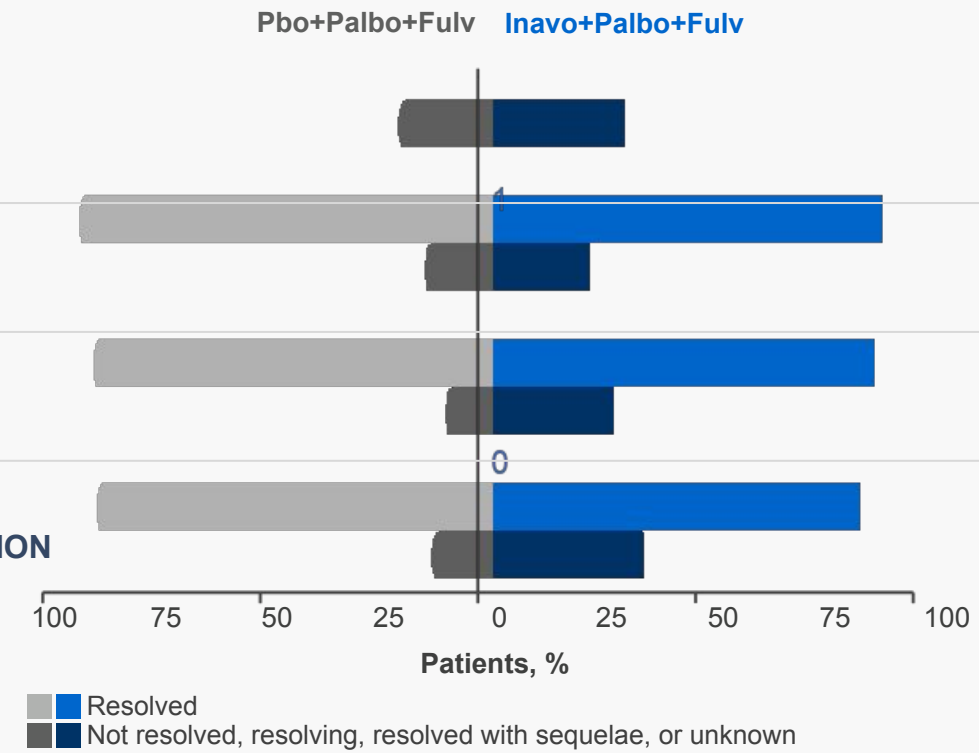
1. Turner NC, et al. *N Engl J Med* 2024;391:1584-1596. 2. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025. 3. . F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

KEY SELECTED ADVERSE EVENTS

Incidence of key selected AEs



Resolution of key selected AEs[a,b]

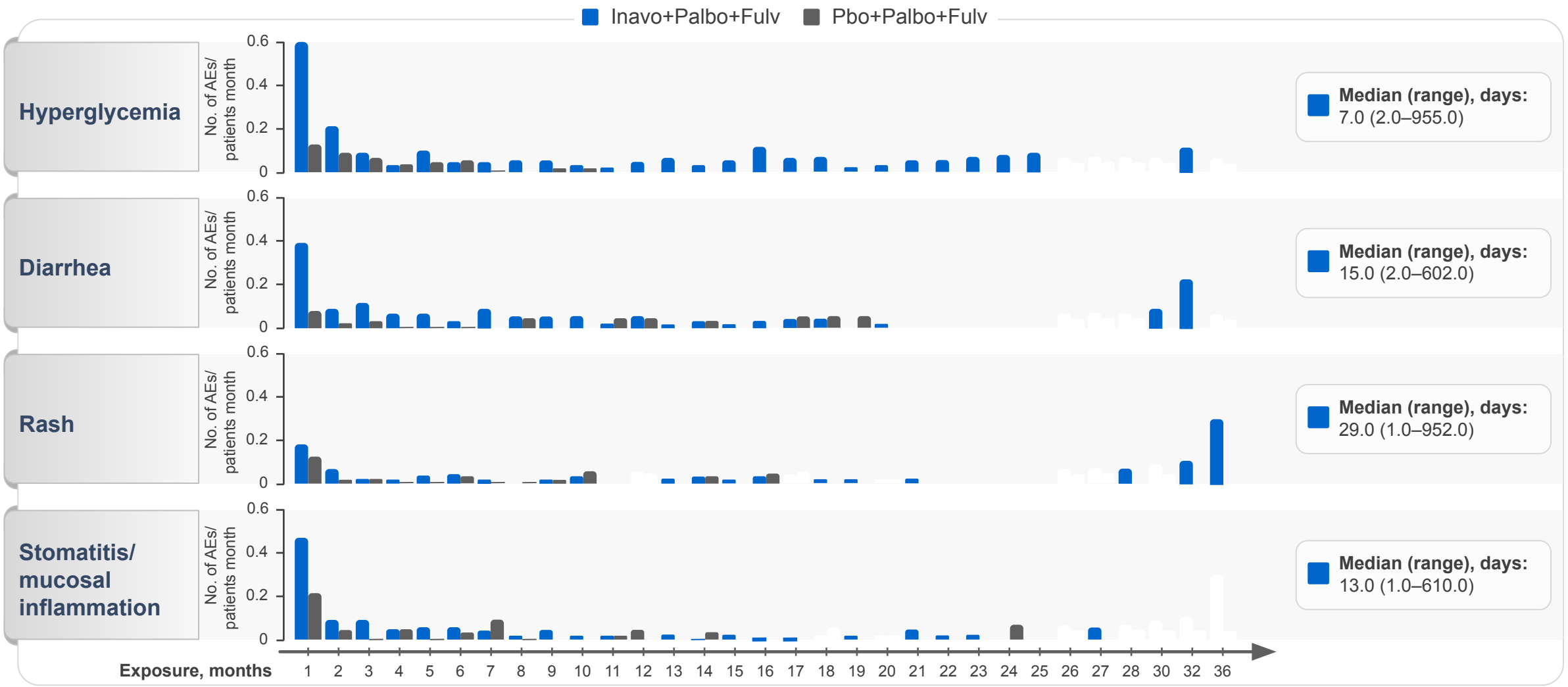


[a] The majority of key selected AEs had resolved ("resolution" was per investigator decision) by the CCOD; some patients were enrolled close to the CCOD, and AE follow-up is ongoing for these patients. [b] Denominators are patients with at least one AE (hyperglycemia, Inavo+Palbo+Fulv: n=95, Pbo+Palbo+Fulv: n=14; diarrhea, Inavo+Palbo+Fulv: n=78, Pbo+Palbo+Fulv: n=26; rash, Inavo+Palbo+Fulv: n=41, Pbo+Palbo+Fulv: n=28; and stomatitis/mucosal inflammation, Inavo+Palbo+Fulv: n=83, Pbo+Palbo+Fulv: n=43).

AE=adverse event; CCOD=clinical cutoff date; Fulv=fulvestrant; Inavo=inavolisib; OS=overall survival; Palbo=palbociclib; Pbo=placebo.

Juric D, et al. Presented at: American Society of Medical Oncology; May 31–June 4, 2024; Chicago, IL.

TIME TO ONSET OF KEY SELECTED ADVERSE EVENTS[a]



[a] Median time to onset of first occurrence of the AE (ie, if an AE was resolved and recurred in the same patient) is not included a second time in this dataset. AE=adverse event; Fulv=fulvestrant; Inavo=inavolisib; OS=overall survival; Palbo=palbociclib; Pbo=placebo.

Juric D, et al. Presented at: American Society of Medical Oncology; May 31–June 4, 2024; Chicago, IL.

CONCOMITANT MEDICATIONS FOR KEY SELECTED ADVERSE EVENTS

Patients, n/N (%)	Inavo+Palbo+Fulv (n=162)	Pbo+Palbo+Fulv (n=162)
Received ≥1 concomitant medication for:		
Hyperglycemia	66/162 (40.7)	1/162 (0.6)
Diarrhea	46/162 (28.4)	6/162 (3.7)
Rash	26/162 (16.0)	19/162 (11.7)
Stomatitis/mucosal inflammation	69/162 (42.6)	26/162 (16.0)
Most common concomitant medications per AE:		
Metformin: hyperglycemia	62/66 (93.9)	1/1 (100)
Loperamide: diarrhea	38/46 (82.6)	6/6 (100)
Hydrocortisone (topical): rash	5/26 (19.2)	3/19 (15.8)
Steroid (mouthwash): stomatitis/mucosal inflammation	42/69 (60.9)	12/26 (46.1)
Prophylactic use	(20)	(14.2)

AE=adverse event; Fulv=fulvestrant; Inavo=inavolisib; OS=overall survival; Palbo=palbociclib; Pbo=placebo.
Juric D, et al. Presented at: American Society of Medical Oncology; May 31–June 4, 2024; Chicago, IL.

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PHASE I (GO39374) SAFETY INFORMATION

CTCAE GRADING CRITERIA FOR HYPERGLYCEMIA IN INAVO120 AND PHASE 1 (GO39374)

- Hyperglycemia was graded according to CTCAE **v5.0** in INAVO120 and as assessed by the investigator*[1,2]
- Hyperglycemia was graded according to CTCAE **v4.0** in the Phase 1/1b (GO39374) and as assessed by the investigator.*

CTCAE version[3]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Version 5 (released November 27, 2017)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Version 4 (released June 14, 2010)	Fasting glucose >ULN–160 mg/dL (>ULN–8.9 mmol/L)	Fasting glucose >160–250 mg/dL (>8.9–13.9 mmol/L)	Fasting glucose >250–500 mg/dL (>13.9–27.8 mmol/L); hospitalization indicated	Fasting glucose >500 mg/dL (>27.8 mmol/L); life-threatening consequences	Death

The INAVO120 study start date was January 29, 2020.[4] The Phase 1/1b (GO39374) study start date was December 13, 2016.[5]

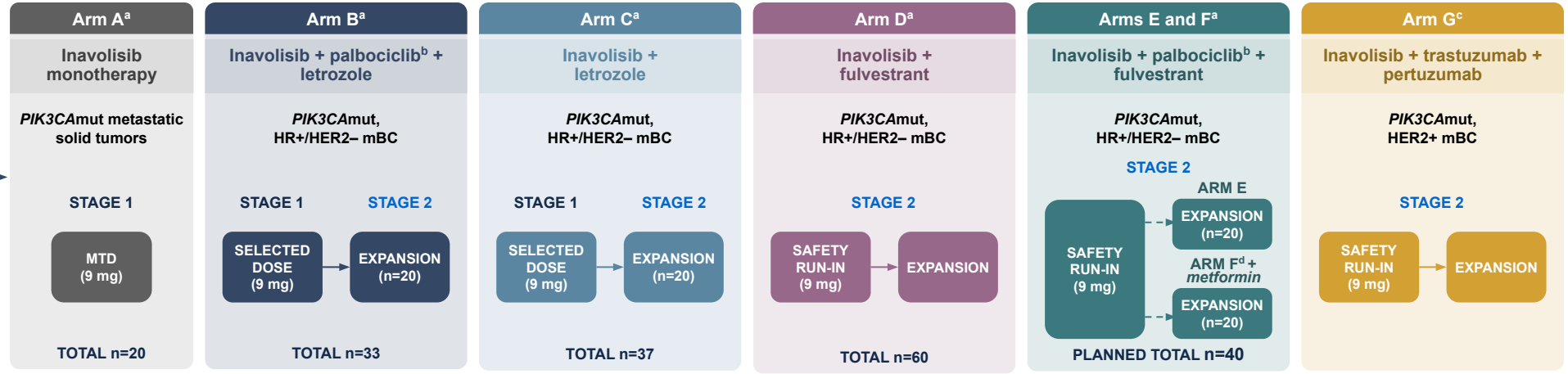
*Per the INAVO120 study protocol, not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets certain criteria defined in the study protocol. It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

CTCAE=Common Terminology Criteria for Adverse Events.

1. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025. 2. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025. 3. NIH. Division of Cancer Treatment and Diagnosis. Cancer Therapy Evaluation Program. Available at https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events. 4. INAVO120 study information. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025. 5. Phase 1/1b (GO39374) study information. Available at https://clinicaltrials.gov/study/NCT03006172. Accessed March 18, 2025.

GO39374: A PHASE 1/1b STUDY OF INAVOLISIB ± ET ± PALBOCICLIB IN PATIENTS WITH *PIK3CA*mut HR+ MBC[1–3]

- *PIK3CA*mut in tumor tissue or ctDNA
- ECOG PS 0 or 1
- Life expectancy ≥12 weeks
- Adequate hematological and organ function, including blood counts, liver, and kidney function



Inclusion criteria specific to each arm:

- **Stage I, Arm A:** Locally advanced, recurrent, or metastatic, *PIK3CA*-mutant, incurable solid tumor malignancy, including breast cancer
- **Stages I and II, Arms B and C:** Postmenopausal female participants with locally advanced or metastatic *PIK3CA*-mutant, HR+/HER2– BC
  Stage II, Arms D, E, and F: Female participants with locally advanced or metastatic *PIK3CA*-mutant, HR+/HER2– BC
- **Stage II, Arm D:** Prior treatment with CDK4/6i
- **Stage II, Arm G:** Female participants with locally advanced or metastatic *PIK3CA*mut, HER2+ BC, and left ventricular ejection fraction ≥50%

Key study endpoints:

- Safety (NCI CTCAE v4)
- Preliminary antitumor activity (RECIST v1.1)
- Pharmacokinetic assessment of inavolisib
- Signaling and pharmacodynamic biomarkers (using ctDNA)

Important Information:

- The sample size in each arm of this Phase 1 study is small. No formal hypothesis testing was conducted and no conclusions can be made.
- The study populations in this Phase 1 study are not the same as in INAVO120.

[a] Arms A, B, C, D, E, and F: Participants will receive oral inavolisib once daily on Days 1–28 of each 28-day cycle. [b] Palbociclib is a Pfizer drug. [c] Arm G: Participants will receive oral inavolisib once daily on Days 1–21 of each 21-day cycle. [d] Patients in Arm F were obese and/or prediabetic (BMI ≥30 kg/m^2 and/or HbA1c ≥5.7%).[5]

AE=adverse event; BC=breast cancer; BMI=body mass index; CDK4/6=cyclin-dependent kinase 4 and 6; CTCAE v4=Common Terminology Criteria for Adverse Events version 4; ctDNA=circulating tumor DNA; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; HbA1c=hemoglobin A1c; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; i=inhibitor; mBC=metastatic breast cancer; MTD=maximum tolerated dose; mut=mutated; NCI=National Cancer Institute; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST v1.1=Response Evaluation Criteria In Solid Tumors version 1.1.

1. ClinicalTrials.gov identifier: NCT03006172. Updated June 17, 2025. Accessed August 28, 2025. https://clinicaltrials.gov/study/NCT03006172 2. Kalinsky K, et al. Presented at: American Association for Cancer Research; April 24–29, 2020; virtual. Presentation 10349. 3. Oliveira M, et al. Presented at: San Antonio Breast Cancer Symposium; December 11–14, 2020; San Antonio, TX. Poster PS11–11. 4. Bedard P, et al. Presented at: San Antonio Breast Cancer Symposium; December 8–11, 2020; virtual. Poster PD1-02.

Phase 1/1b (GO39374) ARMS E AND F: ADDITIONAL INFORMATION

Disclaimer: The sample size in this study is small. No formal hypothesis testing was conducted and no conclusions can be made. The study population is not the same as in INAVO120.

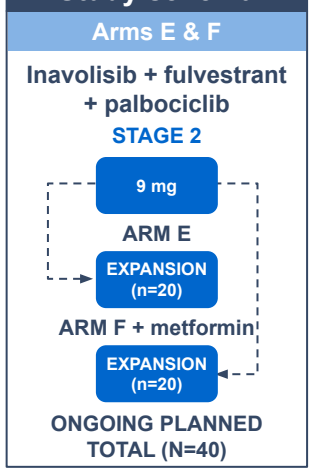
Methods

- Safety (NCI CTCAE v4), PK, and preliminary antitumor activity via RECIST v1.1 of inavolisib 9 mg PO QD + palbociclib 125 mg 21 of 28 days + fulvestrant 500 mg IM on Day 1 (and C1D15) of 28-day cycles were assessed in Arms E and F until intolerable toxicity or PD.
- This was a parallel, nonrandomized analysis.
- **Fasting glucose was ≤140 mg/dL and HbA1c <7%**
- **In Arm F, patients were obese, prediabetic, or both (BMI ≥30 kg/m^2, HbA1c ≥5.7%, or both).**
- **Patients in Arm F received prophylactic metformin ≤2000 mg daily, starting at 500 mg at C1D1, before initiating inavolisib at C1D15.**
- Additional key eligibility criteria included pre-/postmenopausal status, *PIK3CA*mut tumors as per local or central tumor testing, ECOG PS 0–1, no prior PI3K or CDK4/6i therapy, and ≤1 prior chemotherapy for Arm E (no restrictions on prior CDK4/6i therapy or chemotherapy for Arm F). **Patients with diabetes requiring medication or HbA1c >7% were excluded.**
- *PIK3CA*mut allele frequency was assessed in ctDNA from serial plasma collections using FoundationACT™ (Foundation Medicine; Cambridge, MA).

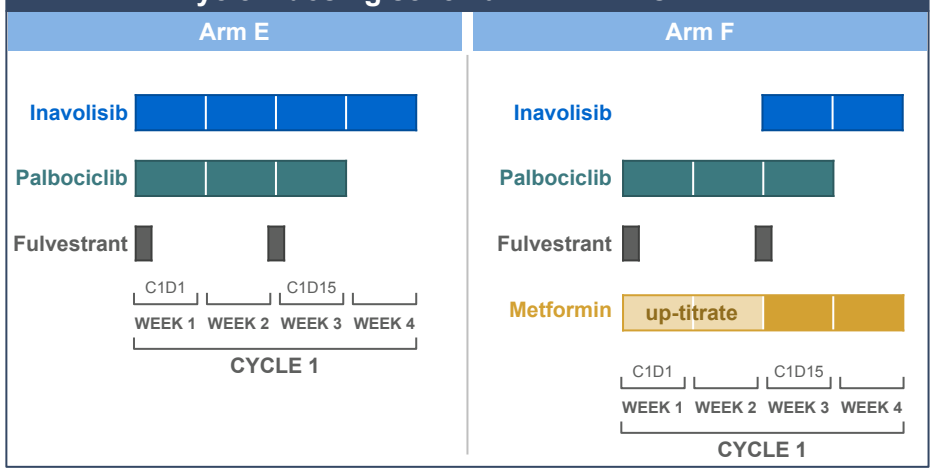
Patient characteristics and treatment exposure

	Arm E (n=20)	Arm F (n=16)
Median age, years (range)	55 (33–73)	65 (33–73)
Median BMI, kg/m^2 (range)	25 (19.2–38.0)	33 (28.4–42.1)
ECOG PS 0, n (%)	10 (50)	8 (50)
≥2 prior lines of therapy for mBC, n (%)	5 (25)	13 (81)
Prior fulvestrant, n (%)	3 (15)	12 (75)
Prior CDK4/6 inhibitor, n (%)	0	10 (63)
Median inavolisib treatment duration, months (range)	6.8 (1.1–17.7)	6.3 (1.2–15.3)
Median cumulative inavolisib dose intensity, %	93	91
Median cumulative palbociclib dose intensity, %	86	95

Study schema



Cycle 1 dosing schema in Arm E vs Arm F



Median cumulative fulvestrant dose intensity was 100% in both arms. AE=adverse event; BMI=body mass index; C=cycle; CDK4/6=cyclin-dependent kinase 4 and 6; CTCAE v4=Common Terminology Criteria for Adverse Events version 4; ctDNA=circulating tumor DNA; D=day; ECOG PS=Eastern Cooperative Oncology Group performance status; HbA1c=hemoglobin A1c; i=inhibitor; IM=intramuscular; mBC=metastatic breast cancer; mut=mutated; NCI=National Cancer Institute; PD=progressive disease; PI3K=phosphatidylinositol 3-kinase; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PK=pharmacokinetics; PO=by mouth; QD=daily; RECIST v1.1=Response Evaluation Criteria In Solid Tumors version 1.1. Bedard P, et al. Presented at: San Antonio Breast Cancer Symposium; December 8–11, 2020; virtual. Poster PD1-02.

PHASE 1/1b (GO39374) ARMS E AND F SAFETY: INAVO + FULV + PALBO (± METFORMIN)

- Patients in Arm F were obese and/or prediabetic and received metformin ≤2000 mg daily; inavolisib was started on C1D15.

Treatment-related AEs, n (%)[a]	Arm E (n=20)		Arm F (n=16)	
MedDRA-preferred term	**All grades**	**Grades 3–4**	**All grades**	**Grades 3–4**
Total number of patients with ≥1 AE (%)	20 (100)	16 (80)	14 (88)	12 (75)
Neutropenia	17 (85)	13 (65)	9 (56)	9 (56)
Stomatitis[b]	16 (80)	2 (10)	8 (50)	–
Hyperglycemia	**12 (60)**	**3 (15)**	**11 (69)**	**7 (44)**
Diarrhea	9 (45)	1 (5)	8 (50)	–
Thrombocytopenia[c]	9 (45)	4 (20)	3 (19)	1 (6)
Anemia	7 (35)	1 (5)	4 (25)	2 (13)
Nausea	5 (25)	–	8 (50)	–
Decreased appetite	5 (25)	–	4 (25)	–
Fatigue	5 (25)	–	3 (19)	1 (6)
Alopecia	4 (20)	–	3 (19)	–
Asthenia	4 (20)	–	–	–
Vision blurred	–	–	4 (25)	–
Dyspepsia	–	–	4 (25)	–

The available clinical data for prophylactic metformin use are limited. Caution should be used when interpreting the results.

- No unexpected safety signals were observed
- Hyperglycemia was frequent in patients who were obese and/or prediabetic (Arm F), despite initiating metformin prior to Inavolisib.

Adverse events were graded according to NCI CTCAE v4.0. [a] AEs occurring in ≥4 patients, except those AEs related to metformin. [b] Stomatitis grouped term includes glossodynia, mucositis, mucosal inflammation, mouth ulceration, and lip ulceration. [c] Thrombocytopenia grouped term = thrombocytopenia, decreased platelet count. AE=adverse event; C=cycle; CTCAE v4.0=Common Terminology Criteria for Adverse Events version 4.0; D=day; MedDRA=Medical Dictionary for Regulatory Activities; NCI=National Cancer Institute. Bedard P, et al. Presented at: San Antonio Breast Cancer Symposium; December 8–11, 2020; virtual. Poster PD1-02.

PHASE 1/1b (GO39374): HYPERGLYCEMIA AEs RELATED TO ANY STUDY TREATMENT

- Grade 4 hyperglycemia was a dose-limiting toxicity in 1 patient who received 12 mg of inavolisib in Arm A (dose exceeded the MTD)
- Seventy-three patients (43%) required treatment for hyperglycemia; 27 (16%) were managed with only one medication
- The most frequent antihyperglycemic medications were metformin (39%), empagliflozin (15%), sitagliptin (14%), and pioglitazone (9%)
- Insulin was administered to 10 patients (6%), typically in the acute care setting and for short-term use
- One patient experienced grade 3 hyperglycemia, resulting in drug withdrawal in Arm B

	Arm A: Inavolisib (n=20)	Arm B: Inavolisib + palbociclib + letrozole (n=33)	Arm C: Inavolisib + letrozole (n=37)	Arm D: Inavolisib + fulvestrant (n=44)	Arm E: Inavolisib + palbociclib + fulvestrant (n=20)	Arm F: Inavolisib + palbociclib + fulvestrant + metformin (n=16)	All (N=170)
Grade							
Any	14 (70)	19 (58)	25 (68)	26 (59)	12 (60)	11 (69)	107 (63)
1	4 (20)	8 (24)	10 (27)	8 (18)	4 (20)	1 (6)	35 (21)
2	6 (30)	5 (15)	8 (22)	7 (16)	5 (25)	3 (19)	34 (20)
3	3 (15)	6 (18)	7 (19)	9 (20)	3 (15)	7 (44)	35 (21)
4	1 (5)	0	0	2 (5)	0	0	3 (2)
Treatment-related SAEs	1 (5)	0	0	2 (5)	0	0	3 (2)
Inavolisib dose modifications (interruption/reduction/discontinuation)							61 (36)
Inavolisib dose reduction							15 (9)
Median time to AE onset (n=107)							9 days
Median time to first antihyperglycemic medication (n=71). For Arm F, this is median time to second medication							15 days
Median time to second antihyperglycemic medication (n=46). For Arm F, this is median time to third medication							36 days

The available clinical data for prophylactic metformin use are limited. Caution should be used when interpreting the results.

Data are n patients (%), unless otherwise stated. **Adverse events were graded according to NCI CTCAE v4.0**.
AE=adverse event; CTCAE v4.0=Common Terminology Criteria for Adverse Events version 4.0; MTD=maximum tolerated dose; NCI=National Cancer Institute; SAE=serious adverse event.
Oliveira M, et al. Presented at: San Antonio Breast Cancer Symposium; December 8–11, 2020; virtual. PS11-11.

DESCRIPTIVE AD HOC ANALYSIS OF HYPERGLYCEMIA IN PREDIABETIC/OBESE PATIENTS WITHIN THE PHASE 1/1b (GO39374)

Methods[1]

- All patients across Arms A through F (n=190) from the Phase 1/1b (GO39374) were included in the analysis.
- Data are reported across all arms unless indicated.
- Patients with baseline risk factors for hyperglycemia were defined by:
  - **Prediabetes** (as defined per the ADA[2]): HbA1c ≥5.7% and <6.5%; fasting blood glucose ≥100 mg/dL and <126 mg/dL)
  - **Obesity** (as defined per the WHO[3]): BMI ≥30 kg/m2.
- Adverse events were reported using NCI-CTCAE v4, which utilizes fasting laboratory glucose values for hyperglycemia severity grading, rather than clinical interventions used in v5.

Limitations of the analysis:

- The Phase 1/1b study occurred in a setting with rigorous monitoring of glucose levels and safety management guidelines, which may limit the interpretation and the applicability to standard of care clinical practice.
- This analysis in prediabetic and/or obese patients was not pre-specified in the study protocol.
- The patient population was predominantly white and heavily pre-treated for advanced/metastatic cancer.

ADA=American Diabetes Association; BMI=body mass index; HbA1c, glycated hemoglobin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; WHO, World Health Organization.

1. https://diabetes.org/about-diabetes/diagnosis#:~:text=What%20is%20Prediabetes%3F,to%20be%20diagnosed%20as%20diabetes (accessed April 29, 2025); 2. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed April 29, 2025). 3. Oliveira M, et al. Presented at: American Society of Clinical Oncology; May 30–Jun 3, 2025; Chicago, IL.

PHASE 1/1b (GO39374): PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS

Characteristics	Overall patient population (n = 191)*	Prediabetic and/or obese patients (n = 110)
Median age, years (range)	59 (31–85)	63 (33–85)
Female, n (%)	190 (>99)	109 (>99)
Race: White/Asian/Black or African-American/Unknown/Multiple, n (%)	139 (73)/5 (3)/3 (2)/43 (23)/1 (1)	80 (73)/3 (3)/2 (2)/25 (23)/0
ECOG PS 0, n (%)	109 (57)	58 (53)
HbA_{1c} ≥5.7% and <6.5%, n (%)	54 (28)	54 (49)
Fasting glucose ≥100 mg/dL and <126 mg/dL, n (%)	60 (31)	60 (55)
BMI ≥30 kg/m^2, n (%)/(BMI range, kg/m^2)	49 (26)/(17–51)	49 (45)/(17–51)
Median lines of prior systemic therapy for metastatic disease, n (range)	2 (1–10)	2 (1–10)
Exposure	**(n = 190)**	**(n = 110)**
Patients assigned to inavolisib **9 mg QD (MTD)**	166	95
Median time on treatment, months (range)	7.2 (0.2–70.7)	7.3 (0.2–70.7)
Median inavolisib cumulative dose intensity, %	**96**	**92**

Prediabetic and/or obese patients were a majority of the Phase 1/1b study population; inavolisib dose intensity was high in this population.

*191 patients enrolled; 190 treated with any study treatment.
BMI=body mass index; ECOG PS=Eastern Cooperative Oncology Group performance status; HbA1c=glycated hemoglobin; MTD=maximum tolerated dose; QD=daily.
Oliveira M, et al. Presented at: American Society of Clinical Oncology; May 30–Jun 3, 2025; Chicago, IL.

PHASE 1/1b (GO39374): INCIDENCE AND SEVERITY OF HYPERGLYCEMIA

- Hyperglycemia was frequent in prediabetic and/or obese patients

Patients, n (%)	Overall patient population (n = 190)	Prediabetic and/or obese patients (n = 110)
Any grade	**129 (68)**	**89 (81)**
Grade 1	44 (23)	21 (19)
Grade 2	39 (21)	30 (27)
Grade 3–4	**46 (24)**	**38 (35)**
Grade 3	42 (22)	37 (34)
Grade 4	4 (2)	1 (1)

Patients, n (%)	Prediabetic and/or obese patients (n = 110)		
	One risk factor (n = 67)	Two risk factors (n = 33)	Three risk factors (n = 10)
Any grade	51 (76)	29 (88)	9 (90)
Grade 3–4	20 (30)	13 (39)	5 (50)

Hyperglycemia was assessed according to NCI-CTCAE v4.

Risk factors for prediabetic and/or obese patients: HbA1c ≥5.7% and <6.5%; fasting blood glucose ≥100 mg/dL and <126 mg/dL; or BMI ≥30 kg/m^2.
BMI=body mass index; HbA1c=glycated hemoglobin; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
Oliveira M, et al. Presented at: American Society of Clinical Oncology; May 30–Jun 3, 2025; Chicago, IL.

PHASE 1/1b (GO39374): DOSE REDUCTION OR DISCONTINUATION DUE TO HYPERGLYCEMIA

AE of hyperglycemia – action taken with inavolisib, patients (%)	Overall patient population (n = 190)	Prediabetic and/or obese patients (n = 110)
Any	73 (38)	56 (51)
Drug interrupted	60 (32)	46 (42)
Dose reduced	18 (9)	15 (14)
Drug withdrawn	**1 (1)**	**1 (1)**

- Median inavolisib cumulative dose intensity: 96% in the overall population; 92% in prediabetic and/or obese patients

Please note: The Phase 1/1b study occurred in a setting with rigorous monitoring of glucose levels and safety management guidelines.

AE=adverse event

Oliveira M, et al. Presented at: American Society of Clinical Oncology; May 30–Jun 3, 2025; Chicago, IL.

PHASE 1/1b (GO39374): MANAGEMENT OF HYPERGLYCEMIA

Hyperglycemia management	Overall patient population (n = 190)	Prediabetic and/or obese patients (n = 110)
Any medications, patients %	90 (47)	70 (64)
Most common medications, patients (%)		
Metformin*	77 (41)	58 (53)
Empagliflozin (class: SGLT2i)	30 (16)	28 (26)
Sitagliptin (class: DPP-4i)	29 (15)	25 (23)
Pioglitazone	18 (9)	15 (14)
Insulin	12 (6)	9 (8)
Number of unique medications, patients (%)†	**n = 90**	**n = 70**
1	33 (17)	21 (19)
2	23 (12)	21 (19)
3	21 (11)	17 (16)
4+	13 (7)	11 (10)

Metformin use	Prediabetic Prediabetic and/or obese patients (excluding Arm F) (n = 92)
Median study day start (range)	14 (1–1,710)
Median starting dose	1,000 mg
Maximum dose (in ≥4 patients), patients (%)	n = 55
1,000 mg	20 (36)
2,000 mg	17 (31)
1,500 mg	4 (7)
500 mg	4 (7)

* Metformin use excluded Arm F (prophylactic metformin was administered as part of study treatment). † Medications administered sequentially or concomitantly.
DPP-4i=dipeptidyl peptidase-4 inhibitor; SGLT2i=sodium-glucose transport protein 2 inhibitor.
Oliveira M, et al. Presented at: American Society of Clinical Oncology; May 30–Jun 3, 2025; Chicago, IL.

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ADVERSE EVENT MANAGEMENT INFO FOR HYPERGLYCEMIA

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PATHOPHYSIOLOGY OF PI3K INHIBITOR-ASSOCIATED HYPERGLYCEMIA[1–8]

The PI3K pathway is important for regulating glucose homeostasis

- The p110α isoform of PI3K mediates insulin responses in muscle, liver, and adipose tissue
- Activation of PI3K results in a signaling cascade involving AKT and glucose transporters that facilitates glucose uptake

Inhibition of p110α can result in hyperglycemia

- Inhibition of p110α blocks the intracellular response to insulin signaling, leading to…
  - decreased glucose transport and uptake
  - increased glycogenolysis and gluconeogenesis
  - a transitory state of insulin resistance and hyperglycemia, and an increase in circulating insulin
    - preclinical data suggest that the resulting hyperinsulinemia can partially reactivate the PI3K pathway

Hyperglycemia is considered an on-target effect of PI3K inhibition

AE=adverse event; AKT=protein kinase B; p110α=phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PI3K=phosphatidylinositol 3-kinase.

1. Liu D, et al. *Cancer Med*. 2022;11:1796–1804. 2. Sopasakis VR, et al. *Cell Metab*. 2010;11:220–230. 3. Goncalves MD, et al. *N Engl J Med*. 2018;379:2052–2062. 4. Gallagher EJ, et al. *NPJ Breast Cancer*. 2024;10:12. 5. Gonclaves MD, et al. *Int Cancer Ther*. 2022;21:15347354211073163. 6. Fruman DA, et al. *Cell*. 2017;170:605–635. 7. Hoxhaj G, et al. *Nat Rev Cancer*. 2020;20:74–88. 8. Esposito A, et al. *JAMA Oncology*. 2019;5:1347–1354.

WARNINGS & PRECAUTIONS FOR HYPERGLYCEMIA[1]

- Severe or fatal hyperglycemia, including ketoacidosis, can occur in patients treated with Itovebi. Ketoacidosis with a fatal outcome has occurred in the postmarketing setting.
- The safety of Itovebi in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment has not been studied.
- Before initiating treatment with Itovebi, evaluate renal function, test fasting glucose levels (FPG or FBG), HbA1c levels, and optimize fasting glucose.
- After initiating treatment with Itovebi, or in patients who experience hyperglycemia after initiating treatment with Itovebi, monitor or self-monitor fasting glucose levels once every 3 days for the first week (Day 1 to 7), then once every week for the next 3 weeks (Day 8 to 28), then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated. Monitor $HbA1_C$ every 3 months and as clinically indicated.
- Manage hyperglycemia with anti-hyperglycemic medications as clinically indicated. During treatment with anti-hyperglycemic medication, continue monitoring fasting glucose levels. Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycemic treatment and close monitoring of fasting glucose levels.
- Consider consultation with a healthcare professional experienced in the treatment of hyperglycemia, and initiation of fasting glucose monitoring at home for patients who have risk factors for hyperglycemia or who experience hyperglycemia. Advise patients of the signs and symptoms of hyperglycemia and counsel patients on lifestyle changes.
- Based on the severity of the hyperglycemia, Itovebi may require dose interruption, reduction, or discontinuation.

HbA1c=glycosylated hemoglobin

1. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025.

ADDITIONAL INFORMATION ON KETOACIDOSIS[1,2]

- In the phase 3 trial, INAVO120 (WO41554, NCT04191499), no cases of ketoacidosis were reported. However, cases of life-threatening ketoacidosis have been reported in patients receiving Itovebi in the post-marketing setting.
- Ketoacidosis is a medical emergency characterized by hyperglycemia, electrolyte derangements, metabolic acidosis, and ketonemia. The mainstays of treatment include restoration of circulating volume, insulin therapy, electrolyte replacement, and treatment of any underlying precipitating event. Without optimal treatment, ketoacidosis could result in morbidity and mortality.
- A Dear Healthcare Provider (DHCP) letter was issued by Genentech on March 10, 2025, to inform HCPs of this and important safety information for Itovebi.

1. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025. 2. Itovebi® (inavolisib) [Important Drug Warning]. Genentech, Inc. March 5, 2025. Available at https://www.gene.com/download/pdf/Itovebi_DHCP_Important-Drug-Warning_March2025.pdf

MANAGEMENT OF HYPERGLYCEMIA IN THE INAVO120 STUDY[1,2] (1 of 2)

Evaluate FPG/FBG and HbA_{1c} and optimize blood glucose prior to starting Inavolisib and at regular intervals during treatment[1]

Fasting glucose level	Actions[2]		
	Initial inavolisib management	Medical management	Monitoring recommendations
>ULN to 160 mg/dL (>ULN–8.9 mmol/L)	**Continue** current dose level of inavolisib	• Encourage patients to adopt a diabetic diet • Consider consultation with an endocrinologist or diabetologist • Consider oral anti-diabetic medication (eg, metformin) for patients at high risk[a]	• Provide home glucose monitoring to patients at high risk,[a] and educate to check fasting glucose at home • Recheck in 3 days, and adjust or add anti-diabetic medications as needed[b]
>160 to 250 mg/dL (>8.9–13.9 mmol/L)	**Interrupt** inavolisib dose[c]	• Encourage patients to adopt a diabetic diet • Consider consultation with an endocrinologist or diabetologist • Start or increase dose of an oral anti-diabetic medication (eg, metformin, SGLT2 inhibitor)[d]	• Initiate fasting home glucose monitoring • Recheck in 3 days and adjust or add anti-diabetic medications as needed[b] → When hyperglycemia resolves to ≤160 mg/dL (≤8.9 mmol/L)… → …**resume** current dose level of inavolisib → If fasting blood glucose persists >200–250 mg/dL (>11.1–13.9 mmol/L) for 7 days despite interventions → …discuss with the Medical Monitor[c]

Information provided is general guidance from the INAVO120 study protocol and is not advice or recommendations. It is not intended as a substitute for the Itovebi® USPI Table 2. Treatment decisions are ultimately at the discretion of the treating HCP and per local institutional guidelines. Patients were advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

[a] High-risk factors for diabetes include prediabetes, overweight, obesity, BMI ≥30 kg/m^2, HbA1c ≥5.7%, >45 years of age, family history of diabetes, certain ethnicities, inactive lifestyle, and history of gestational diabetes. [b] Fasting glucose should be checked by finger stick or lab value (if patient has a scheduled appointment) **PRIOR** to dosing. **Oral antidiabetic medications should be titrated to the maximum allowed dosages to achieve control of blood glucose to ≤160 mg/dL or 8.9 mmol/L. For example, metformin may be administered to the maximum dose allowed per local prescribing information, given in divided doses, as tolerated**. Refer to the local prescribing information of the individual oral antidiabetic agent for dosing guidelines. [c] If, in the investigator's opinion, the benefit-risk assessment favors continued inavolisib dosing without interruption, inavolisib may be continued without interruption upon discussion with the Medical Monitor once patients are managed on antidiabetic agent(s) and fasting glucose ≤200 mg/dL (≤11.1 mmol/L). It is recommended that patients be instructed to utilize a glucometer to monitor fasting glucose and to call the clinic if fasting glucose >200 mg/dL (>11.1 mmol/L) prior to inavolisib dosing at home. [d] There is a risk of hypoglycemia if insulin or sulfonylureas are used, particularly if these agents are started during periods of inavolisib exposure and doses are not adjusted appropriately during periods of treatment interruption, during which patients' insulin sensitivity may increase rapidly. Short-term insulin is allowed to control blood glucose levels, but the goal should be to maintain blood glucose on oral agents once the acute episode resolves.

AE=adverse event; BMI=body mass index; HbA1c=glycosylated hemoglobin; HCP=health care provider; SGLT2=sodium-glucose co-transporter 2; ULN=upper limit of normal. USPI=United States Prescribing Information.

1. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025. 2. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

MANAGEMENT OF HYPERGLYCEMIA IN THE INAVO120 STUDY[1,2] (2 of 2)

Evaluate FPG/FBG and HbA_{1c} and optimize blood glucose prior to starting Inavolisib and at regular intervals during treatment[1]

Fasting glucose level	Actions[2]			
	Initial inavolisib management	Medical management	Monitoring recommendations	
>250 to 500 mg/dL (>13.9–27.8 mmol/L)	**Interrupt** inavolisib	• Encourage patients to adopt a diabetic diet • Consider consultation with an endocrinologist or diabetologist • Manage hyperglycemia per SOC[a,b] • Start or increase dose of an oral anti-diabetic medication (eg, metformin, SGLT2 inhibitor)[a]	• Initiate fasting home glucose monitoring • Recheck in 3 days and adjust or add anti-diabetic medications as needed[c]	If hyperglycemia resolves to ≤160 mg/dL (≤8.9 mmol/L) within 7 days… → …may **resume** at current dose level of inavolisib If hyperglycemia resolves to ≤160 mg/dL (≤8.9 mmol/L) in ≥8 days… → …**reduce** inavolisib dose by one dose level when treatment resumes[d] If hyperglycemia >250–500 mg/dL (>13.9–27.8 mmol/L) recurs within 30 days… → …**reduce** inavolisib dose by one dose level[d]
>500 mg/dL (>27.8 mmol/L)	**Interrupt** inavolisib	• Encourage patients to adopt a diabetic diet • Consider consultation with an endocrinologist or diabetologist • Manage hyperglycemia per SOC[a,b] • Start or increase dose of an oral anti-diabetic medication (eg, metformin, SGLT2 inhibitor)[a] • Assess for volume depletion and ketosis and administer appropriate IV or oral hydration	• Initiate fasting home glucose monitoring • Recheck in 3 days and adjust or add anti-diabetic medications as needed[c]	When hyperglycemia resolves to ≤160 mg/dL (≤8.9 mmol/L)… → …**reduce** inavolisib dose by one dose level when treatment resumes[d] If hyperglycemia >500 mg/dL (>27.8 mmol/L) recurs within 30 days… → …**permanently discontinue** inavolisib

Information provided is general guidance from the INAVO120 study protocol and is not advice or recommendations. It is not intended as a substitute for the Itovebi® USPI Table 2. Treatment decisions are ultimately at the discretion of the treating HCP and per local institutional guidelines. Patients were advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

[a] There is a risk of hypoglycemia if insulin or sulfonylureas are used, particularly if these agents are started during periods of inavolisib exposure and doses are not adjusted appropriately during periods of treatment interruption, during which patients' insulin sensitivity may increase rapidly. Short-term insulin is allowed to control blood glucose levels, but the goal should be to maintain blood glucose on oral agents once the acute episode resolves. [b] It is recommended that the patient be reassessed within 24 hours and preferably the same day for assessments of hydration status and renal function. [c] Fasting glucose should be checked by finger stick or lab value **PRIOR** to dosing. **Oral anti-diabetic medications should be titrated to the maximum allowed dosages to achieve control of blood glucose to ≤160 mg/dL or 8.9 mmol/L.** Refer to the local prescribing information of the individual oral antidiabetic agent for dosing guidelines. [d] A maximum of two dose reductions was allowed. AE=adverse event; HCP=health care provider; IV=intravenous; SGLT2=sodium-glucose co-transporter 2; SOC=standard of care. USPI=United States Prescribing Information.

1. Itovebi® (inavolisib) [prescribing information]. South San Francisco, CA: Genentech, Inc; 2025. 2. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

MANAGEMENT OF PATIENTS AT HIGH RISK FOR HYPERGLYCEMIA IN THE INAVO120 STUDY

High-risk factors for hyperglycemia[1,2]

- >45 years of age
- HbA1c ≥5.7% (the cutoff for INAVO120 trial was <6.0%)
- Pre-diabetes/diabetes
- Family history of diabetes
- BMI ≥30 kg/m^2
- History of gestational diabetes
- Any other factor that increases the risk of hyperglycemia (e.g., certain ethnicities such as African American, South Asian; inactive lifestyle)

Information provided is general guidance from the INAVO120 study protocol and is not advice or recommendations. Treatment decisions are ultimately at the discretion of the treating HCP and per local institutional guidelines.

Patients were advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

AE=adverse event; BMI=body mass index; HbA1c=hemoglobin A1c; HCP=health care professional.

1. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025. 2. El Sayed N, et al. *Diabetes Care*. 2023;46:S19–S40.

ANTI-HYPERGLYCEMIC USE IN THE INAVO120 STUDY[1,2] (1 of 2) - METFORMIN

Metformin[a]

- **Metformin was recommended as first-line for management of[b]:**
  - sustained fasting glucose >160 mg/dL or >8.9 mmol/L or
  - anytime fasting glucose is >250 mg/dL or >13.9 mmol/L
- **At the investigator's discretion and where allowed by local regulations, prophylactic metformin[c] may be initiated on C1D1 for patients at high risk of hyperglycemia**
- **Monitor for signs and symptoms of:**
  - renal impairment
  - metformin toxicity
  - intolerance or toxicity, including lactic acidosis, which may occur in the setting of acute worsening of renal function or cardiorespiratory illness or sepsis and can be life-threatening
- **Common side effects of metformin:**
  - nausea
  - vomiting
  - diarrhea
  - abdominal pain
  - loss of appetite
- **Metformin does not produce hypoglycemia, but hypoglycemia may occur** with a missed meal, alcohol consumption, or heavy exercise, or when metformin is taken with another type of diabetes medicine

Information provided is general guidance from the INAVO120 study protocol and is not advice or recommendations. Treatment decisions are ultimately at the discretion of the treating HCP and per local institutional guidelines. Patients were advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

[a] Refer to the local prescribing information for metformin. Metformin was recommended to be titrated to the maximum allowed dosages to achieve control of blood glucose to ≤160 mg/dL or 8.9 mmol/L. [b] Investigators were advised to exercise caution in the dosing and management of patients receiving metformin in combination with inavolisib and to be vigilant for signs of renal impairment and metformin toxicity including lactic acidosis, which may occur in the setting of acute worsening of renal function or cardiorespiratory illness or sepsis and can be life-threatening. The most frequently reported AEs with metformin are nausea, vomiting, diarrhea, abdominal pain, and loss of appetite. Metformin does not produce hypoglycemia, but it may occur with a missed meal, alcohol consumption, or heavy exercise, or when it is taken with another type of diabetes medicine. [c] **The available clinical data for prophylactic metformin use are limited (3 patients in INAVO120 and 16 patients in the Phase 1 Arm F), and no conclusions can be drawn.** AE=adverse event; C=cycle; D=day; HCP=health care professional. 1. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025. 4. 2. El Sayed N, et al. *Diabetes Care*. 2023;46:S140–S157.

ANTI-HYPERGLYCEMIC USE IN THE INAVO120 STUDY[1,2] (2 of 2) – OTHER AGENTS

SGLT2 inhibitors, pioglitazone, DPP-4 inhibitors[a]

- **If metformin was not tolerated or not sufficient, another anti-hyperglycemic medication(s) may be added to or used in place of metformin. Preferred agents included:**
  - **SGLT2 inhibitors**
    - Ensure adequate hydration and monitor for vaginal yeast infections
  - **Pioglitazone**
    - Monitor closely for signs of heart failure including fluid retention or edema
  - **DPP-4 inhibitors**
  - Patients administered **insulin** or **sulfonylureas** should be treated with extreme caution when these agents are used to manage hyperglycemia and inavolisib is subsequently interrupted or discontinued[a]; this can lead to rapid escalation of insulin levels and risk of hypoglycemia
  - Short-term **insulin** is allowed to control blood glucose levels, but the goal should be to maintain them on oral agents once the acute episode resolves
- **Review respective prescribing information for dosing and dose titration recommendations, including local hyperglycemic treatment guidelines**

Information provided is general guidance from the INAVO120 study protocol and is not advice or recommendations. Treatment decisions are ultimately at the discretion of the treating HCP and per local institutional guidelines. Patients were advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

[a] Refer to the local prescribing information for each of these agents.

AE=adverse event; DPP-4= dipeptidyl peptidase-4; HCP=health care provider; SGLT2=sodium-glucose co-transporter 2.

1. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025. 2. El Sayed N, et al. *Diabetes Care*. 2023;46:S140–S157.

SUMMARY OF ANTI-HYPERGLYCEMICS DESCRIBED IN THE INAVO120 PROTOCOL[1]

1L Agent	2L Agents	3L Agents	Last-line Agent
Metformin[a] Prophylactic metformin[b] may be initiated on Cycle 1 Day 1 in patients with more than one risk factor for hyperglycemia.	**Sodium-glucose co-transporter 2 inhibitors (SGLT2i), thiazolidinediones** ***Additional 2L agents:*** **Dipeptidyl peptidase-4 (DPP-4) inhibitors**	**Sulfonylureas**[c]	**Insulin**[c] Insulin has a stimulatory effect on PI3K signaling and is associated with an increased risk of hypoglycemia. Therefore, it is considered a last line of therapy for PI3K inhibitor-associated hyperglycemia.

Information provided is general guidance from the INAVO120 study protocol and is not advice or recommendations. Treatment decisions are ultimately at the discretion of the treating HCP and per local institutional guidelines. Patients were advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

- When choosing an anti-hyperglycemic agent, consider possible side effects and onset of action, as well as any adverse events the patient may be experiencing as a result of the PI3K inhibitor treatment. Medications that do not affect the PI3K pathway are preferred.
- Oral anti-hyperglycemic medications should be titrated to the maximum allowed dosages to achieve control of blood glucose to ≤160 mg/dL or 8.9 mmol/L. For example, metformin may be administered to a maximum dose allowed as per local prescribing information, given in divided doses, as tolerated.
- Please see local prescribing information of individual oral anti-hyperglycemic agent for dosing guidelines.

[a] Metformin was recommended to be titrated to the maximum allowed dosages to achieve control of blood glucose to ≤160 mg/dL or 8.9 mmol/L. [b] Investigators were advised to exercise caution in the dosing and management of patients receiving metformin in combination with inavolisib and to be vigilant for signs of renal impairment and metformin toxicity, including lactic acidosis, which may occur in the setting of acute worsening of renal function or cardiorespiratory illness or sepsis and can be life-threatening. The most frequently reported AEs with metformin are nausea, vomiting, diarrhea, abdominal pain, and loss of appetite. Metformin does not produce hypoglycemia, but it may occur with a missed meal, alcohol consumption, or heavy exercise, or when it is taken with another type of diabetes medicine. **[b] The available clinical data for prophylactic metformin use are limited (3 patients in INAVO120 and 16 patients in the Phase 1 Arm F), and no conclusions can be drawn**. [c] There is a risk of hypoglycemia if insulin or sulfonylureas are used, particularly if these agents are started during periods of inavolisib exposure and doses are not adjusted appropriately during periods of treatment interruption, during which patients' insulin sensitivity may increase rapidly. Short-term insulin is allowed to control blood glucose levels, but the goal should be to maintain blood glucose on oral agents once the acute episode resolves.

1. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

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THANK YOU

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