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ITOVEBI® (inavolisib) Safety Information

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

Current as of September, 2025

Veeva Document Number: M-US-00025445(v2.0)

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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).

The information we provide may additionally include relevant references to non-Genentech product information derived from publicly available sources.

FDA=Food and Drug Administration.

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 provided with this presentation.

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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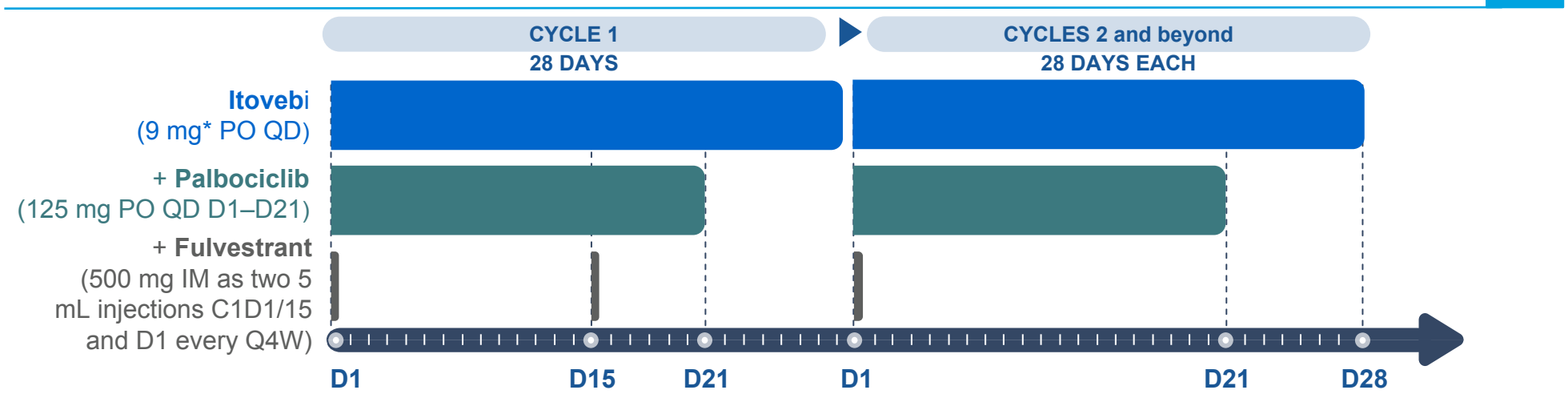
DOSING REGIMEN OVERVIEW



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, fasting plasma glucose (FPG)/blood glucose (FBG), and hemoglobin A1C (HbA1C). 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.

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

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INAVO120 OVERVIEW

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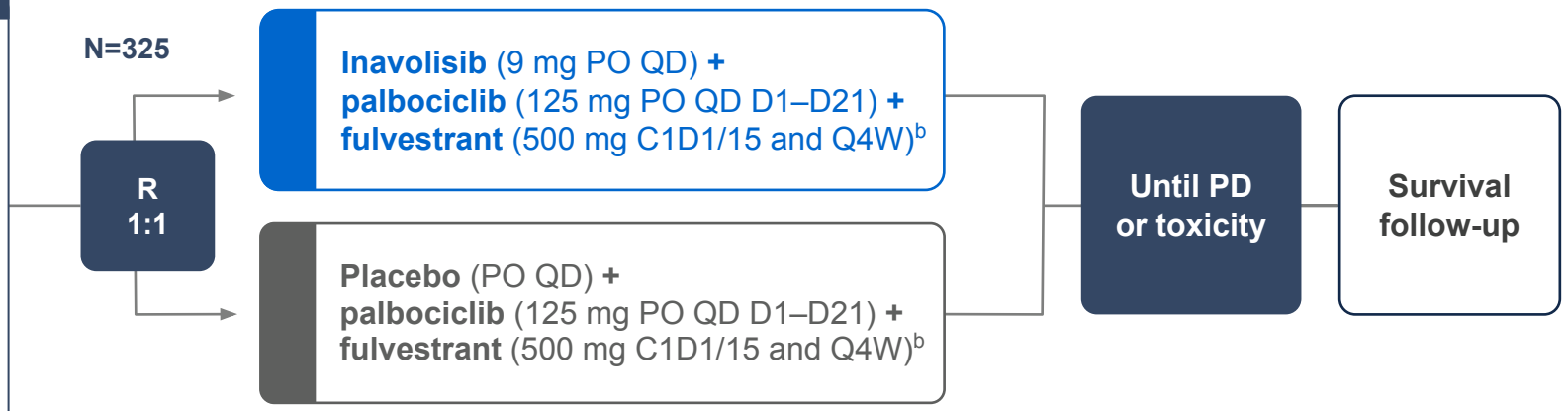
INAVO120 STUDY DESIGN[1]

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 Oct 31;391(17):1584-1596. 2. Cardoso F, et al. *Ann Oncol*. 2018;29:1634–1657. 3. https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

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INAVO120 SAFETY DATA

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ADVERSE EVENTS OVERVIEW FROM INAVO120 (UPDATED ANALYSIS)

Patients, n (%) with at least one:	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=163)
Any-grade AE, n (%)	161 (100)	163 (100)
Grade 3–4 AE	146 (90.7)	138 (84.7)
Grade 5 AE[a]	6 (3.7)	2 (1.2)
Serious AE	44 (27.3)	22 (13.5)
AEs leading to discontinuation of treatment	14 (8.7)	1 (0.6)
Inavolisib/placebo	11 (6.8)	1 (0.6)
Palbociclib	10 (6.2)	0
Fulvestrant	6 (3.7)	0
AEs leading to dose modification/interruption of treatment	140 (87.0)	126 (77.3)
Inavolisib/placebo	117 (72.7)	67 (41.1)
Palbociclib	130 (80.7)	121 (74.2)
Fulvestrant	55 (34.2)	40 (24.5)
AEs leading to dose reduction of treatment		
Inavolisib/placebo	24 (14.9)	6 (3.7)
Palbociclib	65 (40.4)	56 (34.4)
AEs leading to dose interruption of treatment		
Inavolisib/placebo	116 (72.0)	66 (40.5)
Palbociclib	119 (73.9)	106 (65.0)
Fulvestrant	55 (34.2)	40 (24.5)

Data cutoff date: November 15, 2024. **AEs were defined per CTCAE v5 as assessed by the investigator**.

[a] None of the grade 5 AEs were reported as related to study treatment by investigators. The grade 5 AEs reported were cerebral hemorrhage, cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death, and COVID-19 in the Inavolisib arm; COVID-19 pneumonia and cardiac arrest in the placebo group. AE=adverse event; COVID-19=coronavirus disease 2019; CTCAE v5=Common Terminology Criteria for Adverse Events version 5; Fulv=fulvestrant; Inavo=inavolisib; NR=not reported; Palbo=palbociclib; Pbo=placebo. Jhaveri, KL, et al. N Engl J Med. Published online May 31, 2025.

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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.

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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 posttreatment value. [c]Grading according to CTCAE version 4.03. ALT=alanine aminotransferase; CTCAE v4.03=Common Terminology Criteria for Adverse Events version 4.03; 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.

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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://www.ctep.cancer.gov. 4. INAVO120 study information. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

HYPERGLYCEMIA AND FASTING GLUCOSE RATES IN INAVO120 (AT PRIMARY ANALYSIS)

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 Oct 31;391(17):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.

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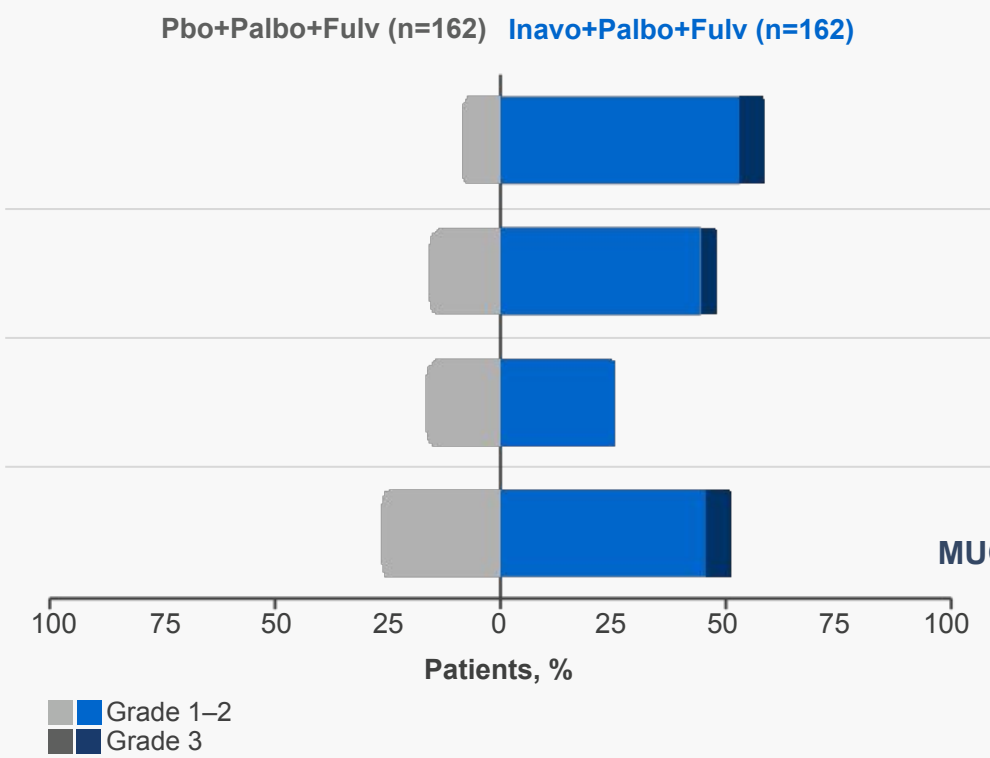
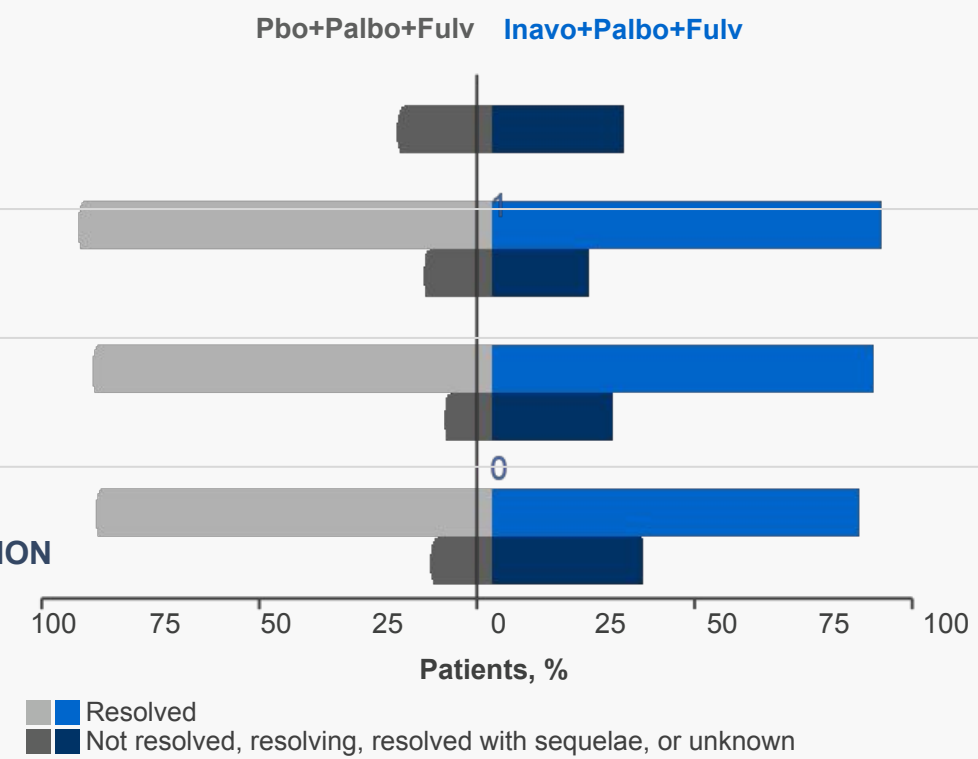
KEY SELECTED ADVERSE EVENTS FROM INAVO120 (AT PRIMARY ANALYSIS)

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.

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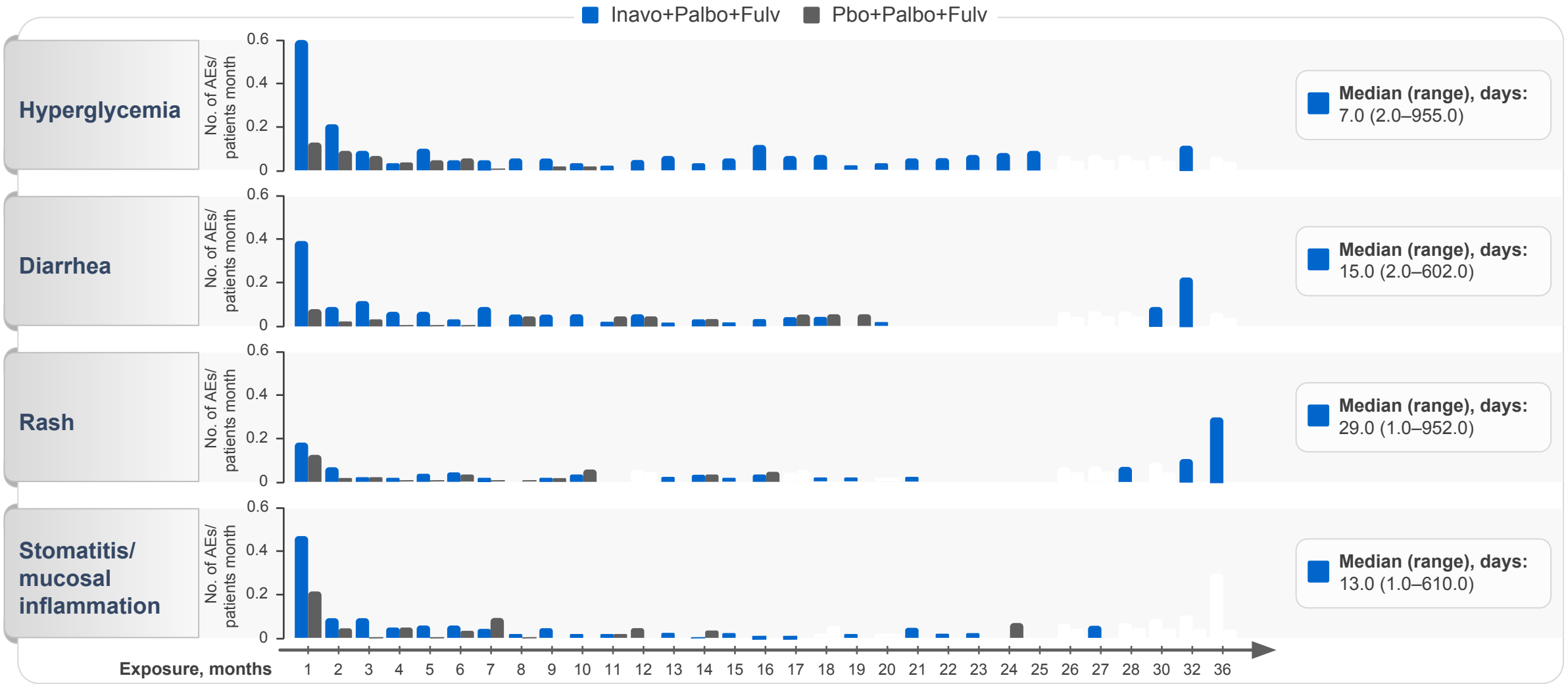
TIME TO ONSET OF KEY SELECTED ADVERSE EVENTS IN INAVO120[a]



[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.

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CONCOMITANT MEDICATIONS FOR KEY SELECTED ADVERSE EVENTS IN INAVO120

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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DOSE MODIFICATIONS FOR ADVERSE REACTIONS

The recommended dose reduction levels of Itovebi for adverse reactions are listed in the table below. Permanently discontinue Itovebi if patients are unable to tolerate the second dose reduction.

Recommendations for Dose Reduction for Adverse Reactions	
Dose Level	**Dose and Schedule**
Recommended starting dose*	9 mg daily
First dose reduction	6 mg daily
Second dose reduction	3 mg daily

*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)].*
- 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, Recommended Evaluation Before Initiating Itovebi (2.2)].*

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PHASE 1/1b (GO39374) SAFETY DATA

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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://www.ctep.cancer.gov. 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.

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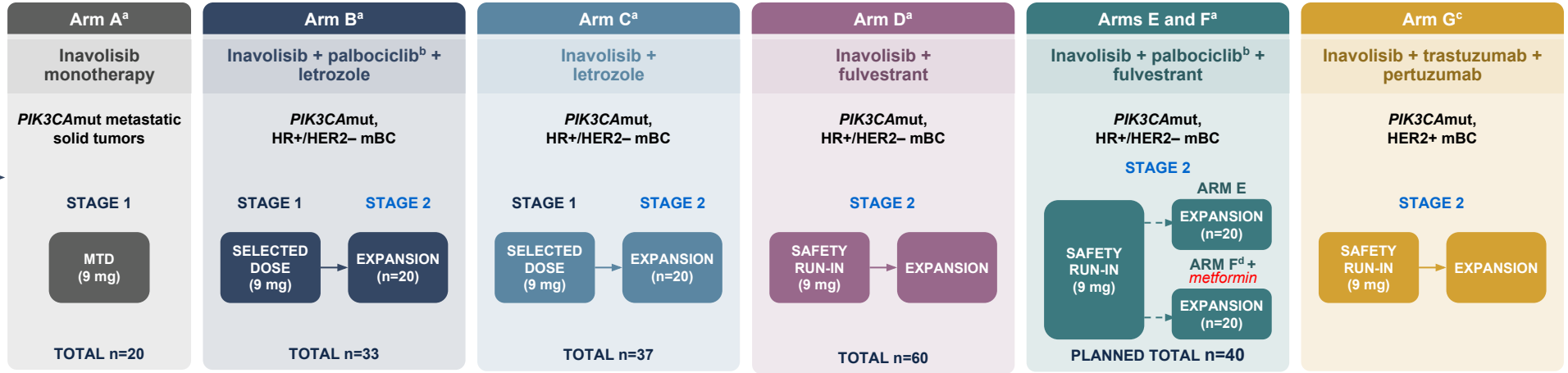
GO39374: A PHASE 1/1b STUDY OF INAVOLISIB ± ET ± PALBOCICLIB IN PATIENTS WITH *PIK3CA*mut HR+ MBC[1–3]

- *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*mut, incurable solid tumor malignancy, including breast cancer
- **Stages I and II, Arms B and C:** Postmenopausal female participants with locally advanced or metastatic *PIK3CA*mut, HR+/HER2– BC
  Stage II, Arms D, E, and F: Female participants with locally advanced or metastatic *PIK3CA*mut, 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%).[4]

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.

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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.

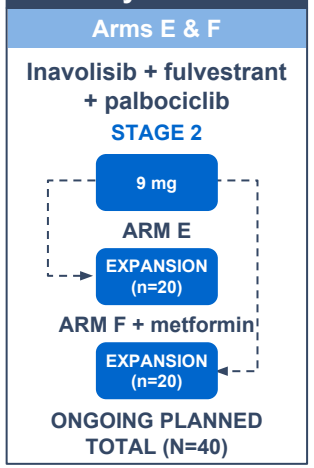
Methods

- 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).

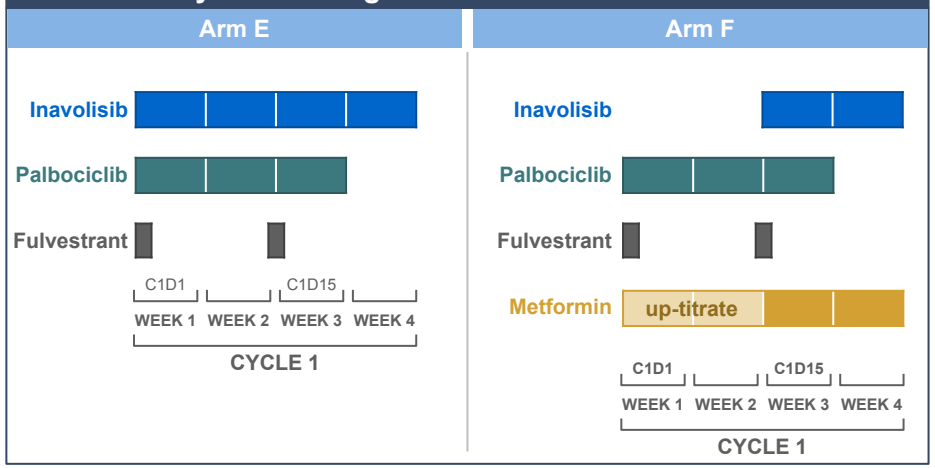
Patient characteristics and treatment exposure

	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. Bedard P, et al. Presented at: San Antonio Breast Cancer Symposium; December 8–11, 2020; virtual. Poster PD1-02.

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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 before 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.

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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.

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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 I/Ib 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.

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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.

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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.

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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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MANAGEMENT OF HYPERGLYCEMIA IN INAVO120

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WARNINGS & PRECAUTIONS FOR HYPERGLYCEMIA

- 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, 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

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

ADDITIONAL INFORMATION ON KETOACIDOSIS

- 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 important safety information for Itovebi.

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

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.

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RISK FACTORS 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
- Family history of diabetes
- BMI ≥30 kg/m^2
- History of gestational diabetes
- Any other factor that increases the risk of hyperglycemia
  (eg, 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.

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MANAGEMENT OF PATIENTS AT HIGH RISK FOR HYPERGLYCEMIA IN INAVO120[1-4]

Information provided is general guidance from the INAVO120 study protocol. 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

General Prophylactic Considerations[1,2]

- Consider instructing patients to utilize a glucometer to monitor fasting glucose at home on a daily basis[*,1]
- Recommend lifestyle changes according to the American Diabetes Association guidelines, that is, dietary advice[†], such as[2-4]:
  - Small frequent meals (e.g. three small meals and two small snacks rather than one large meal)
  - Foods with low carbohydrate content and high fiber
  - Balanced carbohydrate intake over the course of the day
  - Avoid sugar-sweetened beverages and switch to water whenever possible
- Advise consultation a dietician or nutritionist[4]
- Increase daily physical activity and exercise[2]
- Consultation with an endocrinologist or diabetologist is highly recommended[1]
- Prophylactic metformin may be initiated on Cycle 1 Day 1 in patients with more than one risk factor[‡,1]

*Fasting glucose should be checked by finger stick or lab value (if patient has scheduled appointment) **PRIOR** to dosing. †For patients without active gastrointestinal complaints or unintentional weight loss[4]. ‡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. 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-diabetic agent for dosing guidelines.

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(1):S41-S48. 3. El Sayed, N et al. Diabetes Care. 2023;46(1):S68-S96. 4. Goncalves, M and Farooki, A. Integrative Cancer Therapies.2022.21:1-14.

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MANAGEMENT OF HYPERGLYCEMIA IN THE INAVO120 STUDY (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 or ≤8.9 mmol/L… → …**resume** current dose level of inavolisib → If fasting blood glucose persists ≥200–250 mg/dL or >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, obese, BMI ≥30 kg/m^2, HbA1c ≥5.7%, 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 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 local prescribing information of 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 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.

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MANAGEMENT OF HYPERGLYCEMIA IN THE INAVO120 STUDY (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 or 8.9 mmol/L within 7 days…	…may **resume** at current dose level of inavolisib
				If hyperglycemia resolves to ≤160 mg/dL or 8.9 mmol/L in ≥8 days…	…**reduce** inavolisib dose by one dose level when treatment resumes[d]
				If hyperglycemia >250–500 mg/dL or >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 or 8.9 mmol/L…	…**reduce** inavolisib dose by one dose level when treatment resumes[d]
				If hyperglycemia >500 mg/dL or >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 acute episode resolves. [b] It is recommended that the patient is 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 local prescribing information of 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.

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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. 2. El Sayed N, et al. *Diabetes Care*. 2023;46:S140–S157.

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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.

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

1L Agent	2L Agents	3L Agents	Last-line Agent
Metformin[a] At the investigator's discretion and where allowed by local regulations, **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.

*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. [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. [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 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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SUPPORTIVE LITERATURE FOR THE MANAGEMENT OF HYPERGLYCEMIA

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HYPERGLYCEMIA MANAGEMENT: SUPPORTIVE LITERATURE

While there are no widely accepted guidelines for hyperglycemia management of patients prescribed a PI3K inhibitor, we are aware of the following references on the subject that may be helpful:

Consensus guidelines

Gallagher EJ, Moore H, Lacouture ME, et al. Managing hyperglycemia and rash associated with alpelisib: expert consensus recommendations using the Delphi technique. *NPJ Breast Cancer*. 2024;10(1):12.

Clinical trial

Llombart-Cussac A, Pérez-Garcia JM, Borrego MR, et al. Preventing alpelisib-related hyperglycaemia in HR+/HER2−/*PIK3CA*-mutated advanced breast cancer using metformin (METALLICA): a multicentre, open-label, single-arm, phase 2 trial. *EClinicalMedicine*. 2024;71:102520.

Supportive Literature

Moore HN, Gonclaves MD, Johnston AM, et al. Effective Strategies for the Prevention and Mitigation of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia: Optimizing Patient Care. Clin Breast Cancer. 2025 Jan;25(1):1-11.

The following slides present summaries of publicly available information that is specific to alpelisib, which is another PI3Ki and is not manufactured by Genentech. These references do not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information.

Addl=additional; AE=adverse event; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PI3K=phosphatidylinositol 3-kinase.

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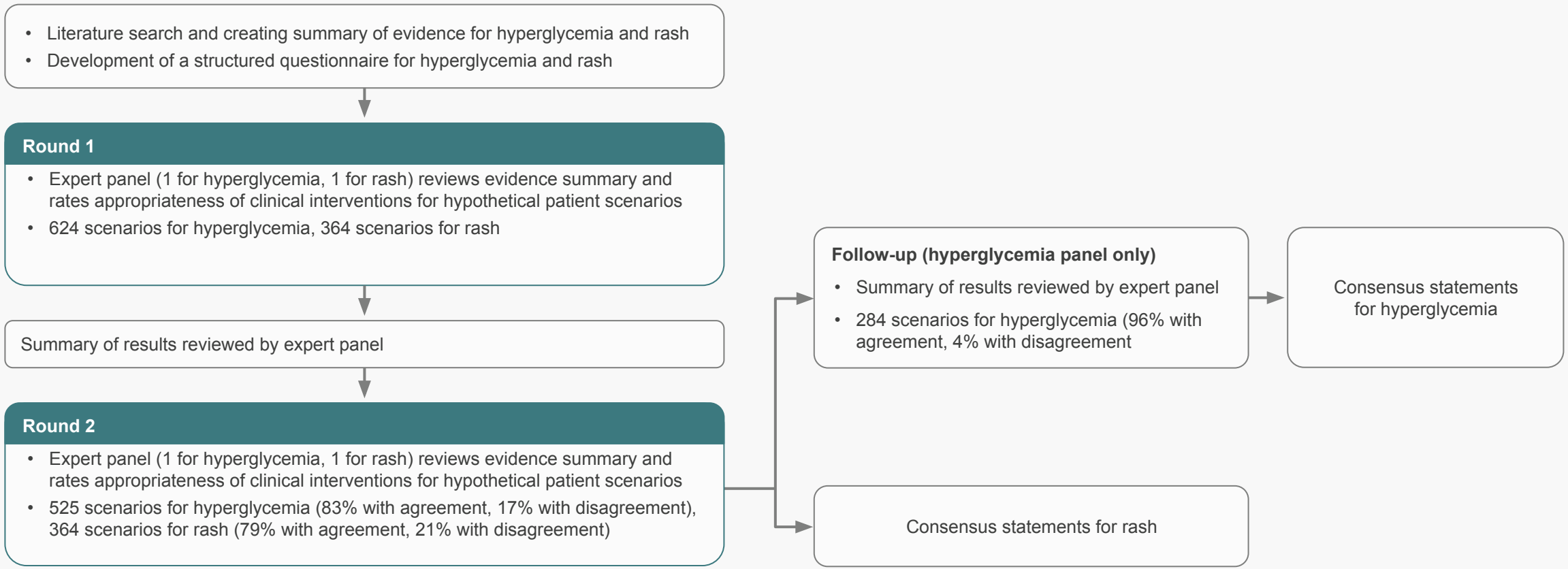
EXPERT RECOMMENDATIONS FOR MANAGING HYPERGLYCEMIA WITH ALPELISIB USING THE DELPHI TECHNIQUE (1 of 5)

Delphi technique methodology



The information on this slide does not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information.

Gallagher EJ, et al. *NPJ Breast Cancer*. 2024;10(1):12.

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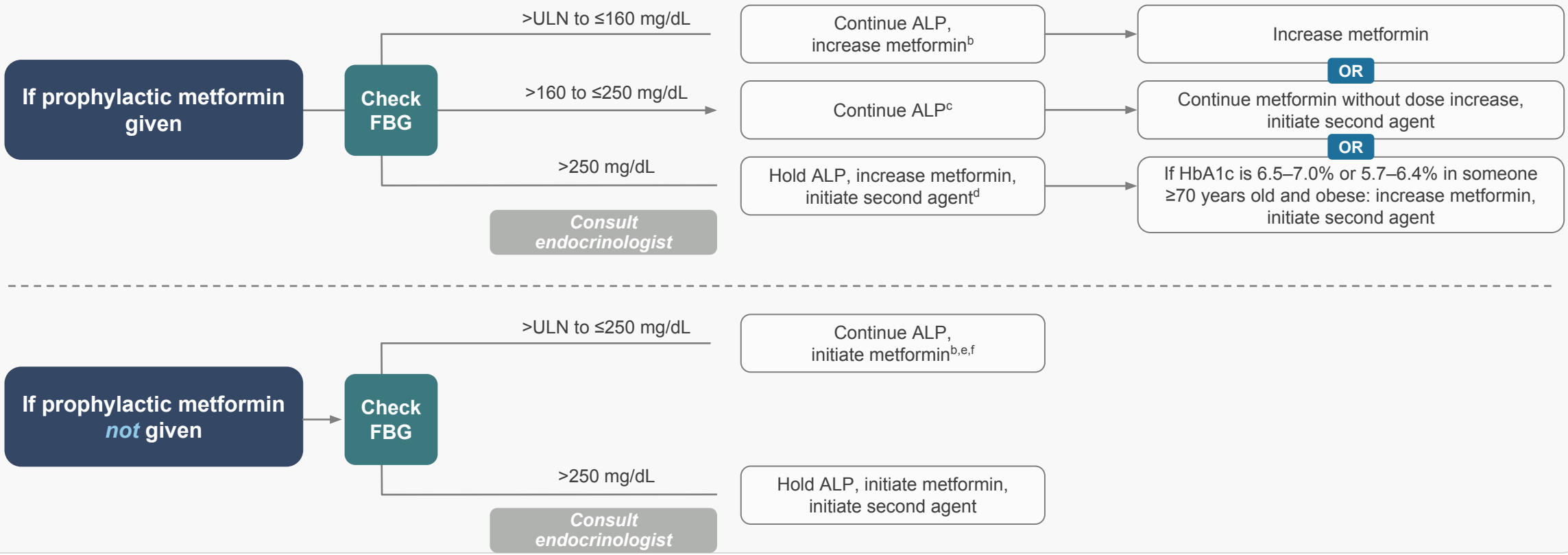
EXPERT RECOMMENDATIONS FOR MANAGING HYPERGLYCEMIA WITH ALPELISIB USING THE DELPHI TECHNIQUE (2 of 5)

Consensus treatment algorithm for the management of the first episode of hyperglycemia associated with alpelisib[1a]



The information on this slide does not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information. [a] Unless otherwise stated for all statements about increasing metformin, assume extended-release or short-acting, and up to MTD. [b] In certain circumstances (eg, select patients who continue to have HbA1c<8.0% or those who are asymptomatic and intolerant to metformin), it may be appropriate to continue ALP without initiating or changing metformin dose. [c] It may also be appropriate to temporarily hold ALP (with the intent to restart at the same dose) and increase metformin in certain patients at high risk (eg, HbA1c>5.7%). [d] If FBG>250 to ≤500 mg/dL, it may also be appropriate to hold or reduce the dose of ALP without first holding and continue metformin without a dose increase (metformin not at MTD) while simultaneously initiating a second agent. [e] With the goal of titrating to a maximum dose of 2000 mg/day within 1 week.[2] [f] If FBG >ULN to ≤250 mg/dL, it may also be appropriate to either (1) continue ALP while simultaneously initiating metformin and a second agent or (2) hold ALP while simultaneously initiating metformin and a second agent in certain patients at high risk (eg, HbA1c ≥6.5%). Addl=additional; AE=adverse event; ALP=alkaline phosphatase; FBG=fasting blood glucose; HbA1c=glycosylated hemoglobin; mgmt.=management; MTD=maximum tolerated dose; ULN=upper limit of normal.

1. Gallagher EJ, et al. *NPJ Breast Cancer*. 2024;10(1):12. 2. Glucophage and Glucophage XR [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2018.

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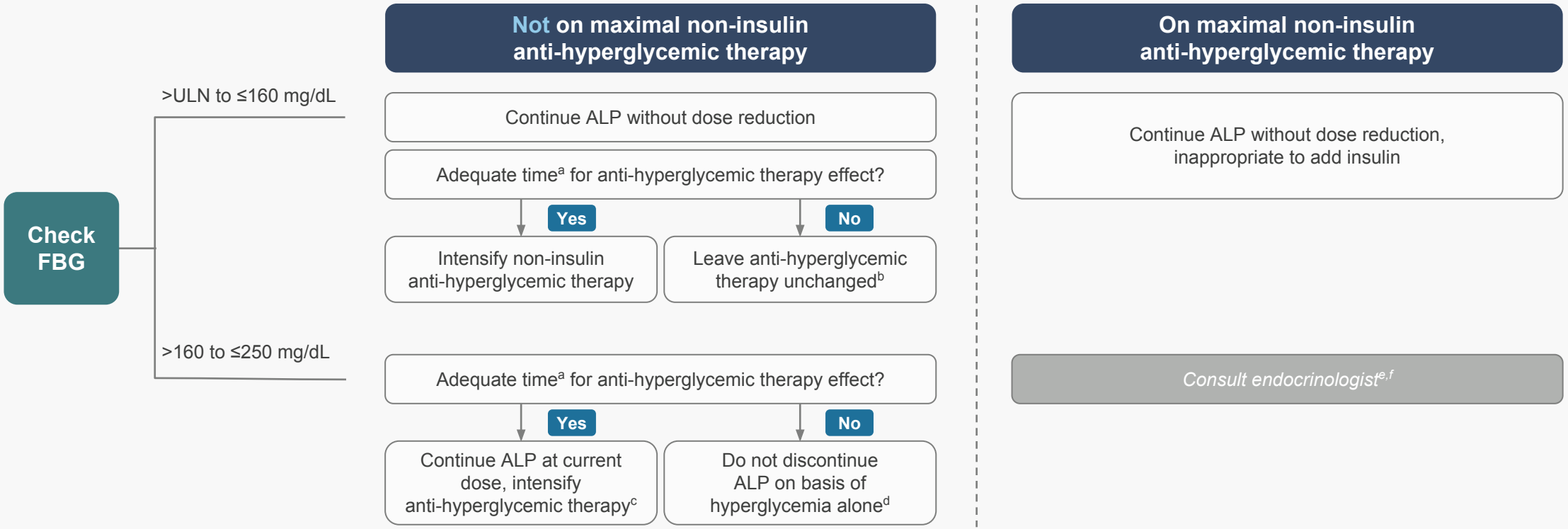
EXPERT RECOMMENDATIONS FOR MANAGING HYPERGLYCEMIA WITH ALPELISIB USING THE DELPHI TECHNIQUE (3 of 5)

Consensus treatment algorithm for the management of subsequent episodes of hyperglycemia associated with alpelisib (1 of 2)



The information on this slide does not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information. [a] Metformin: 2 weeks; SGLT2i: 2 days; DPP4i: 1 week; TZDs: 6 weeks; GLP-1 RA: 1 week. [b] It may also be appropriate to intensify non-insulin antihyperglycemic therapy depending on the specific circumstances. [c] It may be appropriate to consult an endocrinologist to assist with intensifying anti-hyperglycemic treatments. It may also be appropriate to temporarily hold ALP and intensify anti-hyperglycemic treatment. [d] It may be appropriate to continue ALP either with or without intensifying anti-hyperglycemic therapy, or to temporarily hold ALP and intensify anti-hyperglycemic therapy. [e] It may be appropriate to give insulin, depending on individual circumstances. It may also be appropriate to either continue or hold ALP. [f] Or have the patient evaluated in the emergency department if circumstances warrant it. Addl=additional; AE=adverse event; ALP=alpelisib; DPP4i=dipeptidyl peptidase-4 inhibitor; FBG=fasting blood glucose; GLP-1 RA=glucagon-like peptide 1 receptor agonist; HbA1c=glycosylated hemoglobin; inhibitor; SGLT2i=sodium-glucose co-transporter 2 inhibitor; TZD=thiazolidinedione; ULN=upper limit of normal.

Gallagher EJ, et al. *NPJ Breast Cancer*. 2024;10(1):12.

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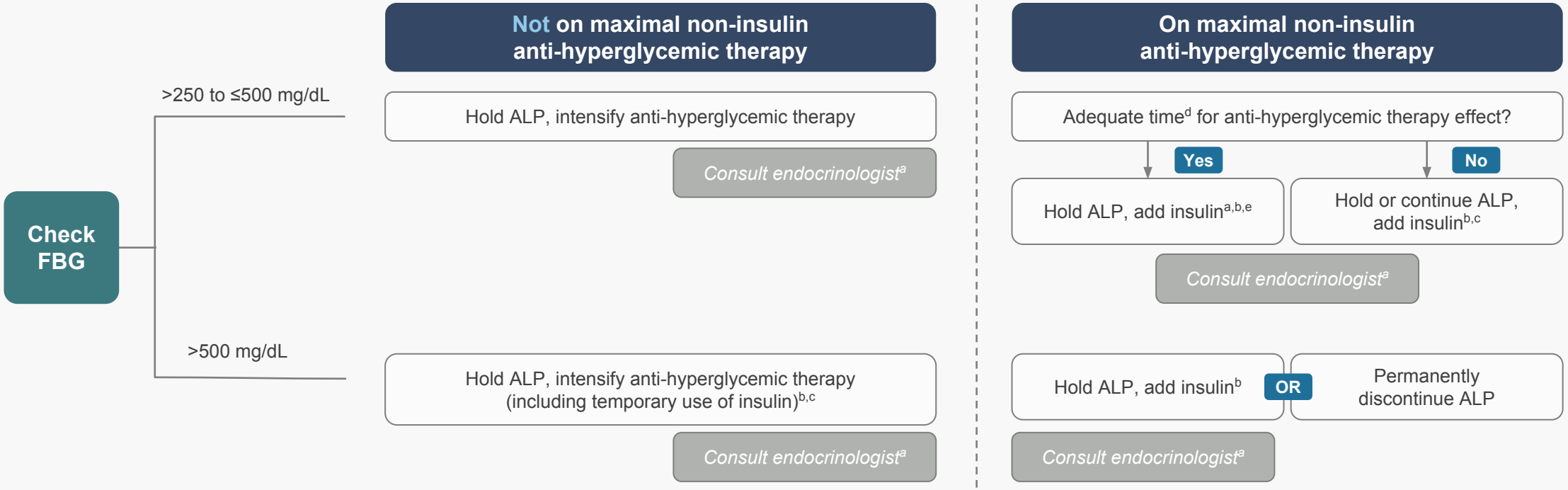
EXPERT RECOMMENDATIONS FOR MANAGING HYPERGLYCEMIA WITH ALPELISIB USING THE DELPHI TECHNIQUE (4 of 5)

Consensus treatment algorithm for the management of subsequent episodes of hyperglycemia associated with alpelisib (2 of 2)[1]



The information on this slide does not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information.

[a] Or have the patient evaluated in the emergency department if circumstances warrant it. [b] Insulin may reverse catabolic weight loss caused by sustained hyperglycemia. Exercise caution on the use of insulin when holding ALP. Holding ALP may likely cause hyperglycemia to resolve, and adding insulin may lead to hypoglycemia. [c] Depending upon individual patient circumstances. Insulin can achieve rapid control of hyperglycemia but carries the potential risk of PI3K pathway stimulation.[2] [d] Metformin: 2 weeks, SGLT2i: 2 days, DPP4i: 1 week, TZDs: 6 weeks, GLP-1 RA: 1 week. [e] It may also be appropriate to continue ALP and add standing insulin. ALP=alpelisib; DPP4i=dipeptidyl peptidase-4 inhibitor; FBG=fasting blood glucose; GLP-1 RA=glucagon-like peptide 1 receptor agonist; HbA1c=glycosylated hemoglobin; SGLT2i=sodium-glucose co-transporter 2 inhibitor; TZD=thiazolidinedione; ULN=upper limit of normal.

1. Gallagher EJ, et al. *NPJ Breast Cancer*. 2024;10(1):12. 2. Goncalves MD, et al. *N Engl J Med*. 2018;379:2052–2062.

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EXPERT RECOMMENDATIONS FOR MANAGING HYPERGLYCEMIA WITH ALPELISIB USING THE DELPHI TECHNIQUE (5 of 5)

- On the basis of expert consensus, patients who are ≥70 years old, have obesity (BMI ≥30 kg/m^2), and HbA1c 5.7–6.4% are considered at highest risk for developing new-onset hyperglycemia, and the recommendation is to refer these patients for endocrinology evaluation before initiating alpelisib
- Providers can consider initiating prophylactic metformin therapy (dose escalation as needed up to 2000 or 2500 mg/day if GFR is >45 mL/min/1.73 m^2) with or without a second-line agent, such as an SGLT2i or a TZD, for patients at high risk waiting for endocrinology evaluation
- The panel agreed that prior to starting alpelisib, it is appropriate to recommend a low-carbohydrate diet (60–130 g/day) for all patients and consult a dietician as needed
- Prophylactic metformin (short-acting or extended-release) is recommended for all patients with baseline HbA1c of 5.7–6.4%, and it may be appropriate for patients with HbA1c <5.7%. In patients at highest risk for developing hyperglycemia, there was disagreement on recommending prophylactic metformin and a second antihyperglycemic agent
- For most patients on alpelisib, the panel recommended weekly FBG monitoring, which can be done using a point-of-care glucose monitor. For patients with an intermediate risk of developing hyperglycemia (obesity and HbA1c 5.7–6.4%), twice-weekly FBG monitoring is preferred. For patients at highest risk of developing hyperglycemia, daily FBG monitoring is recommended; daily and twice-weekly monitoring can also be done with an at-home glucose monitor. If persistent hyperglycemia develops, testing blood glucose twice daily may be considered, once before breakfast with ≥8 hours of fasting prior to testing and once before dinner without fasting
- For patients who developed hyperglycemia while on alpelisib, metformin (short-acting or extended-release) is the preferred first-line anti-hyperglycemic agent. Metformin may be increased up to 2000 mg/day (provided a GFR of >45 mL/min/1.73 m^2), or up to 2500 mg/day. However, experts suggested that the efficacy of 2500 mg/day may not be improved over 2000 mg/day. Either an SGLT2i or a TZD is an appropriate second- or third-line agent, or first-line therapy in patients who cannot tolerate metformin. GLP-1 RA may also be appropriate in these settings if the patient is not experiencing significant gastrointestinal side effects or weight loss. Insulin, sulfonylureas, and DPP4i are generally not appropriate first- or second-line agents. A DPP4i may be an appropriate third-line agent

The information on this slide does not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information.

AE=adverse event; BMI=body mass index; DPP4 dipeptidyl peptidase-4; FBG=fasting blood glucose; GFR=glomerular filtration rate; GLP-1 RA=glucagon-like peptide 1 receptor agonist; HbA1c=glycosylated hemoglobin; i=inhibitor; SGLT2=sodium-glucose co-transporter 2 inhibitor; TZD=thiazolidinedione.

Gallagher EJ, et al. *NPJ Breast Cancer*. 2024;10(1):12.

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METALLICA STUDY DESIGN

Phase 2, single-arm IIS: alpelisib[a] + ET + prophylactic metformin in *PIK3CA*mut HR+/HER2− advanced BC (across 18 sites in Spain only)

Key eligibility criteria

***PIK3CA*mut, HR+/HER2− advanced BC determined on the most recent tumor tissue specimen or plasma ctDNA**

Measurable disease

- ECOG PS of 0 or 1
- Progression during/within 12 months of adjuvant endocrine therapy completion
- ≤1 prior chemotherapy-containing regimen for advanced BC

N=68

Cohort A (normal glycemia)
FPG < 100 mg/dL (5.6 mmol/L) and HbA1c < 5.7%

Cohort B (prediabetes)
FPG 100–140 mg/dL (5.6–7.8 mmol/L) and HbA1c 5.7–6.4%

C1D1 to C1D7: **Metformin** (500 mg PO, BID on D1–3; 1000 mg BID thereafter) **+ ET[b]**

C1D8 to CxDx: **Metformin** (1000 mg PO BID) **+ ET[b] + alpelisib** (300 mg PO, QD starting from C1D8)

Until PD or toxicity

Stratification factors

Visceral disease (yes vs no)

Region (Spain)

Endocrine resistance

- **Primary:** relapse while on the first 2 years of adjuvant ET or progression within the first 6 months of first-line ET for metastatic disease while on ET
- **Secondary:** relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET or progression ≥6 months after initiating ET for metastatic disease, while on ET

Endpoints

Primary

Incidence rate of grades 3–4 hyperglycemia per CTCAE v.4.03 in the first 8 weeks (two cycles) for both cohorts

Key secondary

PFS • ORR, CBR, TTP • Overall safety

Enrollment period: August 2020 to March 2022.

The information on this slide does not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information. [a] Alpelisib is a Novartis drug. [b] ET chosen by the physician was one of the following: fulvestrant (500 mg, intramuscular injection every 2 weeks during the first month, and every 4 weeks thereafter); letrozole (2.5 mg, orally, once daily); or exemestane (25 mg, orally, once daily). Addl=additional; AE=adverse event; BC=breast cancer; BID=twice daily; C=cycle; CBR=clinical benefit rate; CTCAE v4.03=Common Terminology Criteria for Adverse Events version 4.03; ctDNA=circulating tumor DNA; D=day; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; FPG=fasting plasma glucose; HbA1c=glycosylated hemoglobin; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IIS=investigator-initiated study; mut=mutation; ORR=overall response rate; PD=progressive disease; PFS=progression-free survival; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO=by mouth; QD=daily; TTP=time to progression. Llombart-Cussac A, et al. *EClinicalMedicine*. 2024;71:102520.

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METALLICA: BLOOD GLUCOSE MONITORING

Fasting plasma glucose labs: at screening, Days 1 and 8 of Cycle 1 and Day 1 of every subsequent cycle

Self-monitoring blood glucose:

- 6 times/day at C1D8 and C2D1: before and 90 minutes after the start of breakfast, lunch, and dinner
- 4 times/day C1D9, C1D10, and C2D2, C2D3: before breakfast, before lunch, before dinner, and at bedtime
- Daily (fasting, before breakfast) on C1D11–15, C1D21, C2D4–8, C2D15, and C2D21

Patients should contact HCP if fasting blood glucose is ≥160 mg/dL

The information on this slide does not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information.
AE=adverse event; BC=breast cancer; BID=twice daily; C=cycle; D=day; HCP=health care professional.
Llombart-Cussac A, et al. *EClinicalMedicine*. 2024;71:102520.

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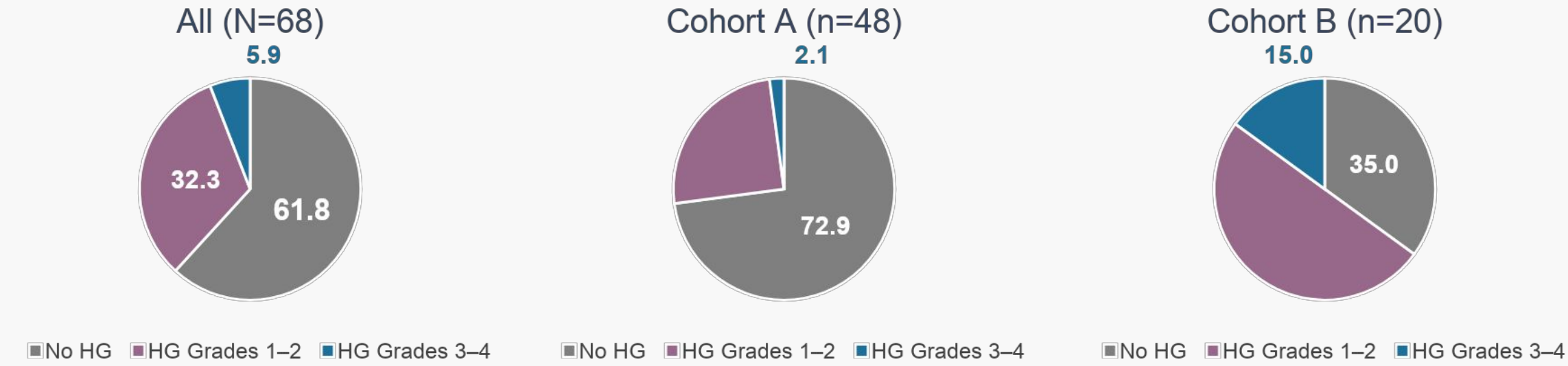
METALLICA STUDY RESULTS

Phase 2 alpelisib[a] + ET + prophylactic metformin in *PIK3CA*mut HR+/HER2− advanced BC

Primary endpoint: incidence rate of grades 3–4 hyperglycemia[b] per CTCAE v.4.03 in the first 8 weeks (two cycles)



Percentages may not total 100% due to rounding

Cohorts A and B met the primary endpoint, with only one grade 3 hyperglycemia (2.1%) in Cohort A and 3 patients with grade 3 hyperglycemia reported (15.0%) in Cohort B in the first 8 weeks

The information on this slide does not include or address inavolisib, and it is not known if these guidelines or outcomes would apply to inavolisib. Please refer to the Itovebi Prescribing Information for inavolisib-specific information.

[a] Alpelisib is a Novartis drug. [b] Glycemia was monitored by combining laboratory assessment of FPG (at screening, Days 1 and 8 of Cycle 1 and Day 1 of every subsequent cycle) and capillary SMBG. SMBG was conducted 6 times per day on Day 8 of Cycle 1 and Day 1 of Cycle 2; 4 times per day on Days 9 and 10 of Cycle 1 and Days 2 and 3 of Cycle 2; and once per day (fasting, before breakfast) on Days 11–15 and Day 21 of Cycle 1 and Days 4–8, 15, and 21 of Cycle 2. Patients were instructed to contact the treating physician if fasting blood glucose levels were 160 mg/dL.

Addl=additional; AE=adverse event; BC=breast cancer; CTCAE v.4.03=Common Terminology Criteria for Adverse Events, version 4.03; ET=endocrine therapy; FPG=fasting blood glucose; HER2=human epidermal growth factor receptor 2; HG=hyperglycemia; HR=hormone receptor; mut=mutation; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SMBG=self-monitoring blood glucose.

Llombart-Cussac A, et al. *EClinicalMedicine*. 2024;71:102520.

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MANAGEMENT OF STOMATITIS/ORAL MUCOSITIS IN INAVO120

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Veeva Document Number: M-US-00025445(v2.0)

WARNINGS & PRECAUTIONS FOR STOMATITIS

- Severe stomatitis can occur in patients treated with Itovebi.
- Stomatitis occurred in 51% of patients treated with Itovebi in combination with palbociclib and fulvestrant, including Grade 3 events in 6% of patients. The median time to first onset was 13 days (range: 1 to 610 days).
- Stomatitis led to interruption of Itovebi in 10%, to dose reduction in 3.7%, and to discontinuation of Itovebi in 0.6% of patients.
- In patients who received Itovebi in combination with palbociclib and fulvestrant, 38% used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis.
- Monitor patients for signs and symptoms of stomatitis. Withhold, reduce dose, or permanently discontinue Itovebi based on severity

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

MANAGEMENT OF STOMATITIS/ORAL MUCOSITIS IN THE INAVO120 STUDY[1,2]

Grade* and presenting symptoms	Actions	
	Initial inavolisib management	Monitoring and management recommendations
1 Asymptomatic or mild symptoms; intervention not indicated	**Continue** current dose level of inavolisib	• Initiate aggressive mouth care • Monitor symptoms and compliance with oral regimen • Re-evaluate within 48–72 hours
2 Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	**Interrupt** inavolisib	• Initiate aggressive mouth care • When stomatitis/oral mucositis improves to grade ≤1, **resume** inavolisib at the same dose • For recurrent grade 2 stomatitis or oral mucositis within 30 days, **reduce** inavolisib dose by one dose level
3 Severe pain; interfering with oral intake	**Interrupt** inavolisib	• Initiate aggressive mouth care • When stomatitis/oral mucositis improves to grade ≤1, resume inavolisib at a **reduced** dose by one dose level • Interrupt palbociclib until recovery to grade ≤2; then may resume palbociclib per local prescribing information[a]
4 Life-threatening consequences; urgent intervention indicated	**Permanently discontinue** inavolisib	• Initiate aggressive mouth care • Manage palbociclib per local prescribing information

Aggressive mouth care should be implemented early to help manage or prevent symptoms

- Aggressive mouth care includes dexamethasone alcohol-free mouthwash (0.5 mg/5 mL) for prophylaxis or treatment
  - Per the SWISH study, patients may use 4 times daily for 8 weeks (10 mL swished for 2 min and spat out), started concurrently with treatment and/or used reactively with first appearance of symptoms
  - No food or drink should be consumed for ≥1 hr after
- Additional mouthwash formulations (eg, combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal, and/or antibiotics) or topical corticosteroids (eg, triamcinolone acetonide, 0.05%–0.5%; fluocinolone acetonide, 0.025%–0.05%; clobetasol propionate, 0.025%) may be implemented
- Avoid alcohol-, hydrogen peroxide-, iodine-, or thyme-containing products, because they may exacerbate the condition. Avoid harsh mouthwashes (eg, Listerine®)
- Diet should be modified (eg, avoidance of spicy foods)

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. Refer to full prescribing information of the individual mouthwash and/or topical corticosteroid agents for dosing guidelines.

*Based on NCI CTCAE v5.0. [a] Consider whether the event is due to inavolisib, palbociclib, or both. Initial dose modification(s) should be made to the agent(s) contributing to the event, and if unknown, consider adjusting both. Addl=additional; AE=adverse event; CTCAE v5.0=Common Terminology Criteria for Adverse Events version 5.0; HCP=health care provider; mgmt.=management; NCI=National Cancer Institute.

1. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025. 2. Rugo H, et al. Lancet Oncol. 2017;18:P654–662.

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MANAGEMENT OF DIARRHEA IN INAVO120

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WARNINGS & PRECAUTIONS FOR DIARRHEA

- Severe diarrhea, including dehydration and acute kidney injury, can occur in patients treated with Itovebi.

- Diarrhea occurred in 48% of patients treated with Itovebi in combination with palbociclib and fulvestrant, including Grade 3 events in 3.7% of patients. The median time to first onset was 15 days (range: 2 to 602 days). Anti-diarrheal medicines were used in 28% (46/162) of patients who received Itovebi in combination with palbociclib and fulvestrant to manage symptoms. Dose interruptions were required in 7% of patients, and dose reductions occurred in 1.2% of patients.

- Monitor patients for signs and symptoms of diarrhea. Advise patients to increase oral fluids and start anti-diarrheal treatment at the first sign of diarrhea while taking Itovebi. Withhold, reduce dose, or permanently discontinue Itovebi based on severity

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

MANAGEMENT OF DIARRHEA IN THE INAVO120 STUDY

Adequate treatment with anti-diarrheals	Loperamide (Imodium®) dose with 4 mg, then 2 mg with every loose stool up to 16 mg/day. May consider using combination of loperamide and Lomotil® (diphenoxylate and atropine) or codeine phosphate. Monitor closely for dehydration or constipation. May initiate 2L therapy (eg, octreotide) if grade ≥2 diarrhea persists after 48 hr of treatment with loperamide and/or Lomotil
Maximum supportive care	Supportive care: initiate appropriate dietary modification, hydration therapy, and electrolyte supplements when clinically indicated. Dietary modification includes stopping all lactose-containing products and eating small meals. Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade®

Grade*	Actions	
	Initial inavolisib management	Monitoring and management recommendations
1	**Continue** current dose level of inavolisib	Adequate treatment with anti-diarrheal medications and maximum supportive care
2	**Interrupt** inavolisib	• Adequate treatment with anti-diarrheals[a] and maximum supportive care • Close monitoring • When diarrhea recovers to grade ≤1, may **resume** inavolisib at the same dose • If diarrhea recurs within 30 days, reduce inavolisib by one dose level
3	**Interrupt** inavolisib	• When diarrhea recovers to grade ≤1, **reduce** inavolisib by one dose level • Interrupt palbociclib until grade ≤2, and manage per local prescribing information[a] • Manage per grade 2 diarrhea guidelines • If diarrhea recurs within 30 days after the first dose reduction, **reduce** inavolisib by one dose level • If diarrhea recurs within 30 days after the second dose reduction, **permanently discontinue** inavolisib
4	**Permanently discontinue** inavolisib	Manage palbociclib per local prescribing information

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. Refer to the full prescribing information of the individual anti-diarrheal agents for dosing guidelines.

*Based on NCI CTCAE v5.0. [a] Consider whether the event is due to inavolisib, palbociclib, or both. Initial dose modification(s) should be made to the agent(s) contributing to the event, and if unknown, consider adjusting both.

2L=second-line; addl=additional; AE=adverse event; CTCAE v5.0=Common Terminology Criteria for Adverse Events version 5.0; HCP=health care provider; mgmt=management; NCI=National Cancer Institute. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025.

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MANAGEMENT OF RASH IN INAVO120

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MANAGEMENT OF RASH IN THE INAVO120 STUDY[1]

Grade*	Actions	
	Initial inavolisib management	Monitoring and management recommendations
1	**Continue** inavolisib	• Monitor for changes in severity • Consider prescribing topical corticosteroids[a] and/or antihistamines
2	**Interrupt** inavolisib	Treat rash per SOC, including topical and oral corticosteroids[b] and antihistamines → • When rash resolves to grade ≤1, **resume** inavolisib at the same dose or one dose level lower per investigator evaluation • If grade 2 rash recurs within 30 days, **reduce** inavolisib by one dose level when treatment resumes
3	**Interrupt** inavolisib	• Interrupt palbociclib until recovery to grade ≤2 and manage per local prescribing information[c] • Treat rash with topical and/or systemic corticosteroids (oral or IV)[b] and antihistamines • Refer to dermatologist for consultation and skin biopsy → If rash resolves to grade ≤1 within 30 days, **reduce** inavolisib/placebo by one dose level when treatment resumes → If rash does not resolve to grade ≤1 within 30 days, **discontinue** inavolisib

- In the INAVO120 study, rash was most commonly treated with topical corticosteroids[2]
- Patients with severe rash should also be monitored for associated signs and symptoms, such as fever and hypotension, that may be suggestive of a systemic hypersensitivity reaction
- Permanently discontinue treatment for any rash with concurrent signs/symptoms strongly suggestive of a severe Type I hypersensitivity or anaphylactic/anaphylactoid reaction or with painful desquamation or mucosal involvement suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis or with other life-threatening complications
- Dermatological consultation is recommended

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. Refer to full prescribing information of the individual corticosteroid and antihistamine agents for dosing guidelines.

*Based on NCI CTCAE v5.0. [a] Suggested topical steroids include hydrocortisone 2.5% to face 2× daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body 2× daily. [b] Suggested oral steroids include methylprednisolone dose pack or prednisone 60 mg daily, followed by taper (eg, 60 mg × 2 days, 40 mg × 2 days, 20 mg × 2 days). [c] Consider whether the event is due to inavolisib, palbociclib, or both. Initial dose modification(s) should be made to the agent(s) contributing to the event, and if unknown, consider adjusting both. Addl=additional; AE=adverse event; CTCAE v5.0=Common Terminology Criteria for Adverse Events version 5.0; HCP=health care provider; IV=intravenous; mgmt.=management; NCI=National Cancer Institute; SOC=standard of care. 1. F. Hoffmann-La Roche Ltd. INAVO120 study protocol. Available at https://clinicaltrials.gov/study/NCT04191499. Accessed April 24, 2025. 2. Juric D, et al. Presented at: American Society of Medical Oncology; May 31–June 4, 2024; Chicago, IL.

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