itovebi™
inavolisib 3 mg • 9 mg tablets

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NOW APPROVED

- In combination with palbociclib and fulvestrant
- For 1L HR+/HER2- mBC
- With *PIK3CA* mutation and endocrine resistance[1]*

*Progression during or within 12 months of completing adjuvant endocrine therapy.

PIK3CA mutations and endocrine resistance can lead to a poor prognosis in mBC[2,3]
Choose the powerful efficacy of the Itovebi regimen[1]

- The FIRST and ONLY regimen with **>2x mPFS** vs palbociclib and fulvestrant:
  15.0 months (95% CI: 11.3-20.5) **vs 7.3 months** (95% CI: 5.6-9.3); **HR=0.43** (95% CI: 0.32-0.59), *P*<0.0001

Clinical safety profile[1]

- **Most adverse reactions were mild to moderate** (grade 1-2)
- **Low permanent discontinuation rate** (6%) due to any adverse reactions

Test for *PIK3CA* mutations at HR+/HER2- mBC diagnosis

1L=first-line; CI=confidence interval; HER2-=human epidermal growth factor receptor 2-negative; HR=hazard ratio; HR+=hormone receptor-positive; mBC=metastatic breast cancer; mPFS=median progression-free survival; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Indication

Itovebi (inavolisib), in combination with palbociclib and fulvestrant, is indicated 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.

Important Safety Information

Warnings and Precautions

Itovebi has warnings and precautions for hyperglycemia, stomatitis, diarrhea, and embryo-fetal toxicity.

Hyperglycemia

Severe hyperglycemia can occur in patients treated with Itovebi.

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.

Choose the powerful efficacy of the Itovebi regimen

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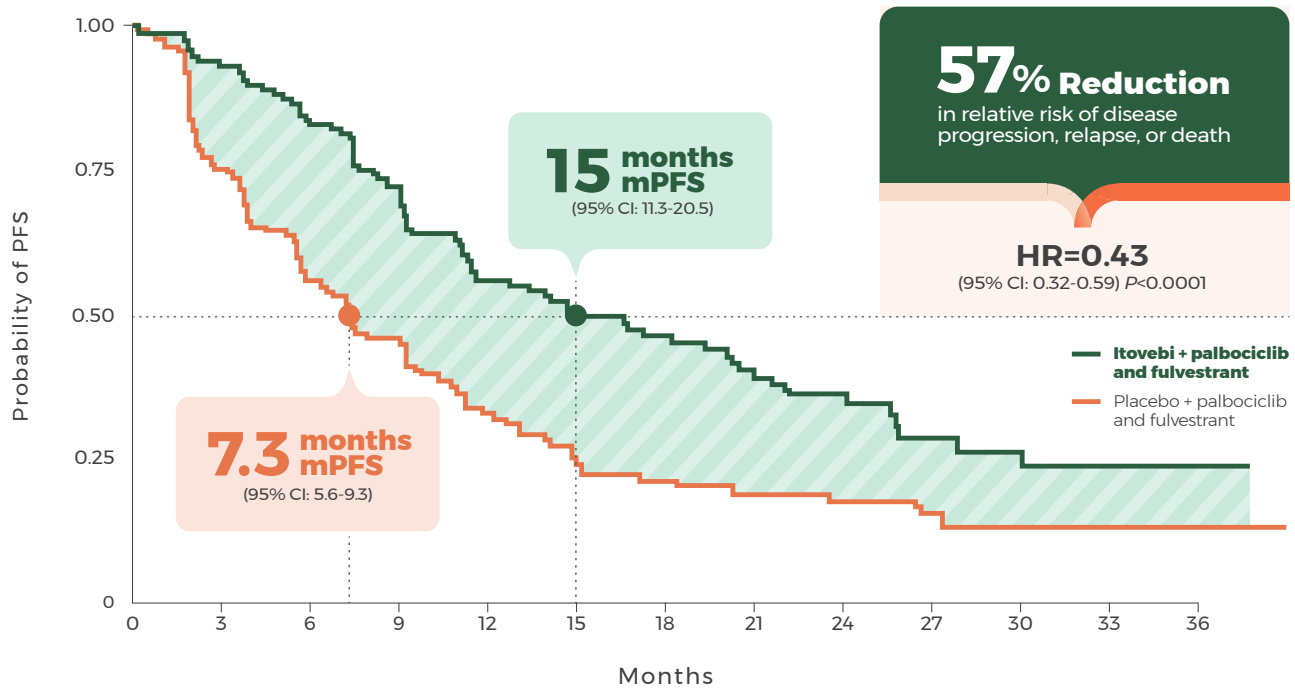
Study design[1]

INAVO120 was a phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of Itovebi in combination with palbociclib and fulvestrant in adult patients with *PIK3CA*-mutated, HR+/HER2- mBC whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. The primary endpoint was PFS by investigator assessment. Secondary endpoints included OS and investigator-assessed ORR and DOR.

Itovebi regimen more than doubled mPFS vs placebo + palbociclib and fulvestrant (primary endpoint)[1]

PROGRESSION-FREE SURVIVAL*†



Patients at risk													
Itovebi + palbociclib and fulvestrant	**161**	**134**	**111**	**92**	**66**	**48**	**41**	**31**	**22**	**13**	**11**	**5**	**1**
Placebo + palbociclib and fulvestrant	164	113	77	59	40	23	19	16	12	6	3	3	1

DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

21.3-month median follow-up.[4]

*Per RECIST version 1.1.[1]

†Based on investigator assessment.[1]

Important Safety Information

Warnings and Precautions *(cont'd)*

Hyperglycemia *(cont'd)*

In INAVO120, 46% (74/162) of patients who received Itovebi were treated with oral anti-hyperglycemic medications and 7% (11/162) were treated with insulin to manage increased fasting glucose. In patients who experienced increased fasting glucose of > 160 mg/dL, 96% (52/54) had an improvement in fasting glucose of at least one grade level with a median time to improvement from the first event of 8 days (range: 2 to 43 days). Among patients with hyperglycemia, the median time to first onset was 7 days (range: 2 to 955 days). Hyperglycemia led to dose interruption in 28%, to dose reduction in 2.5%, and to discontinuation of Itovebi in 1.2% of patients.

Please see Important Safety Information throughout, as well as the accompanying full Prescribing Information.

Choose the powerful efficacy of the Itovebi regimen *(cont'd)*

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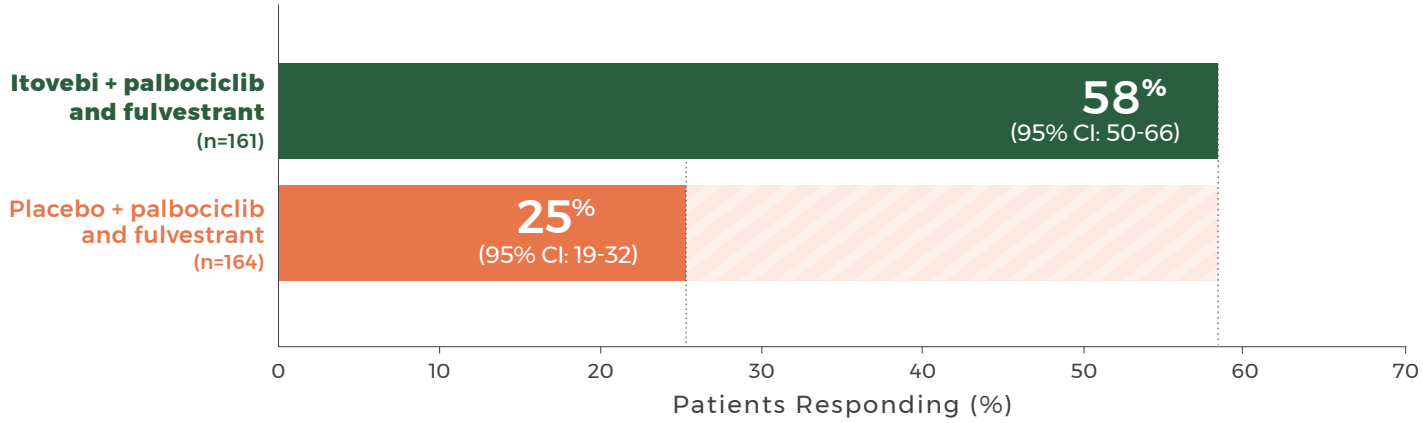
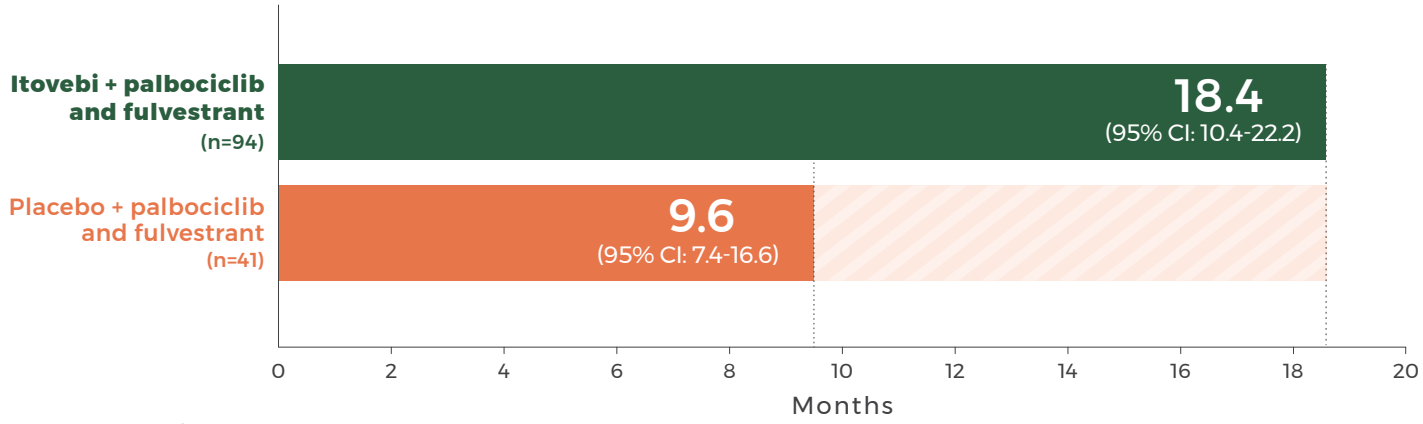
Itovebi regimen more than doubled ORR and nearly doubled mDOR vs placebo + palbociclib and fulvestrant (secondary endpoints)[1]

OBJECTIVE RESPONSE RATE*†‡



MEDIAN DURATION OF RESPONSE†



21.3-month median follow-up.[4]

OS data were immature at the time of the primary analysis of PFS.[1]

mDOR=median duration of response.
*ORR was defined as the proportion of patients with a complete response or partial response on two consecutive occasions ≥4 weeks apart per RECIST v1.1.[4]
†Based on investigator assessment.[1]
‡Based on confirmed ORR.[1]

Important Safety Information

Warnings and Precautions *(cont'd)*

Hyperglycemia *(cont'd)*

The safety of Itovebi in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment have not been studied.

Before initiating treatment with Itovebi, test fasting glucose levels (FPG or FBG), HbA_{1C} 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 HbA_{1C} every 3 months and as clinically indicated.

Please see Important Safety Information throughout, as well as the accompanying full Prescribing Information.

Low permanent discontinuation rate (6%) due to any adverse reactions[1]

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Most adverse reactions (ARs) were mild to moderate (grade 1-2) in the Itovebi arm of INAVO120[1]

The most common (≥20%) adverse reactions, including laboratory abnormalities, were:

Decreased neutrophils	95%	Decreased calcium	42%	Decreased magnesium	27%
Decreased hemoglobin	88%	Fatigue	38%	Rash	26%
Increased fasting glucose	85%	Decreased potassium	38%	Decreased appetite	24%
Decreased platelets	84%	Increased creatinine	38%	COVID-19 infection	23%
Decreased lymphocytes	72%	Increased ALT	34%	Headache	22%
Stomatitis	51%	Nausea	28%		
Diarrhea	48%	Decreased sodium	28%		

ALT=alanine aminotransferase.

- Management of ARs, including hyperglycemia, diarrhea, and stomatitis may require temporary interruption, dose reduction, or discontinuation of Itovebi
- Adverse reactions leading to discontinuation of Itovebi were hyperglycemia (1.2%), stomatitis, gastric ulcer, intestinal perforation, anal abscess, increased ALT, decreased weight, bone pain, musculoskeletal pain, transitional cell carcinoma, and acute kidney injury (0.6% each)

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Important Safety Information

Warnings and Precautions *(cont'd)*

Hyperglycemia *(cont'd)*

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.

Important Safety Information

Warnings and Precautions *(cont'd)*

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.

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%.

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.

Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, Itovebi can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, oral administration of inavolisib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, structural abnormalities, and alterations to growth at maternal exposures approximately equivalent to the human exposure at the recommended dose of 9 mg/day based on area under the curve (AUC).

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with Itovebi and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Itovebi and for 1 week after the last dose.

Most Common Adverse Reactions

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see the accompanying full Prescribing Information for additional Important Safety Information.

References: 1. Itovebi Prescribing Information. Genentech, Inc. 2024. **2.** Lambertini M, Blondeaux E, Bisagni G, et al. Prognostic and clinical impact of the endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer: an individual patient-level analysis from the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) studies. *EClinicalMedicine*. 2023;59:101931. **3.** Fillbrunn M, Signorovitch J, André F, et al. PIK3CA mutation status, progression and survival in advanced HR+/HER2- breast cancer: a meta-analysis of published clinical trials. *BMC Cancer*. 2022;22(1):1002. **4.** Jhaveri KL, Im S-A, Saura C, et al. Inavolisib or placebo in combination with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer: phase III INAVO120 primary analysis. Abstract presented at San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX.

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