

Inavolisib (ITOVEBI) in Breast Cancer

National Drug Monograph

August 2026

VA Pharmacy Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA PRESCRIBING INFORMATION¹

Description / MOA	Inavolisib is a highly selective PI3K inhibitor that targets PI3K α . When used in combination with palbociclib and fulvestrant, the addition of inavolisib was found to increase inhibition of tumor growth more than each combination alone or as doublet combinations.
Indication Under Review	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
Dosage Regimen	9 mg orally once daily with or without food until disease progression or unacceptable toxicity
Under Review	Oral tablets, 3 mg and 9 mg (28 tablets per bottle)
Pretreatment Procedures	<ul style="list-style-type: none"> Test fasting glucose levels (FPG or FBG), HbA1C levels, and optimize fasting glucose before initiating due to the potential for hyperglycemia Verify pregnancy status in females of reproductive potential prior to initiating treatment

EFFICACY CONSIDERATIONS

Trial	INAVO120: Trial of first-line inavolisib/placebo + palbociclib + fulvestrant in patients with PIK3CA-mutated, Hormone Receptor-positive (HR+), Human Epidermal Growth Factor Receptor 2-negative (HER2-), endocrine-resistant advanced breast cancer²
Design	Phase 3, double-blind, placebo controlled, randomized trial, in 28 countries
Population	Inclusion: PIK3CA-mutated, HR+, HER2- locally advanced or metastatic breast cancer, measurable disease (RECIST v1.1), disease progression during or within 12 months of adjuvant endocrine therapy completion (endocrine-resistant disease), no prior therapies for advanced breast cancer, FBG <126mg/dL and HbA1c <6% <ul style="list-style-type: none"> Women with any menopausal status and men were eligible Key exclusion: type 1 diabetes mellitus or type 2 diabetes mellitus that required ongoing treatment at the start of study treatment, metastatic breast cancer
Demographics	Median age 54 yrs (range 27-79); female 98.2% (60% postmenopausal); White 58.8%, Asian 38.2%; ECOG score 0-1; ≥ 3 organs with metastases 51.4%; visceral disease 80%; ER+ PR+ 69.5%, ER+ PR-27.7%, primary endocrine resistance 34.2, secondary endocrine resistance 65.5%
Intervention	Treatment cycles were 28 days each. Inavolisib 9mg PO daily (on days 1-28) with palbociclib 125mg PO (on days 1-21) and fulvestrant 500mg IM on days 1 and 15 of cycle 1 and every ~4 weeks thereafter
Comparator	Placebo (once daily) with the same dose of palbociclib and fulvestrant
Results	Primary end point: progression-free survival (PFS) Secondary end points: overall survival (OS), objective response (ORR) and duration of response

per updated analysis
July 2025

Outcome	Inavolisib/palbociclib/fulvestrant [95% CI] n=161	Placebo/palbociclib/fulvestrant [95% CI] n=164	Significance
Primary: Median PFS (months)	17.2 [11.6-22.2]	7.3 [5.9-9.2]	HR: 0.42 [0.32-0.55] P<0.001 [^]
Secondary: Median OS (months)	34.0 [28.4-44.8]	27.0 [22.8-38.7]	HR: 0.67 [0.48-0.94], P=0.02*
Secondary: Median DoR (months)	19.2 [14.7-28.3]	11.1 [8.5-20.2]	N/A
Secondary: OR (% of patients)	62.7 [54.8-70.2]	28.0 [21.3-35.6]	P<0.001
Median Follow Up (months)	34.2	32.3	N/A

[^] Consistent with the results of the primary analysis which showed statistical significance

* Prespecified boundary for statistical significance = P<0.0469

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	None

Other Warnings	<ul style="list-style-type: none"> • Hyperglycemia: Initiate or optimize anti-hyperglycemic medications as clinically indicated; reserve insulin as last-line.^{6,7} Interrupt, reduce dose, or discontinue if severe hyperglycemia occurs. • Stomatitis: Consider a corticosteroid-containing mouthwash if stomatitis occurs. Monitor patients for signs and symptoms of stomatitis. Withhold, reduce dose, or permanently discontinue based on severity. • Diarrhea: May be severe and can result in dehydration or AKI. Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their healthcare provider if severe diarrhea occurs. Interrupt, reduce dose, or discontinue if severe diarrhea occurs. • Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective non-hormonal contraception.
Most common AR (≥20%)	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
Safety	Inavolisib/palbociclib/fulvestrant vs. placebo/palbociclib/fulvestrant DC due to AEs: 6.8 vs. 0.6%; Serious AEs: 27 vs. 13%; Fatal events 3.7 vs. 1.2% None deemed to be related to study drug.
Drug Interactions	<ul style="list-style-type: none"> • CYP3A and CYP2B6 inducer; Time-dependent inhibitor of CYP3A • Substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)
Pregnancy	Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective non-hormonal contraception.
Lactation	Advise women not to breastfeed during treatment and for 1 week after the last dose.

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY: HR +, HER2 NEGATIVE, RECURRENT UNRESECTABLE OR STAGE IV (M1) BREAST CANCER					
DRUG REGIMEN	VANF	CFU	FDA APPROVED INDICATIONS	TRIAL OUTCOMES/ Other considerations	NCCN CATEGORY
Inavolisib/Palbociclib*/ Fulvestrant* vs. Placebo/ Palbociclib/ Fulvestrant	NF	No	PIK3CA-mutated, HR+, HER2-, endocrine-resistant advanced or metastatic breast cancer ^1	INAVO120 (1L mBC setting) PFS (months): 17.2 vs. 7.3 HR: 0.42 [0.32-0.55] p<0.001 No prior CDK4/6i in study pop'n mOS 34 vs. 27 mos HR: 0.67 [0.48-0.94], P=0.02	Category 1, Preferred
	VA BCCP:		Has not been added to VA BCCP at this time; topic has not been reviewed; on agenda for next quarterly review; recommendations from pathway team may change at that time.		
Alpelisib/Fulvestrant* vs. Placebo/Fulvestrant	NF	Yes	HR+, HER2-, PIK3CA-mutated, advanced or metastatic breast cancer ^2	SOLAR-1 (2L post-AI setting) PFS (months): 11 vs. 5.7 HR 0.65 [0.50-0.85] p=0.0013 mOS 39 vs. 31 mos HR 0.85; p=0.15 (NS) 25% AE discontinuation rate	Category 1, Preferred
	VA BCCP:		Pathway directs to Alpelisib/Fulvestrant in patients with stage IV ER+ or PR+/HER2- who are >12 months since prior adjuvant therapy or newly diagnosed, after a trial of Anastrozole/ ribociclib or Fulvestrant/ribociclib with PIK3CA mutation identified		
Capivasertib/Fulvestrant* vs. Placebo/Fulvestrant	NF	Yes	HR+, HER2- locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/ PTEN- alterations^3	CAPitello-291 (2L post-AI +/- CDK4/6i) PFS (months): 7.3 vs. 3.1 HR: 0.50 [0.38-0.65] p <0.001 mOS data immature With/without CDK4/6i population	Category 1, Preferred
	VA BCCP:		Pathway directs to Capivasertib/Fulvestrant in patients with stage IV ER+ or PR+/HER2- who are >12 months since prior adjuvant therapy or newly diagnosed, after trial of Anastrozole/ribociclib or Fulvestrant/ribociclib with AKT or PTEN mutation identified		

*Indicates the medication is on formulary

VABCCP: VA Breast Cancer Clinical Pathway

POTENTIAL PLACE IN THERAPY OF INAVOLISIB

- Inavolisib (along with palbociclib + fulvestrant) is the first PI3K inhibitor-based triple regimen approved for initial, first-line treatment of endocrine-resistant metastatic disease. Inavolisib triple therapy has higher median PFS compared to dual, preferred regimens. An overall survival benefit was demonstrated in the INAVO trial that was not shown in the SOLAR and CAPItello trials.
- First-line positioning in the NCCN guidelines demonstrates inavolisib-based therapy meets a need for patients with endocrine-resistant, PIK3CA mutations, and metastatic disease upon initial presentation.
- Inavolisib was better tolerated overall than dual regimens (less frequent incidence of Grade 3-4 rash, diarrhea, and discontinuation due to adverse effects). Additionally, there were less frequent occurrences of Grade 3-4 hyperglycemia than alpelisib + fulvestrant (but higher than capivasertib + fulvestrant).
- Patient must have mutation testing completed via a specific assay. Close monitoring is required due to high-grade neutropenia from the palbociclib component.
- Some populations have limited data available, including patients >65 years of age (subgroup was small but analysis showed possible attenuated benefit in this age group) and in patients previously exposed to CD4 4/6 inhibitors.
- Inavolisib triple therapy would be most appropriate for those with the PIK3CA biomarkers that have not had exposure to CDK 4/6 (alpelisib + fulvestrant still best in this case).

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