Dana-Farber Cancer Institute | Susan F. Smith Center for Women's Cancers

Dana-Farber Breast Oncology Center

Consensus Statement Regarding Use of Inavolisib, Palbociclib, and Fulvestrant in Patients with Hormone Receptor-Positive/ HER2-negative Metastatic Breast Cancer

Consensus: Obtained at Breast Oncology Center meetings on 11/22/2024, 2/7/2025, and 4/18/2025.

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Q2. Should inavolisib be used in patients with prior systemic treatments in the metastatic setting (> 1 prior lines of therapy)?	Based on the available data, the combination of inavolisib, palbociclib, and fulvestrant should only be used as a first-line therapy for patients with *PIK3CA*-mutated HR+/HER2- metastatic breast cancer. There are insufficient data to support the use of inavolisib, palbociclib, and fulvestrant in patients with HR+/HER2- metastatic breast cancer who have received any prior lines of therapy in the metastatic setting, and the potential benefits in this population are unknown.
Q3. Is inavolisib appropriate for patients with fasting glucose > 126 mg/dL or HbA1c > 6.0% (diabetic or pre-diabetic patients)?	Treatment with inavolisib is not appropriate for patients meeting criteria for diabetes or pre-diabetes, specifically those with fasting glucose levels > 126 mg/dL or HbA1c levels > 6.0%.
Q4. What supportive measures should accompany inavolisib initiation to ensure safe and effective use?	To monitor for the development of hyperglycemia, patients' fasting blood glucose (FBG) and HbA1c should be monitored at the following timepoints: • FBG and HbA1c at baseline • FBG once every 3 days during week 1 of therapy • FBG once per week during weeks 2-4 of therapy • FBG once every 2 weeks during weeks 5-12 of therapy • FBG once every 4 weeks from week 13 onward as clinically indicated • Monitor HbA1c every 3 months Patients may evaluate FBG at home. To facilitate this, a glucometer, testing strips, and lancets (with patient counselling regarding proper testing procedures) should be made available to the patient. Metformin should be given to patients at high risk of hyperglycemia (BMI > 30 kg/m^2 or HbA1c > 5.7%). For these patients, initiate metformin extended release (ER) 500 mg daily. If this dose is well tolerated and FBG remains > 160 mg/dL, increase by 500 mg weekly up to a maximum dose of 2000 mg/day. • Metformin is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2 • For patients with eGFR 30-45 ml/min/1.73 m^2, do not exceed 1000 mg/day The following additional supportive care measures should be considered at the time of prescription: 1. Start cetirizine prophylactically to help prevent the development of a rash 2. Start dexamethasone mouthwash prophylactically (up to four times per day) to prevent the development of stomatitis 3. Prescribe loperamide to use as needed at the onset of diarrhea

Additional considerations:

- Two cases of life-threatening ketoacidosis have been reported in diabetic patients treated with inavolisib in the post-market setting.[1]
- Ketoacidosis is a medical emergency characterized by hyperglycemia, electrolyte derangements, metabolic acidosis, and ketonemia. 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.[1]
- Hyperglycemia is an identified risk associated with inavolisib and is included as a warning and precaution in the product information. In patients who experience hyperglycemia (including ketoacidosis), the recommended inavolisib dose modification guidance for hyperglycemia in the product information should be followed.[1]

Introduction

Hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer is the most common subtype, which comprises approximately 70% of invasive breast cancer cases.[2] For patients with HR+/HER2- metastatic breast cancer (MBC), the current standard of care first-line therapy is endocrine therapy, usually an aromatase inhibitor (AI), in combination with a CDK4/6 inhibitor.[3-7] Second- and later-line therapies are often selected based on the presence of actionable biomarkers, such as mutations in the ligand-binding domain of *ESR1*[8] or alterations in genes within the PI3K/AKT/mTOR pathway.[9-11]

The PI3K/AKT/mTOR pathway regulates cell growth, proliferation, and metabolism in response to upstream signals such as nutrients, hormones, and growth hormones. Genomic alterations that lead to hyperactivation of this pathway are common in HR+/HER2- MBC and can contribute to endocrine resistance.[12-15] For instance, approximately 35-40% of HR+/HER2- MBC patients have gain of function mutations in *PIK3CA*, which encodes the p110a subunit of PI3K.[16-19] *PIK3CA* mutations usually arise in the primary tumor, and thus can contribute to primary endocrine resistance.[20]

Several targeted therapies are available for HR+/HER2- MBC patients with *PIK3CA* mutations. Alpelisib is a PI3K inhibitor that is FDA approved in combination with fulvestrant for the treatment of postmenopausal patients with *PIK3CA*-mutant HR+/HER2- MBC who experienced disease progression on endocrine therapy.[21] Approval was based on the results of the randomized, double-blind, phase 3 SOLAR-1 trial, in which patients with *PIK3CA*-wild-type and *PIK3CA*-mutant HR+/HER2- MBC were enrolled into separate cohorts and randomized to receive alpelisib plus fulvestrant or placebo plus fulvestrant. Among patients with a *PIK3CA* mutation, the median progression-free survival (PFS) was 11.0 months in the alpelisib group and 5.7 months in the placebo group (HR: 0.65; 95% CI: 0.50 – 0.85; $p < 0.001$). There was no significant difference in PFS between treatment arms among patients with *PIK3CA*-wild-type disease (HR: 0.85; 95% CI: 0.58 – 1.25).[11]

Widespread use of alpelisib is limited by toxicity resulting from inhibition of wild-type PI3Kα. In the SOLAR-1 trial, all-grade adverse events included hyperglycemia (63.7% in the

alpelisib group versus 9.8% in the placebo group), diarrhea (57.7% vs. 15.7%), nausea (44.7% vs. 22.3%), decreased appetite (35.6% vs. 10.5%), rash (35.6% vs. 5.9%), and maculopapular rash (14.1% vs. 1.7%). Grade 3/4 adverse events included hyperglycemia (36.6% vs. 0.7%), rash (9.9% vs. 0.3%), maculopapular rash (8.8% vs. 0.3%), and diarrhea (6.7% vs. 0.3%). Permanent discontinuation of alpelisib or placebo due to adverse events occurred in 25.0% of patients in the alpelisib group and 4.2% in the placebo group.[11]

Capivasertib is a potent and selective inhibitor of all three isoforms of AKT.[22] HR+/HER2- MBC patients with disease progression on at least one line of endocrine therapy (with or without a CDK4/6 inhibitor) with at least one genomic alteration in *PIK3CA*, *AKT1*, or *PTEN* are eligible to receive capivasertib plus fulvestrant.[23] FDA approval was based on the results of the randomized phase 3 CAPItello-291 trial, in which HR+/HER2- MBC patients with disease progression on first-line AI (with or without a CDK4/6 inhibitor) were randomized 1:1 to receive capivasertib or placebo in combination with fulvestrant. Among 708 randomized patients, 289 (40.8%) had a PI3K/AKT/mTOR pathway alteration and 489 (69.1%) had received a prior CDK4/6 inhibitor in the metastatic setting. In the overall study population, the median PFS was 7.2 months (95% CI: 5.5 – 7.4) on capivasertib plus fulvestrant versus 3.6 months (95% CI: 2.8 – 3.7) on placebo plus fulvestrant (HR: 0.60; 95% CI: 0.51 – 0.71; $p < 0.001$). Among patients with PI3K/AKT/mTOR pathway alterations (including approximately 30% of patients with a *PIK3CA* mutation), the median PFS was 7.3 months (95% CI: 5.5 – 9.0) on capivasertib plus fulvestrant versus 3.1 months (95% CI: 2.0 – 3.7) on placebo plus fulvestrant (HR: 0.50; 95% CI: 0.38 – 0.65; $p < 0.001$). Among patients without AKT pathway alterations, the hazard ratio for benefit of capivasertib over placebo was 0.70 (95% CI: 0.56 – 0.88).[9]

In the CAPItello-291 trial, the most frequent all-grade adverse events on the capivasertib plus fulvestrant arm were diarrhea (72.4%), rash (38.0%), and nausea (34.6%). The most common grade $\geq$ 3 adverse events included rash (12.1%), diarrhea (9.3%), and hyperglycemia (2.3%). Adverse events leading to capivasertib dose reduction, interruption, and early discontinuation occurred in 19.7%, 38.9%, and 13.0% of participants on the capivasertib plus fulvestrant arm, respectively.[24]

Preclinical studies demonstrated synergistic activity with triplet combinations of endocrine therapy, CDK4/6 inhibitor, and PI3K inhibitors in *PIK3CA*-mutated breast cancer models.[25] Unfortunately, early clinical trials of these triplet combinations were hampered by significant toxicity.[26,27]

Inavolisib

Inavolisib is a potent, highly selective PI3Kα inhibitor with 300-fold greater affinity for PI3Kα over the other class I PI3K isoforms. In addition, inavolisib also induces the degradation of mutant p110α.[28] This dual mechanism of action was designed to enhance suppression of the PI3K/AKT/mTOR pathway and improve the therapeutic index, with the goal of enabling more effective and tolerable combination strategies in patients with *PIK3CA*-mutant HR+/HER2- MBC.[29]

INAVO120 is a randomized, double-blind, placebo-controlled, phase III trial comparing inavolisib, palbociclib, and fulvestrant to placebo, palbociclib, and fulvestrant as first-line therapy for patients with HR+/HER2- locally advanced or metastatic breast cancer with a *PIK3CA* mutation. Eligible patients had experienced disease progression on or within 12 months of completing adjuvant endocrine therapy and had received no prior therapies in the metastatic setting. Participants were stratified based on the presence of visceral metastases, primary versus secondary endocrine resistance, and geographic region. The trial enrolled 325 participants, who were randomized 1:1 to receive inavolisib (n = 161) or placebo (n = 164) in addition to palbociclib and fulvestrant. The primary endpoint was investigator-assessed PFS.[10]

After a median follow-up of 21.3 months in the inavolisib group and 21.5 months in the placebo group, the median PFS was 15.0 months (95% CI: 11.3 – 20.5) in the inavolisib group and 7.3 months (95% CI: 5.6 – 9.3) in the placebo group (HR: 0.43; 95% CI: 0.32 – 0.59; $p < 0.001$). In a landmark analysis, the 6-month, 12-month, and 18-month PFS was 82.9%, 55.9%, and 46.2% in the inavolisib group and 55.9%, 32.6%, and 21.1% in the placebo group. The objective response rate (ORR) was 58.4% in the inavolisib group and 20.5% in the placebo group. The median duration of response was 18.4 months in the inavolisib group and 9.6 months in the placebo group (HR: 0.57; 95% CI: 0.33 – 0.99).[10]

At the final overall survival (OS) analysis, after a median follow-up of 34.2 months in the inavolisib group and 32.3 months in the placebo group, the median OS was 34.0 months (95% CI: 28.4 – 44.8) in the inavolisib group and 27.0 months (95% CI: 22.8 – 38.7) in the placebo group (HR: 0.67, 95% CI: 0.48 – 0.94; $p = 0.02$). The ORR was 62.7% (95% CI: 54.8% - 70.2%) in the inavolisib group and 28.0% (95% CI: 21.3% - 35.6%) in the placebo group ($p < 0.001$). The updated median PFS was 17.2 months in the inavolisib group and 7.3 months in the placebo group (HR: 0.42, 95% CI: 0.32 – 0.55). The median duration of response was 19.2 months in the inavolisib group and 11.1 months in the placebo group.[30]

In terms of safety, patients treated with the inavolisib triplet combination had higher rates of all grade hyperglycemia (58.6% vs. 8.6% in the placebo arm), diarrhea (48.1% vs. 16.0%), and stomatitis (51.2% vs. 26.5%). Grade 3 or 4 hyperglycemia and stomatitis occurred in 5.6% of patients in the inavolisib arm, compared to 0% in the placebo arm. Use of supportive care medication for stomatitis and hyperglycemia was allowed but not mandated as prophylaxis. Hematologic toxicities, including neutropenia, were frequent and similar in both arms. Discontinuation of any trial agent due to adverse events occurred in 6.8% of patients in the inavolisib arm compared to 0.6% in the placebo arm.[11]

Based on the primary efficacy results of the INAVO120 trial, on October 10, 2024, the U.S. FDA approved inavolisib in combination with palbociclib and fulvestrant for the treatment of patients with HR+/HER2- locally advanced or metastatic breast cancer with a *PIK3CA* mutation as detected by the FDA-approved FoundationOne Liquid CDx companion assay. Patients must have endocrine-resistant disease, defined as recurrence on or after completing adjuvant endocrine therapy.[31]

Development of the Consensus Statements

Dana-Farber Cancer Institute's Breast Oncology Center (BOC) held multidisciplinary meetings on 11/22/2024, 2/7/2025, and 4/18/2025 to discuss recommendations for the use of inavolisib, palbociclib, and fulvestrant in patients with HR+/HER2- metastatic breast cancer. Data were reviewed from the INAVO120 trial. Additional relevant data were reviewed to address the questions in this document as noted below. The gathered evidence was presented for discussion to a multidisciplinary group, which included Dana-Farber physicians, nurses, clinical investigators, lab investigators, translational researchers, administrators, and patient advocates. The discussion and suggestions for improvements continued via email exchanges following the meeting. The final consensus statements were consolidated in April 2025.

The consensus statements can be subject to future variations and periodic updates, based on emerging evidence and new reports from ongoing clinical studies. Therefore, the information provided in this document should not be considered as being complete or inclusive of all proper assessments, treatments or methods of care or as a statement of the standard of care. This information does not mandate any particular course of medical care and is not intended to be a substitute for the independent professional judgment of a health care provider. The document is based on the opinion of a multidisciplinary team at Dana-Farber but does not represent the official institutional position and overall must be considered as a consensus based on the positions and ideas of the Dana-Farber providers.

Clinical Questions

This document summarizes the discussions and consensus among the Dana-Farber BOC group regarding the following clinical questions:

- **Q1. Should inavolisib be used in patients with recurrence after receiving prior exposure to CDK4/6 inhibitors, for example in the adjuvant setting?**
- **Q2. Should inavolisib be used in patients with prior systemic treatments in the metastatic setting (> 1 prior lines of therapy)?**
- **Q3. Is inavolisib appropriate for patients with fasting glucose > 126 mg/dL or HbA1c > 6.0% (diabetic or pre-diabetic patients)?**
- **Q4. What supportive measures should accompany inavolisib initiation to ensure safe and effective use?**

1. Should inavolisib be used in patients with recurrence after receiving prior exposure to CDK4/6 inhibitors, for example in the adjuvant setting?

Currently, two CDK4/6 inhibitors are FDA-approved in the adjuvant setting for patients with early-stage HR+/HER2- breast cancer: abemaciclib and ribociclib.

Under the current FDA approval, patients with high-risk early-stage HR+/HER2- breast cancer may receive two years of adjuvant abemaciclib in combination with standard adjuvant endocrine therapy (5-10 years). High-risk disease is defined as four or more pathologic axillary lymph nodes, or 1-3 pathologic axillary lymph nodes along with a tumor that is grade 3 or ≥ 5 cm in diameter.[32]

FDA approval of adjuvant abemaciclib was based on the results of the open-label, randomized phase 3 monarchE trial. The trial recruited patients with early-stage HR+/HER2- breast cancer with high risk of recurrence, initially defined as four or more pathologic axillary lymph nodes or 1-3 pathologic axillary lymph nodes with at least one of the following features: tumor size ≥ 5 cm, histologic grade 3, or centrally assessed Ki-67 ≥ 20%. Patients were randomized 1:1 to receive two years of adjuvant abemaciclib in combination with standard adjuvant endocrine therapy or endocrine therapy alone. At the primary outcome analysis, which occurred after a median follow-up of 19.1 months, the 2-year invasive disease-free survival (iDFS) was 92.3% in the abemaciclib plus endocrine therapy group and 89.3% in the endocrine therapy group (HR: 0.713; 95% CI: 0.583 - 0.871; nominal 2-sided p = 0.009). The 2-year distant relapse-free survival (DRFS) was 93.8% in the abemaciclib plus endocrine therapy group and 90.8% in the endocrine therapy group (HR: 0.687; 95% CI: 0.551 - 0.858; nominal 2-sided p = 0.0009).[33,34]

Ribociclib is FDA approved in combination with an aromatase inhibitor for the adjuvant treatment of people with stage II-III HR+/HER2- breast cancer at high risk of recurrence, including patients with node-negative (N0) disease.

Approval was based on the results of the open-label, randomized phase 3 NATALEE trial, which enrolled patients with stage II-III HR+/HER2- breast cancer. Patients with stage IIB or III disease were eligible to participate, regardless of nodal status. Patients with stage IIA disease were eligible if they met at least one of the following criteria: pathologic involvement of at least one lymph node; grade 3 tumor; grade 2 tumor with Ki-67 ≥ 20% or high genomic risk. Participants were randomized to receive three years of ribociclib plus standard adjuvant endocrine therapy (5 years) or endocrine therapy alone. At the first interim analysis (after a median follow-up of 34 months), the 3-year iDFS was 90.4% on the ribociclib plus endocrine therapy arm and 87.1% on the endocrine therapy arm (HR: 0.748; 95% CI: 0.618 – 0.906; p = 0.0014). The iDFS benefit was consistent across patient subgroups.[35] At the second interim analysis (an additional 5.6 months from the first interim analysis), the 3-year iDFS was 90.7% on the ribociclib plus endocrine therapy arm and 87.6% on the endocrine therapy arm (HR: 0.749; 95% CI: 0.628 – 0.892; p = 0.0006). The benefit of ribociclib was observed across patient subgroups, including those with node-negative, stage II, or stage III disease.[36]

Based on these approvals, it is reasonable to expect that a sizable percentage of HR+/HER2- breast cancer patients who are eligible to receive inavolisib, palbociclib, and fulvestrant in the advanced disease setting will have received either abemaciclib or ribociclib in the adjuvant setting. However, there is a dearth of evidence regarding the efficacy of the triplet combination in patients who received a CDK4/6 inhibitor for early-stage disease. In the INAVO120 trial, only four participants (1.2%) had received a prior CDK4/6 inhibitor for early-stage disease, including three on the inavolisib arm (1.9%) and one on the placebo arm (0.6%).[10]

For patients with recurrent HR+/HER2- breast cancer who received a CDK4/6 inhibitor in the adjuvant setting, the timing of recurrence may be a crucial factor in treatment decision making. Patients who experience disease recurrence within one year of completing an adjuvant CDK4/6 inhibitor may have aggressive disease that is refractory to both endocrine therapy and CDK4/6 inhibition. Thus, in these patients, additional endocrine-based regimens may be insufficient, including endocrine therapy in combination with a CDK4/6 inhibitor. Rather, alternative therapies like chemotherapy or an ADC may be more appropriate. For patients who experience disease recurrence one year or more after completing an adjuvant CDK4/6 inhibitor, the triplet combination of inavolisib, palbociclib, and fulvestrant may be an effective treatment option.

Based on the abovementioned considerations, the BOC group came to the following consensus:

Consensus Statement

Treatment with inavolisib, palbociclib, and fulvestrant can be considered in some patients with HR+/HER2- metastatic breast cancer who experience recurrence after receiving a prior CDK4/6 inhibitor in the adjuvant setting.

This combination may be considered particularly for patients who experienced disease recurrence one year or more after completing treatment with an adjuvant CDK4/6 inhibitor.

2. Should inavolisib be used in patients with prior systemic treatments in the metastatic setting (> 1 prior lines of therapy)?

In the INAVO120 trial, eligible patients included those who had not received any prior systemic therapies in the metastatic setting.[10] This means there are currently no efficacy data available for the triplet combination of inavolisib, palbociclib, and fulvestrant following disease progression on a prior CDK4/6 inhibitor with endocrine therapy. Based on the available data, the most appropriate use of inavolisib, palbociclib, and fulvestrant is as a first-line therapy for HR+/HER2- MBC patients with a *PIK3CA* mutation.

However, the FDA approval of the triplet combination of inavolisib, palbociclib, and fulvestrant does not specify restriction of this regimen to first-line therapy for metastatic disease.[31] FDA approval also did not include the disease-free interval criterion applied in

INAVO120, which required disease progression on or within 12 months of completion of adjuvant endocrine therapy.[10] These differences suggest that the regulatory approval encompasses a potentially broader patient population than the trial's inclusion criteria, including patients who may have received prior treatment in the metastatic setting.

For HR+/HER2- MBC patients with disease progression on first-line endocrine therapy with a CDK4/6 inhibitor, the efficacy of additional CDK4/6 inhibition beyond progression is still under study.

The randomized, multicenter, phase 2 MAINTAIN trial evaluated the efficacy of endocrine therapy with either ribociclib or placebo in patients with HR+/HER2- MBC who experienced disease progression on prior endocrine therapy with a CDK4/6 inhibitor. Participants were randomized 1:1 to receive ribociclib or placebo in combination with endocrine therapy (fulvestrant or exemestane). In terms of prior CDK4/6 inhibitor exposure, 86.5% of participants had previously received palbociclib, 11.7% had received ribociclib, 2% had received abemaciclib, and 3% had received palbociclib and another CDK4/6 inhibitor. After a median follow-up of 18.2 months, the median PFS was 5.29 months (95% CI: 3.02 – 8.12) among patients who received ribociclib versus 2.76 months (95% CI: 2.66 – 3.25) among patients who received placebo (HR: 0.57; 95% CI: 0.39 – 0.85; p = 0.006). The benefit of ribociclib over placebo was observed in patients who had previously received palbociclib (HR: 0.58; 95% CI: 0.38 – 0.89) or ribociclib (HR: 0.50; 95% CI: 0.15 – 1.70).[37]

The double-blind, randomized, phase 3 postMONARCH trial evaluated the efficacy of abemaciclib plus fulvestrant among HR+/HER2- MBC patients who experienced disease progression on a first-line CDK4/6 inhibitor plus AI. Participants were randomized 1:1 to receive abemaciclib or placebo plus fulvestrant. At a median follow-up of 13 months, the median PFS was 6.0 months (95% CI: 5.6 – 8.6) in the abemaciclib group and 5.3 months (95% CI: 3.7 – 5.6) in the placebo group (HR: 0.73; 95% CI: 0.57 – 0.95; nominal p = 0.017).[38]

The randomized, multicenter, phase 2 PACE trial evaluated the efficacy of palbociclib plus endocrine therapy in HR+/HER2- MBC patients who experienced disease progression on a prior CDK4/6 inhibitor plus endocrine therapy. Patients were randomized 1:1:1 into three treatment groups: palbociclib plus fulvestrant, palbociclib plus avelumab and fulvestrant, and fulvestrant alone. The primary endpoint was to evaluate PFS with the combination of palbociclib plus fulvestrant versus fulvestrant alone.[39] Prior CDK4/6 inhibitors included palbociclib (90%), ribociclib (4.5%), abemaciclib (4.1%), and palbociclib and ribociclib (1.4%). After a median follow-up of 24 months, the median PFS was 4.6 months (90% CI: 3.6 – 5.9) in the fulvestrant plus palbociclib group versus 4.8 months (90% CI: 2.1 – 8.2) in the fulvestrant monotherapy group (HR: 1.11, 90% CI: 0.79 – 1.55; p = 0.62). The median OS was 24.6 months (90% CI: 21.5 – 33.3) in patients treated with fulvestrant plus palbociclib versus 27.5 months (90% CI: 21.1 – 38.0) in patients treated with fulvestrant (HR: 1.02; 90% CI: 0.67 – 1.56).[40]

Given the lack of efficacy data of the triplet combination of inavolisib, palbociclib, and fulvestrant after the first line and the uncertain utility of additional CDK4/6 inhibition after progression on endocrine therapy with a CDK4/6 inhibitor, most members of the BOC group

were hesitant about treating patients with inavolisib, palbociclib, and fulvestrant after progression on endocrine therapy with a CDK4/6 inhibitor.

Consensus Statement

Based on the available data, the combination of inavolisib, palbociclib, and fulvestrant should only be used as a first-line therapy for patients with *PIK3CA*-mutated HR+/HER2- metastatic breast cancer.

There are insufficient data to support the use of inavolisib, palbociclib, and fulvestrant in patients with HR+/HER2- metastatic breast cancer who have received any prior lines of therapy in the metastatic setting, and the potential benefits in this population are unknown.

3. Is inavolisib appropriate for patients with fasting glucose > 126 mg/dL or HbA1c > 6.0% (diabetic or pre-diabetic patients)?

Hyperglycemia is an on-target effect of PI3K inhibition, and as such is a common adverse event among patients receiving treatment with PI3K inhibitors.[41,42] In light of this, eligibility criteria for the INAVO120 trial included fasting blood glucose < 126 mg/dL and HbA1c levels < 6.0%. Even still, 58.6% of patients on the inavolisib arm experienced any-grade hyperglycemia, and 5.6% experienced hyperglycemia of grade 3 or 4.[10] The incidence of hyperglycemia was 65.6% among patients with a body-mass index (BMI) ≥ 30 kg/m^2 (obese patients) versus 56.8% among patients with a BMI < 30 kg/m^2. As a result, 40.7% of participants on the inavolisib arm required concomitant medication to manage hyperglycemia, most commonly metformin (93.9% of cases).[43]

In addition to INAVO120, a phase 1/1b study (NCT03006172) evaluated the rates of hyperglycemia among patients with *PIK3CA*-mutated HR+/HER2- MBC treated with inavolisib monotherapy (n = 20), inavolisib plus fulvestrant (n = 60), inavolisib plus letrozole (n = 37), inavolisib plus palbociclib and letrozole (n = 33), inavolisib plus palbociclib and fulvestrant (n = 20), or inavolisib with palbociclib, fulvestrant, and prophylactic metformin (n = 21). Patients were required to have fasting blood glucose ≤ 140 mg/dL and HbA1c < 7% (except for patients who received prophylactic metformin, in whom requirements were HbA1c ≥ 5.7% and BMI ≥ 30 kg/m^2). Inavolisib was administered at 3 mg, 6 mg, 9 mg, or 12 mg QD orally (MTD: 9 mg). Fasting blood glucose was monitored at baseline, weekly for the first two treatment cycles, then at least once per month and at treatment discontinuation.[44]

Patients with pre-diabetes (defined in this study as fasting blood glucose ≥ 100 mg/dL to 126 mg/dL and HbA1c ≥ 5.7% to < 6.5%) and/or obesity (BMI ≥ 30 kg/m^2) comprised more than half the study population (n = 110/191; 57.6%). Inavolisib dose intensity was high in patients with pre-diabetes and/or obesity, with 95/110 patients (86.4%) in this population treated at the MTD of 9 mg, and a median inavolisib cumulative dose intensity of 92%.[44]

Hyperglycemia was frequent among the overall patient population (any-grade: 68%; grade 3-4: 24%) and among pre-diabetic/obese patients (any-grade: 81%; grade 3-4: 35%). The inavolisib dose was reduced in 9% of the overall patient population and 14% of pre-diabetic/obese patients due to hyperglycemia. Hyperglycemia was not a common cause of inavolisib discontinuation, either in the overall patient population (1%) or pre-diabetic/obese patients (1%). Moreover, hyperglycemia was generally manageable with dose modifications and oral anti-hyperglycemic medications, particularly metformin.[44]

Ketoacidosis is a rare but serious complication of hyperglycemia induced by PI3K inhibitors. In the INAVO120 trial, no cases of ketoacidosis were reported.[43] However, two cases of life-threatening ketoacidosis have been reported in diabetic patients treated with inavolisib in the post-market setting.[1]

Based on these findings, the BOC group recommended that treatment with inavolisib, palbociclib, and fulvestrant is not appropriate for breast cancer patients who meet the criteria for diabetes or pre-diabetes (fasting blood glucose > 126 mg/dL or HbA1c > 6.0%).

Consensus Statement

Treatment with inavolisib is not appropriate for patients meeting criteria for diabetes or pre-diabetes, specifically those with fasting glucose levels > 126 mg/dL or HbA1c levels > 6.0%.

4. What supportive measures should accompany inavolisib initiation to ensure safe and effective use?

Due to the risk of hyperglycemia, fasting blood glucose (FBG) should be monitored at baseline, once every 3 days during week 1 of therapy, once per week during weeks 2-4, once every 2 weeks during weeks 5-12, and then once every 4 weeks thereafter as clinically indicated. Patients may monitor their fasting blood glucose at home. To facilitate this, patients should be offered fasting blood glucose testing supplies (glucometer, testing strips, and lancets) along with counseling regarding proper testing procedures.

HbA1c should be evaluated at baseline and then every 3 months as clinically indicated.

Metformin extended release (ER) prophylaxis of 500 mg once daily should be initiated in patients with HbA1c > 5.7% and/or BMI > 30 kg/m^2. If metformin ER 500 mg once daily is well tolerated and FBG remains > 160 mg/dL, increase by 500 mg weekly up to a maximum dose of 2000 mg/day. It is important to note that metformin is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. For patients with eGFR 30-45 mL/min/1.73 m^2, do not exceed 1000 mg metformin ER per day.

Multidisciplinary management and coordination with both oncology nursing and pharmacy may help provide optimal support for each patient. This includes the provision of supportive measures as described in the consensus statement below, as well as counseling

on lifestyle interventions to maintain optimal blood glucose, such as eating a low-carbohydrate diet (60-130 grams/day) and getting regular exercise.[45]

Moreover, given the complexity of this three-drug regimen, including the required supportive medications and monitoring, enhanced adherence support strategies should be implemented for patients with a history of suboptimal treatment compliance.

Aside from hyperglycemia, other important adverse events associated with inavolisib include diarrhea, stomatitis, and rash. In the INAVO120 trial, 28.4% of the participants on the inavolisib arm received concomitant supportive medication(s) for diarrhea, 16.0% for rash, and 42.6% for stomatitis.[43] Early use of dexamethasone mouthwash as a treatment or prophylaxis for stomatitis was recommended based on the results of the SWISH study.[46] Supportive medications for diarrhea and rash were given as needed.[10]

Consensus Statement

To monitor for the development of hyperglycemia, patients' fasting blood glucose (FBG) and HbA1c should be evaluated at the following time points:

- FBG and HbA1c at baseline
- FBG once every 3 days during week 1 of therapy
- FGG once per week during weeks 2-4 of therapy
- FBG once every 2 weeks during weeks 5-12 of therapy
- FBG once every 4 weeks from week 13 onward as clinically indicated
- Monitor HbA1c every 3 months

Patients may evaluate FBG at home. To facilitate this, a glucometer, testing strips, and lancets (with patient counselling regarding proper testing procedures) should be made available to the patient.

Metformin should be given to patients at high risk of hyperglycemia (BMI > 30 kg/m^2 or HbA1c > 5.7%). For these patients, initiate metformin extended release (ER) 500 mg daily. If this dose is well tolerated and FBG remains > 160 mg/dL, increase by 500 mg weekly up to a maximum dose of 2000 mg/day.

- Metformin is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2.
- For patients with eGFR 30-45 mL/min/1.73 m^2, do not exceed 1000 mg per day.

The following additional supportive care measures should be considered at the time of prescription:

1. Start cetirizine prophylactically to help prevent the development of a rash
2. Start dexamethasone mouthwash prophylactically (up to four times per day) to prevent the development of stomatitis
3. Prescribe loperamide to use as needed at the onset of diarrhea

References

1. Subject: ITOVEBI™ (inavolisib): Cases of serious life-threatening ketoacidosis. Genentech. March 2025. https://www.gene.com/download/pdf/Itovebi_DHCP_Important-Drug-Warning_March2025.pdf.
2. Howlader, N.*, et al.* US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst* **106**(2014).
3. Finn, R.S.*, et al.* Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med* **375**, 1925-1936 (2016).
4. Hortobagyi, G.N.*, et al.* Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med* **375**, 1738-1748 (2016).
5. Goetz, M.P.*, et al.* MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol* **35**, 3638-3646 (2017).
6. Johnston, S.*, et al.* MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer* **5**, 5 (2019).
7. Tripathy, D.*, et al.* Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol* **19**, 904-915 (2018).
8. Bidard, F.-C.*, et al.* Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *Journal of Clinical Oncology* **40**, 3246-3256 (2022).
9. Turner, N.C.*, et al.* Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med* **388**, 2058-2070 (2023).
10. Turner, N.C.*, et al.* Inavolisib-Based Therapy in PIK3CA-Mutated Advanced Breast Cancer. *N Engl J Med* **391**, 1584-1596 (2024).
11. Andre, F.*, et al.* Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med* **380**, 1929-1940 (2019).
12. Miller, T.W., Rexer, B.N., Garrett, J.T. & Arteaga, C.L. Mutations in the phosphatidylinositol 3-kinase pathway: role in tumor progression and therapeutic implications in breast cancer. *Breast Cancer Res* **13**, 224 (2011).
13. Miller, T.W., Balko, J.M. & Arteaga, C.L. Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. *J Clin Oncol* **29**, 4452-4461 (2011).
14. Miller, T.W.*, et al.* Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. *J Clin Invest* **120**, 2406-2413 (2010).
15. Sobhani, N.*, et al.* The prognostic value of PI3K mutational status in breast cancer: A meta-analysis. *J Cell Biochem* **119**, 4287-4292 (2018).
16. Cancer Genome Atlas, N. Comprehensive molecular portraits of human breast tumours. *Nature* **490**, 61-70 (2012).

17. Cizkova, M., *et al.* PIK3CA mutation impact on survival in breast cancer patients and in ERalpha, PR and ERBB2-based subgroups. *Breast Cancer Res* **14**, R28 (2012).
18. Anderson, E.J., *et al.* A Systematic Review of the Prevalence and Diagnostic Workup of PIK3CA Mutations in HR+/HER2- Metastatic Breast Cancer. *Int J Breast Cancer* **2020**, 3759179 (2020).
19. Cristofanilli, M., *et al.* Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* **17**, 425-439 (2016).
20. Dupont Jensen, J., *et al.* PIK3CA mutations may be discordant between primary and corresponding metastatic disease in breast cancer. *Clin Cancer Res* **17**, 667-677 (2011).
21. U.S. Food and Drug Administration. FDA approves alpelisib for metastatic breast cancer. May 24, 2019. https://www.fda.gov/news-events/press-announcements/fda-approves-first-pi3k-inhibitor-breast-cancer#:~:text=Today%2C%20the%20U.S.%20Food%20and,negative%2C%20PIK3CA%2Dmutated%2C%20advanced.
22. Davies, B.R., *et al.* Preclinical pharmacology of AZD5363, an inhibitor of AKT: pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. *Mol Cancer Ther* **11**, 873-887 (2012).
23. U.S. Food and Drug Administration. FDA approves capivasertib with fulvestrant for breast cancer. November 16, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer.
24. Rugo, H.S., *et al.* Capivasertib and fulvestrant for patients with hormone receptor-positive advanced breast cancer: characterization, time course, and management of frequent adverse events from the phase III CAPItello-291 study. *ESMO Open* **9**, 103697 (2024).
25. Vora, S.R., *et al.* CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3K inhibitors. *Cancer Cell* **26**, 136-149 (2014).
26. Tolaney, S.M., *et al.* Phase Ib Study of Ribociclib plus Fulvestrant and Ribociclib plus Fulvestrant plus PI3K Inhibitor (Alpelisib or Buparlisib) for HR(+) Advanced Breast Cancer. *Clin Cancer Res* **27**, 418-428 (2021).
27. Pascual, J., *et al.* Triplet Therapy with Palbociclib, Taselisib, and Fulvestrant in PIK3CA-Mutant Breast Cancer and Doublet Palbociclib and Taselisib in Pathway-Mutant Solid Cancers. *Cancer Discov* **11**, 92-107 (2021).
28. Hanan, E.J., *et al.* Discovery of GDC-0077 (Inavolisib), a Highly Selective Inhibitor and Degrader of Mutant PI3Kalpha. *J Med Chem* **65**, 16589-16621 (2022).

29. Song, K.W.*, et al.* RTK-Dependent Inducible Degradation of Mutant PI3Kalpha Drives GDC-0077 (Inavolisib) Efficacy. *Cancer Discov* **12**, 204-219 (2022).
30. Jhaveri, K.L.*, et al.* Overall Survival with Inavolisib in PIK3CA-Mutated Advanced Breast Cancer. *N Engl J Med* (2025).
31. U.S. Food and Drug Administration. FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer. October 10, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inavolisib-palbociclib-and-fulvestrant-endocrine-resistant-pik3ca-mutated-hr-positive.
32. U.S. Food and Drug Administration. FDA approves abemaciclib with endocrine therapy for early breast cancer. October 12, 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-endocrine-therapy-early-breast-cancer.
33. Johnston, S.R.D.*, et al.* Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol*, JCO2002514 (2020).
34. Joyce A. O'Shaughnessy, S.J., Nadia Harbeck, Masakazu Toi, Young-Hyuck Im, Mattea Reinisch, Zhimin Shao, Pirkko Liisa Kellokumpu Lehtinen, Chiun-Sheng Huang, Alexey Tryakin, Matthew Goetz, Hope S Rugo, Elzbieta Senkus, Laura Testa, Michael Andersson, Kenji Tamura, Guenther G. Steger, Lucia Del Mastro, JoanneCox, Tammy Forrester, Sarah Sherwood, Xuelin Li, Ran Wei, Miguel Martin, Priya Rastogi. Abstract GS1-01: Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. in *San Antonio Breast Cancer Symposium* (Virtual, 2020).
35. Slamon, D.J.*, et al.* Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: Primary results from the phase III NATALEE trial. *Journal of Clinical Oncology* **41**, LBA500-LBA500 (2023).
36. Gabriel Hortobagyi, D.S., Denise Yardley, Chiun-Shen Huang, Peter A. Fasching, John Crown, Aditya Bardia, Stephen Chia, Seock-Ah Im, Miguel Martín, Sherene Loi, Binghe Xu, Sara Hurvitz, Carlos Barrios, Michael Untch, Rebecca Moroose, Frances Visco, Federico Parnizari, Farhat Ghaznawi, Zheng Li, Sorcha Waters, Arunava Chakravartty, Dennis Slamon. (GS03-03) Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial. in *San Antonio Breast Cancer Symposium* (San Antonio, TX, USA, 2023).
37. Kalinsky, K.*, et al.* Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor

Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. *J Clin Oncol* **41**, 4004-4013 (2023).
38. Kalinsky, K.*, et al.* Abemaciclib Plus Fulvestrant in Advanced Breast Cancer After Progression on CDK4/6 Inhibition: Results From the Phase III postMONARCH Trial. *J Clin Oncol*, JCO2402086 (2024).
39. Mayer, E.L.*, et al.* Palbociclib after CDK and endocrine therapy (PACE): A randomized phase II study of fulvestrant, palbociclib, and avelumab for endocrine pre-treated ER+/HER2- metastatic breast cancer. *Journal of Clinical Oncology* **36**, TPS1104-TPS1104 (2018).
40. Mayer, E.L.*, et al.* PACE: A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab After Progression on Cyclin-Dependent Kinase 4/6 Inhibitor and Aromatase Inhibitor for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor-Negative Metastatic Breast Cancer. *J Clin Oncol*, JCO2301940 (2024).
41. Gallagher, E.J.*, et al.* Managing hyperglycemia and rash associated with alpelisib: expert consensus recommendations using the Delphi technique. *NPJ Breast Cancer* **10**, 12 (2024).
42. Nunnery, S.E. & Mayer, I.A. Management of toxicity to isoform alpha-specific PI3K inhibitors. *Ann Oncol* **30**, x21-x26 (2019).
43. Juric, D.*, et al.* First-line inavolisib/placebo + palbociclib + fulvestrant (Inavo/Pbo+Palbo+Fulv) in patients (pts) with PIK3CA-mutated, hormone receptor-positive, HER2-negative locally advanced/metastatic breast cancer who relapsed during/within 12 months (mo) of adjuvant endocrine therapy completion: INAVO120 Phase III randomized trial additional analyses. *Journal of Clinical Oncology* **42**, 1003-1003 (2024).
44. Oliveira, M.*, et al.* Phase I/Ib study of inavolisib (INAVO) alone and in combination with endocrine therapy ± palbociclib (PALBO) in patients (pts) with PIK3CA-mutated, hormone receptor–positive, HER2-negative locally advanced/metastatic breast cancer (HR+, HER2– LA/mBC): Analysis of hyperglycemia (HG) in prediabetic/obese pts. *Journal of Clinical Oncology* **43**, 1004-1004 (2025).
45. Moore, H.N.*, et al.* Effective Strategies for the Prevention and Mitigation of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia: Optimizing Patient Care. *Clin Breast Cancer* **25**, 1-11 (2025).
46. Rugo, H.S.*, et al.* Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *Lancet Oncol* **18**, 654-662 (2017).