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Positive Quality Intervention: Inavolisib (Itovebi™) Patient Management

Description: This document will provide awareness of the PI3K inhibitor, inavolisib, for patients receiving treatment for hormone receptor (HR)-positive, HER2-negative, advanced/metastatic breast cancer and will discuss counseling, monitoring parameters, and patient management strategies to optimize adherence and improve patient outcomes.

Background: Inavolisib is a kinase inhibitor that works in the PI3K pathway with selective inhibition of the p110α subunit that is indicated in combination with palbociclib and fulvestrant for the treatment of adult patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer who have disease recurrence on or within 12 months after the completion of adjuvant endocrine therapy with a PIK3CA mutation.[1] In the phase III INAVO120 study, the median progression-free survival (mPFS) was 15.0 months in the inavolisib/fulvestrant/palbociclib group as compared to 7.3 months in the placebo/fulvestrant/palbociclib group (hazard ratio (HR), 0.43; 95% confidence interval (CI), 0.32, 0.59; P<0.0001). The most frequent adverse events of any grade with ≥20% incidence in patients receiving inavolisib/fulvestrant/palbociclib compared to the placebo group were neutropenia (88.9% vs 90.7%), thrombocytopenia (48.1% vs 45.1%), stomatitis (51.2% vs 26.5%), anemia (37% vs 36.4%), hyperglycemia (58.6% vs 8.6%), diarrhea (48.1% vs 16%), nausea (27.8% vs 16.7%) and rash (25.3% vs 17.3%). Adverse events leading to discontinuation were reported in 6.8% of the patients receiving inavolisib and 0.6% with placebo. Adverse events leading to dose modification/interruption of treatment were reported in 82.7% of the patients receiving inavolisib and 74.7% with placebo.[2]

PQI Process: Upon initiation of Inavolisib (Itovebi™)

- Ensure the patient meets indication and is an adult female/male with HR-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer
    - These patients should have disease recurrence on or after completion of adjuvant endocrine therapy.[1] Per NCCN guidelines, can consider for disease progression on adjuvant endocrine therapy or with early disease relapse within 12 months of adjuvant endocrine therapy completion.[2,3]
    - PIK3CA mutation status can be identified using the FDA approved companion diagnostics http://www.fda.gov/companiondiagnostics.
    - For pre- and peri-menopausal patients, gonadotropin-releasing hormone (GnRH) agonist should be administered in accordance with current clinical practice guidelines; for males consider administering a GnRH agonist.
- Inavolisib is dosed 9 mg by mouth once daily with or without food until disease progression or unacceptable toxicity occurs. Inavolisib should be prescribed in combination with palbociclib and fulvestrant.
- Dosage guidance: Evaluate fasting blood glucose, HbA1c and then optimize fasting blood glucose PRIOR to inavolisib initiation. INAVO120 included patients with a HbA1c < 6%
- Please see Table 1 and Table 2 for dosing considerations of inavolisib. Refer to the fulvestrant and palbociclib Full Prescribing Information for recommended fulvestrant and palbociclib dosing information and associated guidance.

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- Inavolisib is primarily metabolized by hydrolysis with minimal metabolism by CYP3A but is a P-gp and BCRP substrate.
    - Pharmacists should review all concomitant prescription medications, vitamins and supplements, and over-the-counter medications.
- Inavolisib is a CYP3A and CYP2B6 inducer as well as a CYP3A (time-dependent) inhibitor. Review all concomitant medications.
- Dose modification is necessary in patients with moderate renal impairment. If eGFR 30-<60 ml/minute, inavolisib should be dose reduced to 6 mg once daily. Inavolisib has not been studied in patients with an eGFR <30 and thus should be avoided.
- Discuss incidence of diarrhea, mucositis, hyperglycemia and cutaneous adverse events
- Monitoring parameters
    - Obtain HgbA1c, FBG, CMP and CBC with differential at baseline
    - Consider initiation of prophylaxis for hyperglycemia prevention
        - Metformin has been shown to prevent PI3K-induced hyperglycemia[4,5]
    - There are no data for inavolisib in Type 1 diabetes or insulin-dependent diabetes.
- Advise females of reproductive potential and males with female partners of reproductive potential to use contraception during treatment with inavolisib and for one week after the last dose

Patient-Centered Activities:

- Counsel to administer once daily
    - Take with or without food at approximately the same time each day
    - Do not take two doses at once; missed doses can be taken if within 9 hours of scheduled time
    - If you miss a dose, document the missed dose and report it to your healthcare provider
- Ensure proper monitoring for adverse effects
- Evaluate medication adherence at follow-up assessment and provide counseling to improve compliance if needed
- Provide strategies to reduce the incidence of and manage adverse events[1]
    - Hyperglycemia
        - Low carbohydrate diet. Consider referral to a dietician.
        - Monitor blood sugar closely. Fasting glucose levels should be checked once every 3 days for the first week (Day 1 to 7), then once every week for the next 3 weeks (Days 8 to 28), then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated. HbA1c should be monitored every 3 months. Median time for hyperglycemia onset was 7 days.
        - Hyperglycemia should be managed with antihyperglycemics that do not reactivate the PI3K pathway. Insulin is not ideal and should be avoided if possible. The mechanism of hyperglycemia should not be confused with and should not be managed like Type 2 Diabetes.[1,4,5]
    - Diarrhea
        - Start loperamide at the first episode of diarrhea
        - Increase oral fluids

  - Mucositis
    - Consider corticosteroid (i.e. dexamethasone) mouthwash for prophylaxis and/or management. 38% of patients used corticosteroid mouthwash within INAVO120
  - Cutaneous
    - Topical steroid creams such as hydrocortisone cream
- Ensure patient has supportive care mediations and monitoring supplies such as:
  - Blood glucose meter + test trips + lancets
  - Metformin or SGLT2 inhibitor for hyperglycemia prophylaxis. Insulin sensitizers have the best supporting data.
  - Antiemetics such as ondansetron or prochlorperazine
  - Antidiarrheals such as loperamide
  - Corticosteroid mouthwash such as dexamethasone mouthwash
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. **Itovebi™** (inavolisib) [package insert]
2. Turner N et al. Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer. N Engl J Med. 2024 Oct 31;391(17):1584-1596. doi: 10.1056/NEJMoa2404625. PMID: 39476340.
3. National Comprehensive Cancer Network. Breast Cancer (Version 1.2025). https://www.nccn.org/professionls/physician_gls/pdf/breast.pdf. Accessed January 25, 2025..
4. Gallagher EJ et al. Managing hyperglycemia and rash associated with alpelisib: expert consensus recommendations using the Delphi technique. NPJ Breast Cancer. 2024 Jan 31;10(1):12. doi: 10.1038/s41523-024-00613-x. PMID: 38297009; PMCID: PMC10831089.
5. Moore HN 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. doi: 10.1016/j.clbc.2024.09.017. Epub 2024 Sep 28. PMID: 39462728.

Supplemental Information:

Table 1: Inavolisib Dose Reduction Levels for Adverse Reactions[1]

Dose Reduction	Dosage	Number/Strength Tablets
Starting dose	9 mg daily	1 x 9 mg tablet
1st reduction	6 mg daily	2 x 3 mg tablets
2nd reduction	3 mg daily	1 x 3 mg tablet

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Table 2: Inavolisib Dose Modification Guidelines for Adverse Reactions

Diarrhea	Grade 1 <4 stools over baseline	NO adjustment required Initiate or intensify supportive care
	Grade 2 4-6 stools over baseline	Hold until recovery ≤ grade 1 then resume at same dose Initiate or intensify supportive care Recurrence à hold until recovery ≤ grade 1 then reduce by 1 dose level
	Grade 3 ≥7 stools over baseline	Hold until recovery ≤ grade 1 Initiate or intensify supportive care Reduce by 1 dose level
	Grade 4 Life-threatening	Permanently discontinue
Mucositis	Grade 1 Asymptomatic or mild	NO adjustment required Initiate or intensify therapy i.e. corticosteroid containing mouthwash
	Grade 2 Moderate pain or ulcer that does not interfere with oral intake; modified diet	Hold until recovery ≤ grade 1 and resume at same dose Initiate or intensify therapy i.e. corticosteroid containing mouthwash Recurrence àhold until recovery ≤ grade 1then reduce by 1 dose level
	Grade 3 Severe pain interfering with oral intake	Hold until recovery ≤ grade 1 Initiate or intensify therapy i.e. corticosteroid containing mouthwash Reduce by 1 dose level
	Grade 4 Life-threatening	Permanently discontinue
Cutaneous	Grade 1	No adjustment necessary
	Grade 2	• Consider holding inavolisib until recovery to Grade ≤1 • Resume inavolisib at the same dose level
	Grade 3	First event: • Hold inavolisib until recovery to Grade ≤1 • Resume at the same dose level or one lower dose level based on clinical evaluation Recurrent: • Hold inavolisib until recovery to Grade ≤1 • Resume inavolisib at one lower dose level
	Grade 4	Permanently discontinue
Hyperglycemia	Fasting glucose levels (FPG or FBG) > ULN to 160 mg/dL (> ULN – 8.9 mmol/L)	• No adjustment required. • Consider dietary modifications and ensure adequate hydration.

		• Initiate or intensify oral anti-hyperglycemic medications for patients with risk factors for hyperglycemia.
	Fasting glucose levels > 160 to 250 mg/dL (> 8.9 – 13.9 mmol/L)	• Withhold inavolisib until FPG or FBG ≤ 160 mg/dL (≤ 8.9 mmol/L). • Initiate or intensify anti-hyperglycemic medications. • Resume inavolisib at the same dose level. • If FPG or FBG persists > 200 – 250 mg/dL (> 11.1 – 13.9 mmol/L) for 7 days under appropriate anti-hyperglycemic treatment, consider consultation with a healthcare professional experienced in the treatment of hyperglycemia.
	Fasting glucose levels > 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L)	• Hold inavolisib • Initiate or intensify anti-hyperglycemic medications. • Administer appropriate hydration if required. • If FPG or FBG decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) within 7 days, resume inavolisib at the same dose level. • If FPG or FBG decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) in ≥ 8 days, resume inavolisib at one lower dose level. • If FPG or FBG > 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L) recurs within 30 days, hold inavolisib until FPG or FBG decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) and resume inavolisib at one lower dose level
	Fasting glucose levels > 500 mg/dL (> 27.8 mmol/L)	• Hold inavolisib • Initiate or intensify anti-hyperglycemic medications. • Assess for volume depletion and ketosis and administer appropriate hydration. • If FPG or FBG decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L), resume inavolisib at one lower dose level. • If FPG or FBG > 500 mg/dL (> 27.8 mmol/L) recurs within 30 days, permanently discontinue inavolisib.