PICK THE BEST PATH: OPTIMIZING PIK3CA MUTATION-TARGETED HR+/HER2-PIK3CA-MUTATED THERAPY AND HYPERGLYCEMIA MANAGEMENT

Editor's Note: The is a transcript of a presentation on December 18, 2025. It has been edited and condensed for clarity. To obtain credit for participation **CLICK HERE.**

PIK3CA Mutations in Breast Cancer
Discussion Points
Virginia Kaklamani, MD:

- Breast cancer is the most common cancer and the second leading cause of cancer-related death among women in the US.
- Breast cancer is classified according to molecular characteristics, including expression of hormone receptors (HRs) and overexpression of human epidermal growth factor 2 (HER2)
- Breast cancers that are HR-positive/HER2-negative (HR+/HER2-) are the most common subtype, accounting for 70% of all cases.
- The 5-year survival rate of localized HR+/HER2- breast cancer is 100%, while metastatic HR+/HER2- breast cancer is 36.5%.
- Novel therapeutic strategies that address resistance and improve outcomes in HR+/HER2- breast cancer are needed.
- The phosphatidyl-3-kinase (PI3K) signaling pathway is involved in cell growth and proliferation, playing an important role in breast cancer development and progression.
- Approximately 40% of patients with HR+/HER2- metastatic breast cancer have a mutation in the PIK3CA gene.
- PIK3CA mutations lead to activation of the PI3K/AKT/mTOR signaling pathway, resulting in endocrine therapy resistance and poor prognosis.

Faculty Commentary:
Virginia Kaklamani, MD: Breast cancer's the most common type of cancer among women in the western world, including the US, and it's the second leading cause of cancer-related deaths. The most common type of breast cancer is estrogen receptor-positive breast cancer and several advances in the field have led to a significant improvement in overall survival, with the overall survival of metastatic hormone receptor-positive (HR+) breast cancer surpassing 5 years. This is because of several novel therapies, including CDK4/6 inhibitors, as well as PI3 kinase inhibitors. PI3 kinase mutations are mutations that happen in 40% of breast cancers and they are early events. They're events that we find in the primary tumor and then they're also found in the metastatic tumor. These mutations lead to activation of the PI3/AKT pathway and cancers that have these sorts of alterations tend to be more aggressive, with worse outcomes.

References

American Cancer Society. Key statistics for breast cancer. Published May 5, 2025. Accessed November 17, 2025. https://www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html

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. doi:10.1186/s12885-022-10078-5

National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer stat facts: Female breast cancer subtypes. SEER. Accessed November 17, 2025. https://seer.cancer.gov/statfacts/html/breast-subtypes.html

Tolaney SM, Punie K, Carey LA, et al. Real-world treatment patterns and outcomes in patients with HR+/HER2- metastatic breast cancer treated with chemotherapy in the United States. *ESMO Open*. 2024;9(9):10369. doi:10.1016/j.esmoop.2024.103691

Tufail M, Hu JJ, Liang J, et al. Predictive, preventive, and personalized medicine in breast cancer: targeting the PI3K pathway. *J Transl Med*. 2024;22:15. doi:10.1186/s12967-023-04841-w

Appropriate Candidates for Biomarker Testing

Case Background

MT is a 58-year-old postmenopausal female with biopsy-proven HR+/HER2-negative metastatic breast cancer who is being evaluated at your clinic for further treatment. She was initially diagnosed 2.5 years ago with stage II HR+/HER2- breast cancer. She had surgery, chemotherapy, and adjuvant endocrine therapy with the aromatase inhibitor letrozole. After 1.5 years on letrozole therapy, metastatic disease was detected in the bone and liver. Her medical history includes hypertension well controlled with lisinopril, and recently diagnosed prediabetes for which she is currently untreated. On physical examination, blood pressure is normal, body mass index (BMI) is 35 kg/m^2 and Eastern Cooperative Oncology Group (ECOG) performance status is 0.

Question 1

For which of the following biomarkers would it be appropriate to test in planning this patient's further treatment?

A. Cyclin dependent kinase 4/6 (CDK 4/6)
B. Homologous recombination deficiency
C. PIK3CA mutation
D. Progesterone receptor

The correct answer is: C (PIK3CA mutation)

Answer rationale:

- Testing for a PIK3CA mutation would be appropriate in this patient with HR+/HER2- metastatic breast cancer. PIK3CA testing is currently recommended for patients with locally recurrent or metastatic HR+/HER2- breast cancer who would be candidates for PI3K inhibitor therapy, but current guidelines are not clear when such testing should be performed (first-line vs subsequent-line).
- Prior to the INAVO120 trial results, PIK3CA mutation testing was recommended while a patient with HR+/HER2- metastatic breast cancer was receiving first-line treatment with endocrine therapy plus a CDK4/6 inhibitor to assess for eligibility for subsequent-line use with the PI3K inhibitor alpelisib.
- The INAVO120 trial results and subsequent approval of the combination of inavolisib (PI3K inhibitor), palbociclib (CDK4/6 inhibitor), and fulvestrant in patients with endocrine-resistant, PIK3CA-mutated, HR+, HER2-, locally advanced or metastatic breast cancer following recurrence on or after completion of adjuvant endocrine therapy necessitate PIK3CA testing at the time of metastatic recurrence in order to be able to consider this option in the first-line treatment setting.
- Other recommended mutations to test for in this setting for potential use of targeted therapies include estrogen receptor 1 (ESR1). Patients with ESR1 mutations would be eligible for first-line treatment with a selective estrogen receptor degrader (SERD) like elacestrant or imlunestrant.
- Additional testing of hormone receptors like the progesterone receptor is not necessary since the patient already has established HR+ cancer.
- CDK4/6 is a protein kinase and is the target for CDK4/6 inhibitors like palbociclib; it is not a targetable mutation.
- There is not enough evidence to recommend testing for homologous recombination deficiency, which is an impairment in one of the cell's key DNA repair mechanisms, in breast cancer at this time.

Faculty Commentary

Virginia Kaklamani, MD: When a patient is diagnosed with metastatic HR+ breast cancer, it's important for us to understand the kind of breast cancer this is molecularly. It's important to do next-generation sequencing, either with a liquid biopsy or tissue biopsy, to look at certain biomarkers. One biomarker that we look at is PIK3CA, because we have targeted therapies for it, but this is not the only one. We want to look at BRCA1 and BRCA2 alterations. We want to look at ESR1 mutations as well. The PIK3CA mutations tend to be early events, so we expect to see them in the first line if they're going to be present. ESR1 mutations develop over time, when a tumor is subjected to endocrine

therapy, so we may not see them in that first-line setting. We may see them in the second- or third-line setting. The reason we care about PIK3CA mutations in the first line is because we have inavolisib which is approved in the first line in tumors that have endocrine resistance. It's used in combination with palbociclib and fulvestrant.

References

Clark AS, Cobain EF, Dayao Z, et al. Biomarkers for systemic therapy in metastatic breast cancer: ASCO guideline update Q and A. *JCO Oncol Pract*. 2022;18(12):830-832. doi:10.1200/OP.22.00506

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. doi:10.1186/s12885-022-10078-5

Gradishar WJ, Moran MS, Abraham J, et al.. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer, Version 5.2025. Published October 16, 2025. Accessed November 11, 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Henry NL, Somerfield MR, Dayao Z, et al. Biomarkers for systemic therapy in metastatic breast cancer: ASCO guideline update. *J Clin Oncol*. 2022;40(27):3205-3221. doi:10.1200/JCO.22.01063

Jhaveri KL, Im SA, Saura C, et al. Overall survival with inavolisib in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2025;393(2):151-161. doi:10.1056/NEJMoa2501796

Nader-Marta G, Tolaney SM, Mayer EL. Inavolisib-based triplet therapy for PIK3CA-mutated hormone receptor+/HER2- breast cancer: clinical implications and practical considerations*. JCO Oncol Adv.* 2025;(2):e2500041. doi:10.1200/OA-25-00041\

Tufail M, Hu JJ, Liang J, et al. Predictive, preventive, and personalized medicine in breast cancer: targeting the PI3K pathway. *J Transl Med.* 2024;22:15. doi:10.1186/s12967-023-04841-w

Turner NC, Im SA, Saura C, et al. Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2024;391(17):1584-1596. doi:10.1056/NEJMoa2404625

Testing Methods and Actionable Results

Case Background (continued)

In this woman with metastatic HR+/HER2- breast cancer, liquid biopsy (circulating tumor DNA [ctDNA]) results come back positive for a PIK3CA E453K activating mutation and no other actionable mutations.

Question 2

Which one of the following is correct regarding this patient's test results?

A. Tissue biopsy is needed to confirm the results
B. Liquid biopsy is not an appropriate method for testing for PIK3CA mutations.
C. This patient is eligible for treatment with inavolisib plus palbociclib and fulvestrant
D. This patient is eligible for treatment with alpelisib plus fulvestrant

The correct answer is: C (This patient is eligible for treatment with inavolisib plus palbociclib and fulvestrant)

Answer rationale:

- Current guidelines allow for either next generation sequencing of tumor tissue or ctDNA in plasma to determine eligibility for PI3K-targeted therapy.
- There is a risk of false-negatives with ctDNA plasma testing, so if the PIK3CA result is negative, repeat testing of a tissue specimen using next-generation sequencing (NGS) is recommended. Repeat testing is not needed if the ctDNA plasma test result is positive.
- In the SOLAR-1 trial, patients were required to have at least 1 of 11 prespecified PIK3CA mutations in exons 7, 9, and 20 to be eligible for treatment with alpelisib. These included: C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, H1047Y. It's unknown whether other

mutations are associated with response to alpelisib. The patient in this case does not have 1 of the 11 prespecified mutations.

- Alpelisib-containing regimens are typically considered for subsequent-line treatment of PIK3CA-mutated, HR-positive/HER2-negative metastatic breast cancer. This patient is being considered for treatment in the first-line setting.
- In the INAVO120 trial, there were no prespecified PIK3CA mutations, so patients with any type of PIK3CA-activating mutation were considered for treatment with inavolisib plus palbociclib plus fulvestrant. Patients with newly recurrent PIK3CA-mutated, HR-positive/HER2-negative metastatic breast cancer being treated in the first-line setting were included in this clinical trial.

Faculty Commentary

Joanne Mortimer, MD: As Dr. Kaklamani pointed out in this very common type of breast cancer, our treatments are increasingly dictated by somatic mutations and, therefore, we are serially getting changes in those mutations by obtaining either ctDNA by liquid or by biopsy. In the case of the PI3K mutation, we previously looked at it as next-line therapy, but because of the inavolisib indication, we now recommend looking for PIK3CA with first relapse. On initial tumor DNA, we're looking for a number of mutations, ESR1 mutations, as well as PIK3CA. The initial trials using alpelisib looked at 11 distinct mutations. That is no longer what we're looking at. Inavolisib is effective in all PIK3CA mutations and so, when we get the ctDNA or the tumor DNA, we are looking for all PIK3CA mutations as candidates for therapy.

References

André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940. doi:10.1056/NEJMoa1813904

Clark AS, Cobain EF, Dayao Z, et al. Biomarkers for systemic therapy in metastatic breast cancer: ASCO guideline update Q and A. *JCO Oncol Pract*. 2022;18(12):830-832. doi:10.1200/OP.22.00506

Gradishar WJ, Moran MS, Abraham J, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer, Version 5.2025. Published October 16, 2025. Accessed November 11, 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Henry NL, Somerfield MR, Dayao Z, et al. Biomarkers for systemic therapy in metastatic breast cancer: ASCO guideline update. *J Clin Oncol*. 2022;40(27):3205-3221. doi:10.1200/JCO.22.01063

Jhaveri KL, Im SA, Saura C, et al. Overall survival with inavolisib in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2025;393(2):151-161. doi:10.1056/NEJMoa2501796

Nader-Marta G, Tolaney SM, Mayer EL. inavolisib-based triplet therapy for PIK3CA-mutated hormone receptor+/HER2- breast cancer: clinical implications and practical considerations. *JCO Oncol Adv*. 2025;(2):e2500041. doi:10.1200/OA-25-00041

OncoKB. PIK3CA E453K. Updated October 7, 2025. Accessed November 11, 2025. https://www.oncokb.org/gene/PIK3CA/E453K

Turner NC, Im SA, Saura C, et al. Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2024;391(17):1584-1596. doi:10.1056/NEJMoa2404625

First-Line Treatment Selection

Case Background (continued)

This 58-year-old woman's HR+/HER2- metastatic breast cancer is now confirmed to be PIK3CA-mutated. The patient's medical history includes hypertension and recently diagnosed prediabetes. Physical examination shows normal blood pressure and BMI 35 kg/m^2. ECOG performance status is 0. Laboratory evaluation shows a fasting blood glucose of 112 mg/dL and a hemoglobin A1C of 5.9%. It's currently a 2-month wait for the patient to see the endocrinologist.

Question 3
Which one of the following therapies would be most appropriate for this patient at this time?

A. Capivasertib + fulvestrant
B. Inavolisib + palbociclib + fulvestrant
C. Palbociclib + anastrozole
D. Fulvestrant + anastrozole

The correct answer is: B (Inavolisib + palbociclib + fulvestrant)

Answer rationale:

- This patient has high-risk breast cancer as indicated by disease progression despite adjuvant endocrine therapy and the presence of bone and liver metastases. Therefore, intensive therapy with inavolisib + palbociclib + fulvestrant is indicated at this time despite the risk of hyperglycemia from inavolisib-based therapy in this patient with elevated hemoglobin A1C, fasting glucose, and BMI. Elevated fasting glucose at baseline and the presence of prediabetes are not contraindications to treatment with inavolisib-based therapy. However, patients with A1C >6% and fasting glucose > 126 mg/dL were not included in the INAVO120 trial, so the safety of this regimen in this patient population is unclear.
- Although capivasertib + fulvestrant is FDA-approved for patients with PIK3CA or AKT1 activating mutations or PTEN alterations in patients with locally advanced or metastatic breast cancer following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy, current guidelines recommend use of capivasertib-based treatment in the second-line setting after progression on one or more prior lines of endocrine therapy, including a CDK4/6 inhibitor. This patient is being considered for first-line treatment. If the patient were being considered for subsequent-line treatment, capivasertib-based treatment may be a better choice due to lower incidence of hyperglycemia compared to alpelisib and inavolisib.
- Palbociclib + anastrozole would not be an appropriate choice, as this patient has already progressed on an aromatase inhibitor in the adjuvant setting. If development of hyperglycemia is a major concern (for example if the patient has uncontrolled diabetes), palbociclib + fulvestrant would be an appropriate first-line choice with consideration for a PI3K inhibitor upon progression if hyperglycemia is well controlled.
- Fulvestrant plus anastrozole is an option for the first-line treatment of HR+/HER2- breast cancer, however it would not be appropriate in this patient whose disease has already progressed on an aromatase inhibitor in the adjuvant setting.

Faculty Commentary
Virginia Kaklamani, MD: This is a patient that we're treating in the first-line metastatic setting with a PIK3CA mutation. What we're thinking about is trials that are looking at that first-line setting and the INAVO120 trial is the one that comes to mind. INAVO120 looked at inavolisib, palbociclib, and fulvestrant comparing it to palbociclib and fulvestrant in patients that had PIK3CA-mutated tumors, and it showed improvement in outcomes, including overall survival, which is pretty impressive. We want to try to give inavolisib to this patient. She has a pretty marginal hemoglobin A1C. On the trial, patients were allowed to be enrolled if they had a hemoglobin A1C less than 6%. Hers is 5.9% so we have to be very, very careful. What I've done in the past, especially with these triple combinations, is I don't give all 3 drugs together. I'll give palbociclib/fulvestrant together and wait a month or two. In the meantime, I try to optimize their glycemic control and then add inavolisib. That tends to help them to be able to stay on therapy for the long run.

References
Burstein HJ, DeMichele A, Fallowfield L, Somerfield MR, Henry NL, for the Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels. Endocrine and

targeted therapy for hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer—capivasertib-fulvestrant: ASCO rapid recommendation update. *J Clin Oncol*. 2024;42(12):1450-1453. doi:10.1200/JCO.24.00248

Gradishar WJ, Moran MS, AJ, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer, Version 5.2025. Published October 16, 2025. Accessed November 11, 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Ibrance. Prescribing information. Pfizer; September 2025. Accessed November 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/212436s011lbl.pdf

Itovebi. Prescribing information. Genentech, Inc.; September 2025. Accessed November 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219249s002lbl.pdf

Jhaveri KL, Im SA, Saura C, et al. Overall survival with inavolisib in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2025;393(2):151-161. doi:10.1056/NEJMoa2501796

Moore HN, Goncalves 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;25(1):1-11. doi:10.1016/j.clbc.2024.09.017

Nader-Marta G, Tolaney SM, Mayer EL. Inavolisib-based triplet therapy for PIK3CA-mutated hormone receptor+/HER2- breast cancer: clinical implications and practical considerations. *JCO Oncol Adv*. 2025;(2):e2500041. doi:10.1200/OA-25-00041

Truqap. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2025. Accessed January 16, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s003lbl.pdf

Turner NC, Im SA, Saura C, et al. Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2024;391(17):1584-1596. doi:10.1056/NEJMoa2404625

Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor–positive advanced breast cancer. *N Engl J Med*. 2023;388(22):2058-2070. doi:10.1056/NEJMoa2214131

PI3K Inhibitor-Induced Hyperglycemia Management

Case Background (continued)
In this patient with HR+/HER2-/PIK3CA-mutated metastatic breast cancer, therapy with inavolisib + palbociclib + fulvestrant is started, along with hyperglycemia prophylaxis with metformin 500 mg twice daily. One week after therapy is begun, the patient's fasting blood glucose is 159 mg/dL. The patient reports no missed doses of her breast cancer treatment or metformin.

Question 4
Which one of the following responses to the patient's hyperglycemia would be most appropriate?

A. Increase metformin to 1000 mg twice daily
B. Hold inavolisib for one week and re-test fasting blood sugar in one week
C. Refer to a diabetes educator to assess adherence and provide further patient education
D. Discontinue inavolisib permanently and continue palbociclib + fulvestrant

The correct answer is: A (Increase metformin to 1000 mg twice daily)

Answer rationale:

- A normal fasting blood glucose is less than 100 mg/dL. However, it's not necessary to hold inavolisib until fasting blood glucose levels are >160 mg/dL. For fasting blood glucose levels > upper limit of normal to 160 mg/dL, the recommendation is to

consider dietary modifications, ensure adequate hydration, and initiate or intensify oral antihyperglycemic medications for patients with risk factors for hyperglycemia. This patient is already taking metformin. In the METALLICA trial where metformin was used to prevent or treat hyperglycemia caused by alpelisib, metformin was titrated to a maximum dose of 1000 mg twice daily after 3 days of 500 mg twice daily if no gastrointestinal intolerance occurred.

- In the INAVO120 trial, the median time to onset of hyperglycemia was 7 days. Increased fasting glucose occurred in 85% of patients, with 22%, 12%, and 0.6% experiencing grade 2, grade 3, and grade 4 hyperglycemia, respectively. Prophylactic metformin could be initiated at the investigators' discretion in patients with high risk of hyperglycemia; 40.7% of patients required treatment for hyperglycemia, with metformin being the most commonly used medication in 93.9% of patients.
- Hyperglycemia incidences and onsets of action vary by PI3K and AKT targeted agents for patients with PIK3CA mutations.
- This patient's fasting blood glucose should be repeated in 1 week. For patients starting inavolisib or for those who experience hyperglycemia on inavolisib, fasting blood glucose should be monitored every 3 days for the first week (day 1 to 7), then once a week for the next 3 weeks, then once every 2 weeks for the next 8 weeks, then monthly and as clinically indicated. Hemoglobin A1C should be monitored every 3 months and as clinically indicated.
- Although a certified diabetes educator is an important member of the interprofessional, multidisciplinary team in terms of hyperglycemia education and management, the patient does not appear to be having issues with adherence. Her hyperglycemia indicates she would need counseling on dietary modifications and/or intensification of her current antihyperglycemic treatment.
- It's not necessary to permanently discontinue inavolisib unless patients continue to have hyperglycemia (fasting blood glucose >160 mg/dL) despite 2 dose reductions or if fasting blood glucose > 500 mg/dL recurs within 30 days.

Faculty Commentary
Joanne Mortimer, MD: All these PI3K inhibitors have an effect on glucose because PIK3CA is important in cell sensitivity to insulin. Not surprisingly, when you block that action, blood glucose levels increase. And we've learned a lot about management of toxicity from the first drug, from alpelisib, for which elevations in glucose were very common. The initial monitoring for alpelisib was to do blood sugars weekly for 2 weeks, and then monthly, as indicated, but clinically I think we found that a number of individuals had elevated blood sugars earlier than the initial expected 15- to 16-day peak insulin levels. The need to monitor glucose is true for all of the drugs in these categories and for inavolisib, the recommendation is to monitor every 3 days for the first week, then weekly for 3 weeks and then every 2 weeks for 8 weeks and monthly thereafter. For capivasertib, it's on day 3 or 4 of the dose week on weeks 1, 2 and 4, and weeks 6 and 8, and then monthly as clinically indicated.

Monitoring blood sugars is really important, and when alpelisib first came out, we had a number of individuals who were hospitalized with ketoacidosis. And, largely, this is due to the fact that registration trials include very healthy patients. In the INAVO trial that we've been talking about, patients had to have a hemoglobin A1C of less than 6% and a fasting glucose of less than 126 mg/dL. As we extrapolate this data to the real world and individuals who may not have perfect hemoglobin A1Cs and fasting blood sugars, it's really imperative that we monitor these women closely. For us, we have a very active endocrine department and often we get our diabetic educators involved immediately, so that patients are aware of testing their blood sugar, how to do it, and what the significance of it is.

This particular patient was started on metformin 500 mg twice a day based on the METALLICA study, which was a trial done in patients who were on alpelisib and, in the case of this patient, the recommendation would be to increase their metformin dose from 500 mg twice a day to 1,000 mg twice a day. It's not imperative that their blood sugars remain perfectly normal, but less than 160 mg/dL is ideal. For this particular patient, monitoring them with blood sugars as indicated per package insert and adding metformin and upping the dose for her is what would be indicated. Again, we frequently involve our diabetes educators, as well as our endocrinologists, because some individuals have blood sugars that are not amenable just to metformin.

References

Itovebi. Prescribing information. Genentech, Inc.; September 2025. Accessed November 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219249s002lbl.pdf

Jhaveri KL, Im SA, Saura C, et al. Overall survival with inavolisib in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2025;393(2):151-161. doi:10.1056/NEJMoa2501796

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. doi:10.1016/j.eclinm.2024.102520

Nader-Marta G, Tolaney SM, Mayer EL. Inavolisib-based triplet therapy for PIK3CA-mutated hormone receptor+/HER2- breast cancer: clinical implications and practical considerations. *JCO Oncol Adv*. 2025;(2):e2500041. doi:10.1200/OA-25-00041

Piqray. Prescribing information. Novartis; January 2024. Accessed November 19, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212526s009lbl.pdf

Truqap. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2025. Accessed January 16, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s003lbl.pdf

Turner NC, Im SA, Saura C, et al. Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2024;391(17):1584-1596. doi:10.1056/NEJMoa2404625

Interprofessional, Multidisciplinary Management

Case Background (continued)

This patient with HR+/HER2-/PIK3CA-mutated metastatic breast cancer is treated with inavolisib + palbociclib + fulvestrant, along with metformin 500 mg twice daily, as hyperglycemia prophylaxis. She reports no issues with her current dose of metformin. The team asks her to increase her dose to 1000 mg twice daily and return for repeat blood draw 7 days later. Her repeat fasting blood glucose comes back at 140 mg/dL. She notes that since her diagnosis of metastatic recurrence, she's been very stressed, with minimal exercise and a poor diet.

Question 5:

Which one of the following would be the most appropriate response to the patient's uncontrolled serum glucose?

A. No additional interventions are needed at this time; repeat fasting blood glucose in a month
B. Refer the patient to a dietitian and repeat fasting blood glucose in a week
C. Initiate glipizide 5 mg once daily and refer the patient to a diabetes educator
D. Initiate insulin glargine at 10 units daily and repeat fasting blood glucose in 3 days

The correct answer is: B (Refer the patient to a dietitian and repeat fasting blood glucose in a week)

Answer rationale:

- Dietary modifications can be considered to help lower blood glucose if the fasting blood glucose is ≤160 mg/dL. Collaborating with a dietitian can be an effective way to do this.

- Although this patient's blood glucose may be able to be managed with dietary modifications, additional interventions are needed since the patient's fasting blood glucose is between the upper limit of normal and 160 mg/dL.
- Insulin can reactivate the PI3K pathway and should be considered a last-line agent. Sodium glucose cotransporter 2 inhibitors or thiazolidinediones are preferred second-line agents since their mechanisms of action to lower blood glucose are independent of insulin.
- Although collaboration with a diabetes educator would be a great idea for this patient, sulfonylureas like glipizide should be used as a last-line option for hyperglycemia treatment due to their potential to activate the PI3K pathway.
- SGLT2 inhibitors like empagliflozin are appropriate second-line agents for the management of hyperglycemia caused by PI3K inhibitors. SGLT2 inhibitor mechanism of action is independent of insulin, it doesn't have the same concerns as insulin and sulfonylureas in terms of reactivating the PI3K pathway. Referral to a nutritionist early in the treatment course can help patients with risk factors.
- This patient's fasting blood glucose should be repeated in 1 week. For patients starting inavolisib or for those who experience hyperglycemia on inavolisib, fasting blood glucose should be monitored every 3 days for the first week (day 1 to 7), then once a week for the next 3 weeks, then once every 2 weeks for the next 8 weeks, then monthly and as clinically indicated. Hemoglobin A1C should be monitored every 3 months, and as clinically indicated.

Faculty Commentary

Joanne Mortimer, MD: There are patients, and this was especially true when we were beginning to use alpelisib, who don't respond just to metformin. I would confess not to feeling comfortable managing the long-term toxicity of these agents and often refer them to the endocrinologists who may or may not put a glucose monitoring device on them. Certainly, there are drugs that you should not use. We know that metformin is effective at controlling elevated blood sugars in patients on this class of drugs and we know that from the METALLICA study. But, intuitively, you might want to give them insulin which is the absolutely wrong thing to do because these drugs cause insulin resistance and so adding insulin isn't likely to help the situation. The SGLT2 drugs increase glucose and sodium in the urine, and may be effective in managing PI3K inhibitor-induced hyperglycemia. I don't feel comfortable prescribing these drugs. I generally refer them to endocrinology. At the same time, it's important that patients be educated in diabetic management and so going to the diabetic educators to learn about diet, as well as endocrinologists, in these cases where it's been more and more difficult to manage their elevated blood sugars, is important. And again, this is the real world because our patients don't generally match the registration trials' eligibility and they tend to be overweight, they tend to have higher hemoglobin A1Cs. It really is critical to bring in other teams, sometimes, to ensure that we keep the blood sugars under control.

References

American Diabetes Association Professional Practice Committee. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2025. *Diabetes Care*. 2024;48(Supplement_1):S181-S206. doi:10.2337/dc25-S009

Itovebi. Prescribing information. Genentech, Inc.; September 2025. Accessed November 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219249s002lbl.pdf

Liu D, Weintraub MA, Garcia C, et al. Characterization, management, and risk factors of hyperglycemia during PI3K or AKT inhibitor treatment. *Cancer Med*. 2022;11(8):1796-1804. doi:10.1002/cam4.4579

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. doi:10.1016/j.eclinm.2024.102520

Moore HN, Goncalves 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;25(1):1-11. doi:10.1016/j.clbc.2024.09.017

Nader-Marta G, Tolaney SM, Mayer EL. Inavolisib-based triplet therapy for PIK3CA-mutated hormone receptor+/HER2- breast cancer: clinical implications and practical considerations. *JCO Oncol Adv*. 2025;(2):e2500041. doi:10.1200/OA-25-00041

<u>Subsequent-Line Treatment Selection</u>

Case Background

A 70-year-old postmenopausal woman with HR+/HER2- metastatic breast cancer is evaluated for treatment. She was first diagnosed 18 months ago and was treated with ribociclib plus letrozole. Her disease progressed after 13 months of control. Next generation sequencing detected a PIK3CA H1047R activating mutation, but no other actionable mutations. Her medical history includes hypertension well controlled with lisinopril, inflammatory bowel disease well controlled with loperamide, and type 2 diabetes mellitus treated with metformin 1000 mg twice daily, and empagliflozin 25 mg daily at bedtime. On physical examination, she appears anxious; blood pressure is normal; BMI is 35 kg/m^2. Hemoglobin A1C is 7.4%. She has established care with her endocrinologist and finally has her blood sugars controlled to within a normal range within the last few weeks. She has heard that some cancer medications can alter her blood sugars. She has worked hard to get her blood sugars back to the normal range with diet and her current medications and wants to avoid taking additional medications for diabetes, if possible.

Question 6

Which one of the following targeted treatments for HR+/HER2-/PIK3CA-mutated metastatic breast cancer would be most appropriate for this patient?

A. Alpelisib + fulvestrant
B. Capivasertib + fulvestrant
C. Elacestrant
D. Olaparib

The correct answer is: B (Capivasertib + fulvestrant)

Answer rationale:

- Although both medications can cause hyperglycemia, type 2 diabetes mellitus is not a contraindication to alpelisib or capivasertib-based treatment.
- The incidence of any-grade and ≥ grade 3 hyperglycemia was 63.7% and 36.6% in patients taking alpelisib + fulvestrant in the SOLAR-1 trial and 16.3% and 2.3% in patients taking capivasertib + fulvestrant in the CAPItello-291 trial, respectively. Since this patient wants to minimize the chance of losing glycemic control, capivasertib may be a better option due to lower incidence of hyperglycemia.
- The CAPItello-291 trial (capivasertib + fulvestrant) included a much broader population of patients (including those with impaired glucose tolerance and diabetes controlled with oral medications) than SOLAR-1 (alpelisib + fulvestrant).
- It's important to consider other adverse events outside of hyperglycemia. Capivasertib is more likely to cause diarrhea (any-grade: 72.4%, grade ≥3: 9.3%) than alpelisib (any-grade: 57.7%, grade ≥3: 6.7%). Since this patient has well controlled inflammatory bowel disease, it would still be appropriate to initiate capivasertib with appropriate patient counseling. In addition to rash and diarrhea, both PI3K and AKT inhibitors can cause varying rates of rash and stomatitis.
- Elacestrant is an oral selective estrogen receptor degrader (SERD) indicated for patients with recurrent unresectable or metastatic breast cancer and ESR1 mutations. This patient does not have an ESR1 mutation.

- Olaparib is a PARP inhibitor indicated for patients with recurrent unresectable or metastatic breast cancer and BRCA mutations. This patient does not have a BRCA mutation.

Faculty Commentary

Virginia Kaklamani, MD: Now we're moving from first line to second-line therapy. We still have a patient that has a PI3 kinase-mutated tumor and we're trying to figure out what treatment to give them. And here we're thinking of alpelisib and capivasertib. SOLAR-1 was a trial that looked at alpelisib and CAPItello-291 looked at capivasertib. This patient has a hemoglobin A1C of 7.4% and she would not meet the criteria for alpelisib treatment, but she would for capivasertib. When we look at these inhibitors, we're thinking of 4 toxicities, which are class effects. We're looking at hyperglycemia, rash, stomatitis, and diarrhea and each one of them has a different degree of these toxicities. Capivasertib is more known for its diarrhea, less for its hyperglycemia. Alpelisib, more for the hyperglycemia and rash, less for the diarrhea. Select the right patient medicine based on what the potential toxicity profile of the drug would be but be very careful of the patient's hemoglobin A1C. You may need to prophylax some of these patients with metformin. There are trials that have looked at that, such as the METALLICA trial, but it's important to be able to control the toxicities, so that you can keep them on these treatments in the long run.

References

André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940. doi:10.1056/NEJMoa1813904

Browne IM, André F, Chandarlapaty S, Carey LA, Turner NC. Optimal targeting of PI3K-AKT and mTOR in advanced oestrogen receptor-positive breast cancer. *Lancet Oncol*. 2024;25(4):e139-e151. doi:10.1016/S1470-2045(23)00676-9

Gradishar WJ, Moran MS, Abraham J, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer, Version 5.2025. Published October 16, 2025. Accessed November 11, 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Itovebi. Prescribing information. Genentech, Inc.; September 2025. Accessed November 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219249s002lbl.pdf

Piqray. Prescribing information. Novartis; January 2024. Accessed November 16, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212526s009lbl.pdf

Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor–positive advanced breast cancer. *N Engl J Med*. 2023;388(22):2058-2070. doi:10.1056/NEJMoa2214131

Panel Discussion: Collaboration and Communications Among the Interprofessional, Multidisciplinary Team

Virginia Kaklamani, MD: Dr. Mortimer, we see patients all the time that come in on these PI3 kinase inhibitors. Unfortunately, more and more of our patients have hyperglycemia and increased hemoglobin A1C's. How do you manage these patients? How do you monitor them and when do you think it's good to send them to endocrinology?

Joanne Mortimer, MD: When alpelisib first came out, we truly did have in a 6-month period, 6 patients with diabetic ketoacidosis (DKA). We then embedded a referral to the endocrinologists and/or the diabetes educator in the orders for alpelisib. That became the standard of care. But the subsequent drugs are not nearly as onerous to manage in terms of hyperglycemia. I think alpelisib allowed us to feel some comfort level with ordering metformin and following their blood sugars and, importantly, teaching the patients how to check their own blood sugars and follow them. But still, I think it's important for them to get their diet and exercise discussion and, for those reasons, I would bet a little bit more than half of our patients get referred to endocrinology because we do want to teach them about exercise and diet. I always remember a patient of mine who never could lose

weight and she got one of those Libre devices when she was on alpelisib and lost 45 lbs. It made me realize that when you're trying to control your blood sugar, it's a great way to control your weight and it was something she was unable to do before. When people really follow their blood sugars and keep them controlled, it has a lot of advantages. How about you? Do you do the same thing?

Virginia Kaklamani, MD: I try. My practice includes a lot of Hispanic patients and so I have many patients that already come in with endocrine resistance. I feel that with the patients that I'm going to give a second-line PI3 kinase inhibitor, I have at least a year or 2 to try to prime them, to get them to decrease their hemoglobin A1C, to work on their diet and exercise and have them see the dietitian. It tends to be hard to see endocrinology and so many times I rely on my nurses to monitor blood sugars and metformin and this is something I feel pretty comfortable with. Whenever I give it, I have to remind myself to start with a 500 mg dose twice a day and then go up to 1,000 mg twice a day. Otherwise, they will get diarrhea, which is one of the class effects of this class of agents as well. That makes it even harder to get them started. I think the more we use these drugs, the easier it is and now with the GLP-1s and the SGLT2s, at some point I feel that we will start getting more comfortable in using them and trying to do studies, like the METALLICA study, but also with the GLP-1s and SGLT-2s, so that we can see exactly how to use these agents.

Joanne Mortimer, MD: Do you think there are ethnic and racial differences in toxicities?

Virginia Kaklamani, MD: I know that with my Hispanic patients, because of the hyperglycemia and the endocrine resistance, even the patients that come in with a pretty decent hemoglobin A1C, they tend to have a harder time than my non-Hispanic, White patients. I don't have a lot of Black patients in my practice, but I'm sure that that's also a pretty difficult demographic to treat. One of the things that I see is how important diet is, and it's something that we tend to forget. I remember when I was a junior attending, I walked into the hospital, we were treating a patient with hyperglycemia, and he had just finished his breakfast, and it was pancakes and the plate was full of maple syrup. We couldn't discharge the patient because his blood sugar was still high and the residents were wondering why and I politely asked the patient, "Oh, is this sugar-free maple syrup?" He goes "No, it's wonderful, it's the real deal." And I looked at my residents and I said, "You guys didn't put him on a diabetic diet?" And they all looked like I had 3 heads, realizing that the little things can make such a big impact on these patients.

Joanne Mortimer, MD: Yes. I think there are some odd side effects that emerged that maybe dictated ethnic and racial differences. I have a Japanese woman who was on capivasertib, and she totally lost her taste buds the entire time she was on it and I think these ethnic and racial differences, there are differences in metabolism. She's my only Japanese patient, so I don't know if that's meaningful or not.

Virginia Kaklamani, MD: Speaking of other toxicities, do you prophylax them with antihistamines for rash or what else do you use besides the metformin?

Joanne Mortimer, MD: Yeah, I've stopped using antihistamines in patients other than alpelisib, which we almost never use since the toxicity profile is so unfavorable. I've dropped antihistamines, but there certainly is a fair amount of diarrhea management for the other 2 drugs, that can be necessary. It's not the significance of abemaciclib, but it's kind of erratic how the diarrhea works. It doesn't always respond to antidiarrheal agents and it may respond some to diet. I haven't quite figured it out yet, but it's kind of erratic.

Virginia Kaklamani, MD: Yes, and with capivasertib, I always remind myself that diarrhea leads to dehydration, which leads to hyperglycemia. Sometimes they go together and we need to make sure these patients stay in very close contact with us so we can manage these toxicities when they start. Not a month later when they come into our clinic or they go to the hospital with DKA.

Joanne Mortimer, MD: I guess the last toxicity, and probably the most common toxicity overall, is

fatigue. I wish we had a solution for that, but I generally give my patients lectures on exercise since that is the only thing that seems to modify that toxicity and it does help with their diabetic management too.

Virginia Kaklamani, MD: I completely agree. Dr. Mortimer, we have patients with metastatic disease. They have us as the primary team, but they also have other issues, such as pain management and other symptoms where we refer them to palliative care. When we talk about PI3 kinase inhibitors and the toxicities that are potentially associated with them, how do you structure your team to help your patients through these therapies?

Joanne Mortimer, MD: As I mentioned, because alpelisib was such a significant problem with hyperglycemia, we incorporated an order set in our Beacon order set of EPIC to consult either the diabetic educator or the endocrinologist. And that really has been consistent, less so with the 2 newer drugs than alpelisib, but we still incorporate it, and they're very important. Another group of individuals that we involve are the occupational therapists. We have an exercise program for our patients who are less than enthusiastic about moving. and that is sometimes helpful, too. How about you?

Virginia Kaklamani, MD: There's now clinical trials that have been done in metastatic breast cancer showing that exercise not only improves symptoms, but also improves survival. And this is so underutilized. Obviously, for somebody that has an elevated hemoglobin A1C, trying to get them on an exercise program is a very big deal. Also, trying to get the electronic medical record to be a little more user-friendly for our patients and making sure that our patients are not afraid to use it to ask questions. And that also has been shown in several trials to improve people's survival. That's what we try to do. We try to educate patients to send us a note, to try to communicate with us more and not less, try to involve a pharmacist in our clinics because we all know physicians are busy and nurses are now being asked to do so many other things that it tends to be hard to check up on patients. And sometimes these patients will receive the drugs from a specialty pharmacy. We don't even know when they actually get them, when they actually start them. When I tell them come back to clinic in a month, I'm not sure if they've taken the drugs for a week, 2 weeks, 3 weeks. It's just an unknown. and it gets to be pretty tough.

Joanne Mortimer, MD: As we get busier with all these dual combinations of drugs with our endocrine therapy, there are institutions that employ advanced practice provider- (APP-) run clinics for the PI3K and CDK4/6 inhibitors. We have not embraced that yet. Have you done that?

Virginia Kaklamani, MD: One of our APPs follows our patients, but we haven't had patients come into clinic in between visits to check with the APP. One of the issues that also happens, we ask patients to get a fasting blood sugar. When they come to our clinic with an appointment of 10:00 AM or 12:00 PM, it tends not to be a fasting blood sugar, and we don't get a very good read. These are challenges that we will have to figure out the more oral medications we give and the more these toxicities become an issue for our patients.

Summary of Key Concepts

- PIK3CA testing is currently recommended for patients with locally recurrent or metastatic HR+/HER2- breast cancer who would be candidates for a PI3K inhibitor.
- Prior to the availability of inavolisib + palbociclib + fulvestrant, PIK3CA mutation testing was typically pursued while a patient with HR-positive/HER2-negative metastatic breast cancer was receiving first-line treatment with endocrine therapy plus a CDK4/6 inhibitor to assess for eligibility for subsequent-line use with alpelisib or capivasertib. Early PIK3CA testing at the time of metastatic recurrence will be necessary in order to be able to consider PI3K inhibitor-based treatment in the first-line treatment setting.
- Current guidelines allow for either next generation sequencing of tumor tissue or ctDNA in plasma to determine eligibility for PI3K-targeted therapy. If ctDNA is negative,

repeat testing of tumor tissue is recommended.

- In the SOLAR-1 trial, patients were required to have at least 1 of 11 prespecified PIK3CA mutations. It's unknown whether other mutations are associated with response to alpelisib. In the INAVO120 and CAPItello-291 trial, there were no prespecified PIK3CA mutations, so patients with any type of PIK3CA-activating mutation were considered for treatment.
- Inavolisib + palbociclib + fulvestrant can be considered in the first-line setting for patients with high-risk HR+/HER2-/PIK3CA-mutated locally advanced or metastatic breast cancer in patients who recur on or after completing adjuvant endocrine therapy. Alpelisib + fulvestrant and capivasertib + fulvestrant are usually reserved for the subsequent-line setting in patients with advanced or metastatic breast cancer who progressed on or after an endocrine-based regimen and have PIK3CA-activing mutations (alpelisib) or PIK3CA or AKT1 activating mutations or PTEN alterations (capivasertib).
- Prediabetes and diabetes are not contraindications to treatment with PI3K or AKT inhibitors. However, close glucose monitoring, initiation, or intensification of antihyperglycemics, and the support of an interprofessional, multidisciplinary team including endocrinology will better ensure treatment success.
- PI3K and AKT inhibitors differ in terms of rates of hyperglycemia, rash, diarrhea, fatigue, and stomatitis. Treatment selection may also depend on patient comorbidities and preference.

Faculty Commentary

Joanne Mortimer, MD: Hopefully, what you've garnered from our discussion is that the role of PI3K inhibitors has expanded. It's not just for second-line therapy in patients who've progressed after first-line therapy, but now it's first-line therapy as well. It's important that in addition to looking at ESR1 mutations when we see patients relapse, that we're also looking for PIK3CA because that gives an opportunity to double their progression-free survival by being on 1 of these agents in conjunction with fulvestrant and palbociclib. We always need to get tumor DNA. However you get it, whether it's a liquid biopsy or if you think a liquid biopsy is not accurate to send tissue, but remember that any mutation right now is a candidate for these other 2 agents. Alpelisib had 11 specific mutations as inclusion criteria in the SOLAR-1 trial; the other drugs are applicable to all mutations. And drugs don't work if patients don't take them. Being able to manage the toxicity of these drugs is key to the success of the agents. Recognizing that we need to monitor glucose and watch for diarrhea and manage it so that patients are comfortable, is really important and sometimes that requires additional help from endocrinologists and from supportive care medicine individuals to help ensure that the diarrhea and the blood sugars are adequately controlled.