# Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse

*A Complimentary NCPD Symposium Series Held During the 51st Annual ONS Congress*

## Targeting the PI3K/AKT/mTOR Pathway in HR-Positive Metastatic Breast Cancer

**Friday, May 15, 2026**

**12:15 PM – 1:45 PM**

### Faculty

**Reva Basho, MD**
**Kelly Fischer, MSN, FNP-BC**
**Melissa Rikal, FNP-BC, AOCNP**

### Moderator

**Seth Wander, MD, PhD**

RTP RESEARCH TO PRACTICE

# Faculty

**Reva Basho, MD**
Breast Medical Oncology
Chief Medical Officer
Ellison Medical Institute
Los Angeles, California

**Melissa Rikal, FNP-BC, AOCNP**
Nurse Practitioner
Sarah Cannon Research Institute
Nashville, Tennessee

**Kelly Fischer, MSN, FNP-BC**
Family Nurse Practitioner
Dana-Farber Cancer Institute
Boston, Massachusetts

## Moderator

**Seth Wander, MD, PhD**
Director of Precision Medicine
Termeer Center for Targeted Therapies
Director of Translational Research
Breast Oncology Program
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

RTP
RESEARCH
TO PRACTICE

# Dr Basho — Disclosures

| | |
|---|---|
| **Advisory Committees** | AstraZeneca Pharmaceuticals LP, Celcuity, Novartis, Pfizer Inc |
| **Consulting Agreements** | AstraZeneca Pharmaceuticals LP, Celcuity, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Pfizer Inc |
| **Contracted Research** | AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Genentech, a member of the Roche Group, Scorpion Therapeutics |
| **Data and Safety Monitoring Boards/Committees** | Pfizer Inc |
| **Speakers Bureaus** | DAVA Oncology, MDOutlook |
| **Nonrelevant Financial Relationships** | Community Health Media, OncLive, Targeted Oncology |

# Ms Fischer — Disclosures

No relevant financial relationships to disclose.

# Ms Rikal — Disclosures

| | |
|---|---|
| **Advisory Committees** | Stemline Therapeutics Inc |
| **Consulting Agreements and Speakers Bureaus** | AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc |

# Dr Wander — Disclosures

| | |
|---|---|
| **Consulting Agreements** | Arvinas, AstraZeneca Pharmaceuticals LP, Biotheranostics Inc, A Hologic Company, Biovica International AB, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Menarini Group, Novartis, Pfizer Inc, Puma Biotechnology Inc, Regor Therapeutics, Stemline Therapeutics Inc, Veracyte Inc |
| **Contracted Research** | Arvinas, Genentech, a member of the Roche Group, Lilly, Menarini Group, Nuvation Bio Inc, Pfizer Inc, Phoenix Molecular Designs, Puma Biotechnology Inc, Regor Therapeutics, Sermonix Pharmaceuticals, Stemline Therapeutics Inc |

RTP
RESEARCH
TO PRACTICE

## Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Celcuity, and Genentech, a member of the Roche Group.

## Research To Practice NCPD Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant financial relationships to disclose.

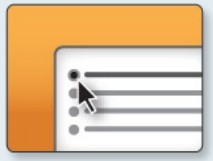
**This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.**

RTP
RESEARCH
TO PRACTICE

# Clinicians in the Meeting Room

**Networked iPads are available.**

**Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.**



**Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.**

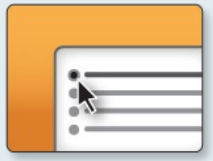
**Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.**

***For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.***

RTP RESEARCH TO PRACTICE

# Clinicians Attending via Zoom

**Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.**



**Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.**

**Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.**

**Get NCPD Credit: An NCPD credit link will be provided in the chat room at the conclusion of the program.**

RTP
RESEARCH
TO PRACTICE

# About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

RTP RESEARCH TO PRACTICE

# RTP RESEARCH TO PRACTICE ONCOLOGY NURSING UPDATE WITH NEIL LOVE, MD

**NONMELANOMA SKIN CANCERS**
**Check out our recent program with Dr Nikhil I Khushalni from Moffitt Cancer Center in Tampa, Florida. Published May 7, 2026.**

Overview of nonmelanoma skin cancers (12 min)

Systemic therapy for nonmelanoma skin cancers (8 min)

Immune checkpoint inhibitors for special patient populations (12 min)

Hedgehog inhibitors for basal cell carcinoma (6 min)

New developments in therapy for nonmelanoma skin cancers (5 min)

CASE: A man in his early 70s with cutaneous squamous cell carcinoma receives cemiplimab (8 min)

CASE: A man in his mid 70s with a history of basal cell carcinoma presents with disease of the ocular surface and receives immunotherapy (6 min)

CASE: A man in his early 70s with recurrent metastatic basal cell carcinoma receives vismodegib followed by cemiplimab on disease progression (6 min)

Subscribe to our Oncology Nursing Update podcast

Feedback (Please!)

RTP RESEARCH TO PRACTICE

# “Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse”
# Eighteenth Annual RTP-ONS NCPD Symposium Series

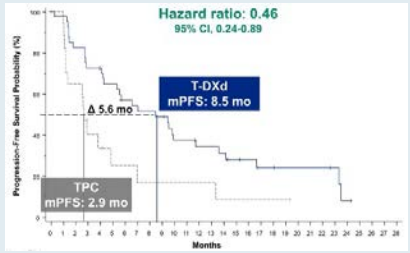
| | |
|---|---|
| Wednesday May 13 | **Antibody-Drug Conjugates**<br>11:15 AM – 12:45 PM CT |
| | **Ovarian Cancer**<br>6:00 PM – 7:30 PM CT |
| Thursday May 14 | **Immunotherapeutic Approaches for Endometrial Cancer**<br>6:00 AM – 7:30 AM CT |
| | **Prostate Cancer**<br>12:15 PM – 1:45 PM CT |
| | **Non-Muscle-Invasive and Muscle-Invasive Bladder Cancer**<br>6:00 PM – 7:30 PM CT |
| Friday May 15 | **Pancreatic Cancer**<br>6:00 AM – 7:30 AM CT |
| | **Targeting the PI3K/AKT/mTOR Pathway in HR-Positive Metastatic BC**<br>12:15 PM – 1:45 PM CT |
| | **Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia**<br>6:00 PM – 8:00 PM CT |
| Saturday May 16 | **CDK4/6 Inhibitors for HR-Positive Breast Cancer**<br>6:00 AM – 7:30 AM CT |
| | **Relapsed/Refractory Multiple Myeloma**<br>12:15 PM – 1:45 PM CT |
| | **Oral SERDs for Breast Cancer**<br>6:00 PM – 7:30 PM CT |

RTP RESEARCH TO PRACTICE

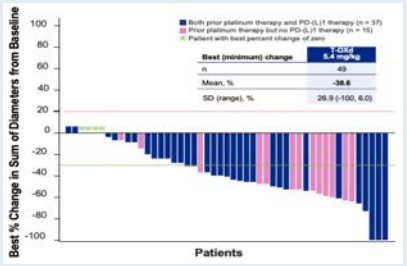
# Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse

## *New Agents, Therapies and Regimens*

- When should it be used, for whom and why?
- How to prevent and manage side effects: dose holds and reductions
  - Kaplan Meier curves — HR and absolute benefit




  - Waterfall plots



# Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse

*A Complimentary NCPD Symposium Series Held During the 51st Annual ONS Congress*

## Targeting the PI3K/AKT/mTOR Pathway in HR-Positive Metastatic Breast Cancer

**Friday, May 15, 2026**

**12:15 PM – 1:45 PM**

### Faculty

**Reva Basho, MD**
**Kelly Fischer, MSN, FNP-BC**
**Melissa Rikal, FNP-BC, AOCNP**

### Moderator

**Seth Wander, MD, PhD**

RTP RESEARCH TO PRACTICE

# Agenda

**Introduction:** Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway

**Module 1:** Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)

**Module 2:** Strategies to Prevent and Manage Hyperglycemia

**Module 3:** Clinical Utility of Capivasertib for HR-Positive mBC

**Module 4:** Mitigation and Management of Gastrointestinal Adverse Events

**Module 5:** Management of Dermatologic Adverse Events

**Module 6:** Potential Role of Gedatolisib in the Management of HR-Positive mBC

**Module 7:** Monitoring and Management of Cytopenias

RTP
RESEARCH
TO PRACTICE

# Agenda

**Introduction: Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway**

**Module 1:** Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)

**Module 2:** Strategies to Prevent and Manage Hyperglycemia

**Module 3:** Clinical Utility of Capivasertib for HR-Positive mBC

**Module 4:** Mitigation and Management of Gastrointestinal Adverse Events

**Module 5:** Management of Dermatologic Adverse Events

**Module 6:** Potential Role of Gedatolisib in the Management of HR-Positive mBC

**Module 7:** Monitoring and Management of Cytopenias

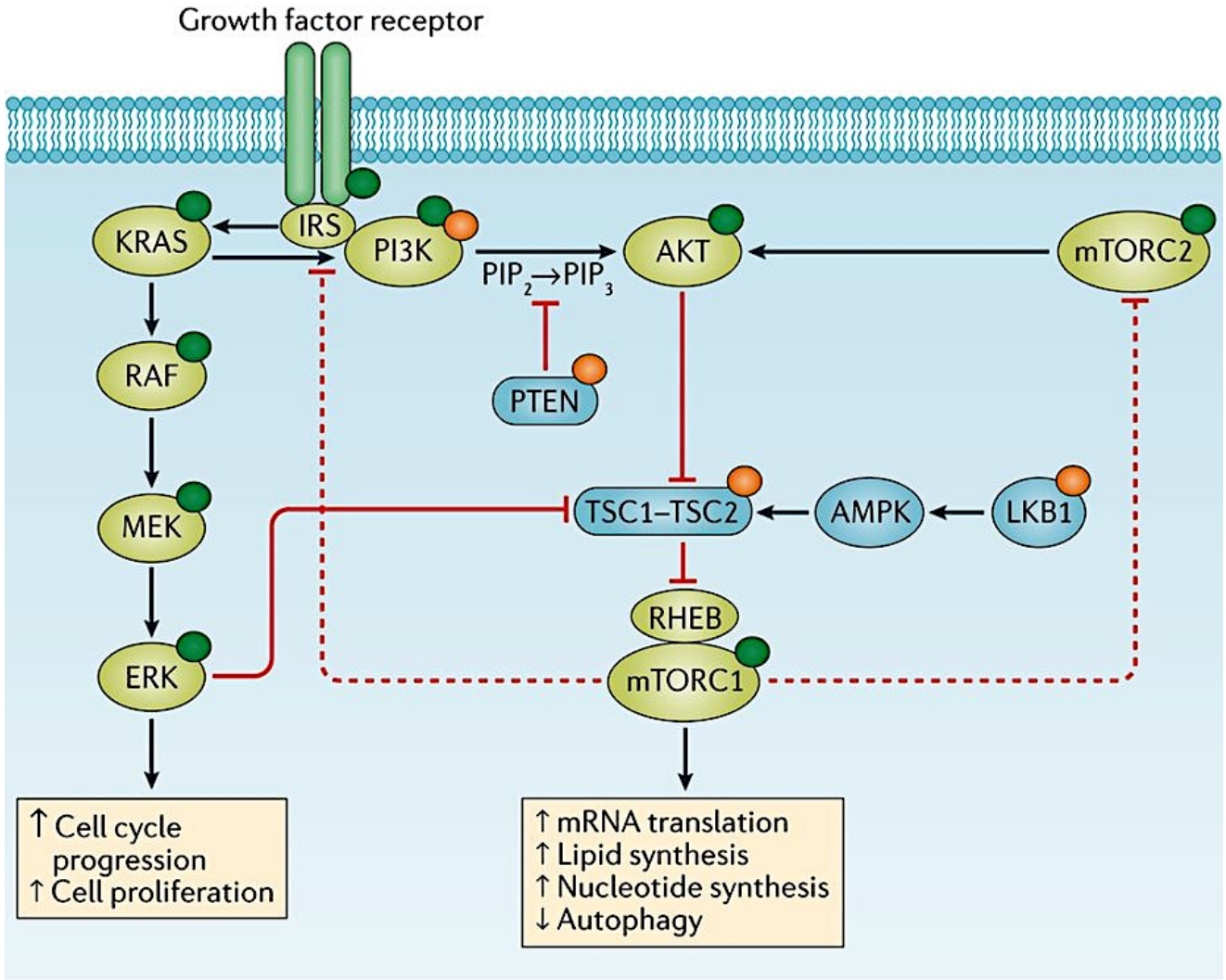
RTP
RESEARCH
TO PRACTICE

Ellison
Medical
Institute

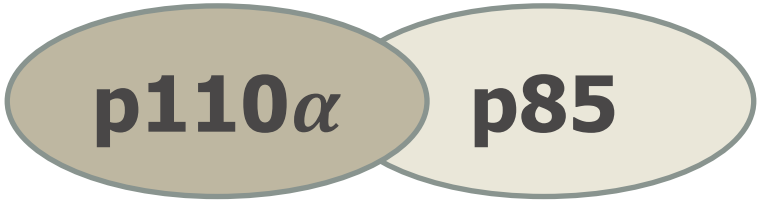
# The Role of the PI3K Pathway in HR+ Breast Cancer

Reva Basho, MD
Associate Professor of Medicine
Chief Medical Officer
Ellison Medical Institute

# The PI3K-AKT Pathway




## PI3K$\alpha$

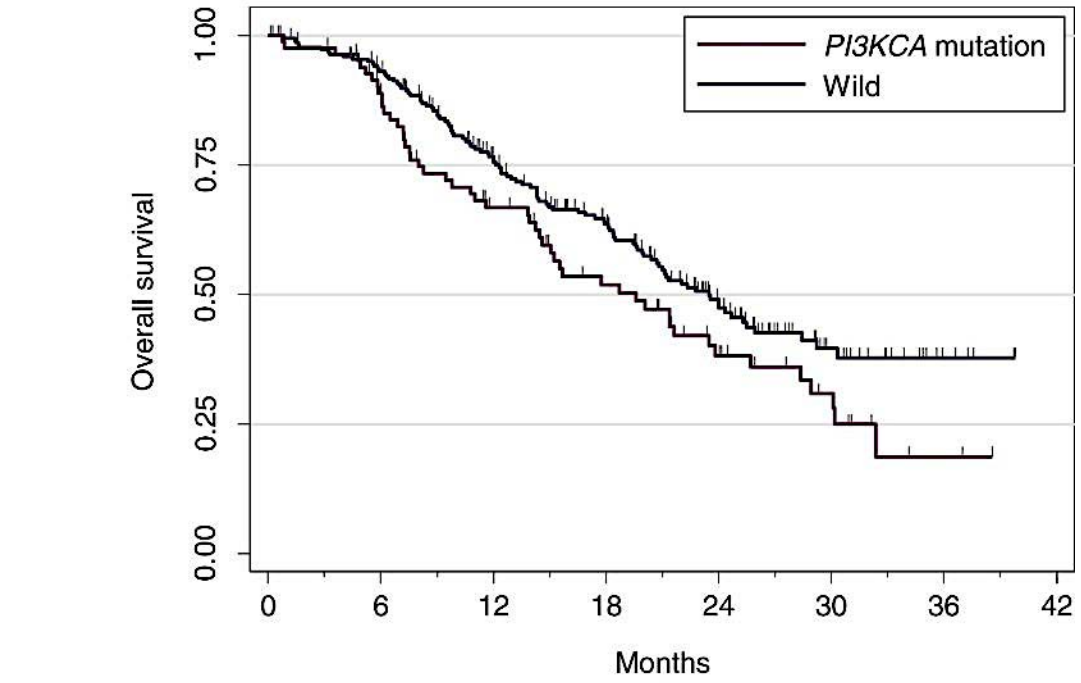



| Gene | HR+ HER2- |
|---|---|
| PIK3CA mut | 40% |
| PTEN mut/loss | 2-4% |
| PIK3R1 mut | 3% |
| AKT1 mut | 2-3% |

Janku. Nat Rev Clin Oncol 2018.
TCGA. Nature 2012.
Bareche. Annals of Oncology 2018.

# PIK3CA Mutation is Associated with Worse Outcomes

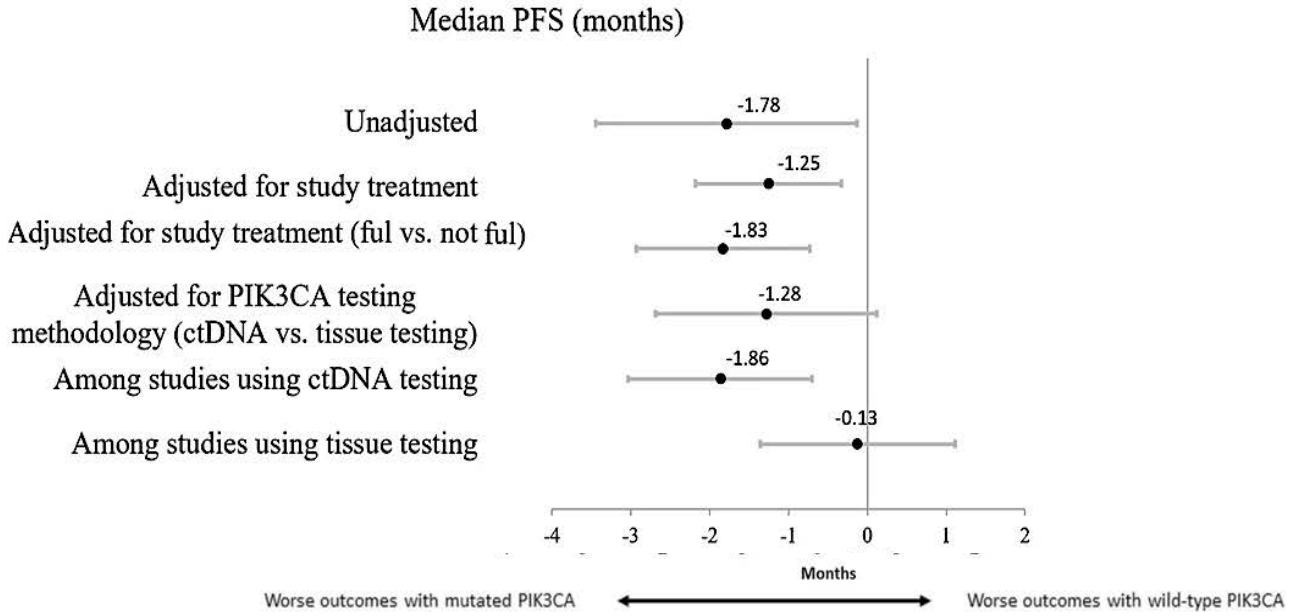
## SAFIR02




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| *PI3KCA* mutation | 104 | 70 | 48 | 33 | 19 | 11 | 2 |
| Wild | 260 | 199 | 146 | 106 | 58 | 22 | 6 |

Mosele. Annals of Oncology 2020.

## Meta-Analysis of Published Trials in HR+ ABC




Fillbrunn. BMC Cancer 2022.

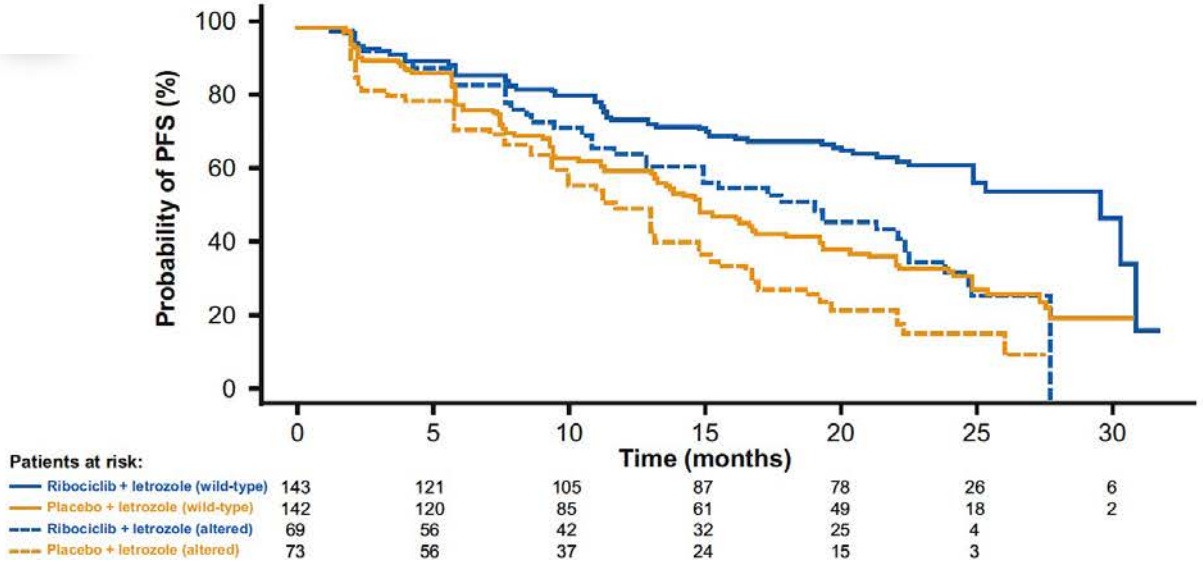
# AI + CDK4/6 Inhibition 1st Line

| Study | Agents | PFS (months) | OS (months) |
|---|---|---|---|
| **PALOMA-2** | Palbociclib + letrozole | 24.8 vs 14.5<br>HR 0.58 (0.46-0.72) | 53.9 vs 51.2<br>HR 0.96 (0.78-1.18) |
| **MONALEESA-2** | Ribociclib + letrozole | 25.3 vs 16.0<br>HR 0.57 (0.46-0.70) | 63.9 vs 51.4<br>HR 0.76 (0.63-0.93) |
| **MONARCH-3** | Abemaciclib + letrozole/ anastrozole | 28.2 vs 14.8<br>HR 0.54 (0.42-0.70) | 66.8 vs 53.7<br>HR 0.80 (0.64-1.02) |

# PI3K-Altered Tumors: Inferior Response to CDK4/6 Inhibition

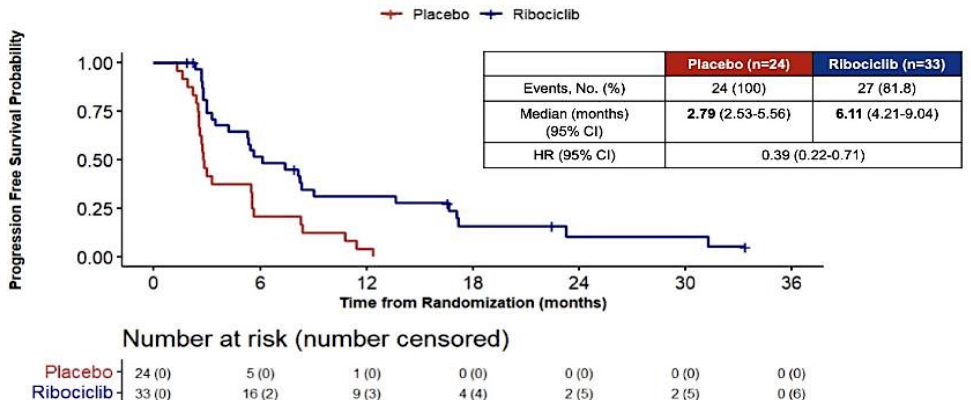
## MONALEESA-2

| | Wild-type *PIK3CA* | | Altered *PIK3CA* | |
|---|---|---|---|---|
| | Ribociclib + letrozole *n*=143 | Placebo + letrozole *n*=142 | Ribociclib + letrozole *n*=69 | Placebo + letrozole *n*=73 |
| PFS events, *n* | 54 | 93 | 40 | 55 |
| Median PFS, months (95% CI) | 29.6 (24.84–NR) | 14.69 (13.04–19.15) | 19.15 (13.01–23.85) | 12.71 (9.23–14.98) |
| Hazard ratio (95% CI) | 0.44 (0.31–0.62) | | 0.53 (0.35–0.81) | |



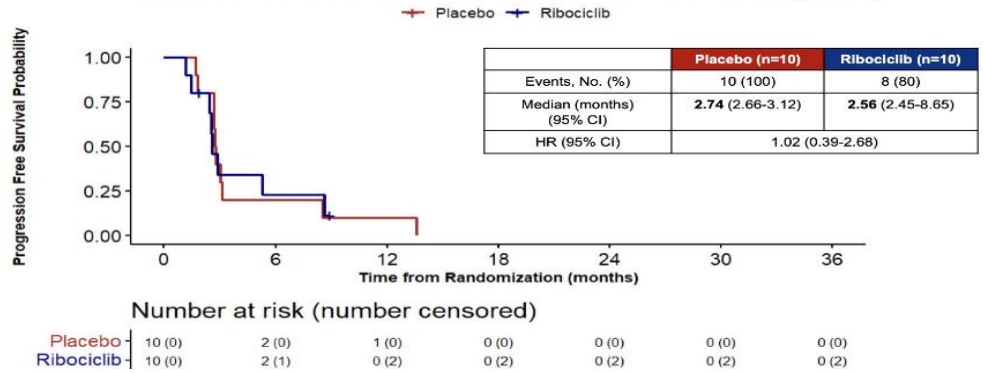

## MAINTAIN

**Fulvestrant + Baseline Without *PIK3CA Mutation* (n=57)**




| | Placebo (n=24) | Ribociclib (n=33) |
|---|---|---|
| Events, No. (%) | 24 (100) | 27 (81.8) |
| Median (months) (95% CI) | **2.79** (2.53-5.56) | **6.11** (4.21-9.04) |
| HR (95% CI) | 0.39 (0.22-0.71) | |

**Fulvestrant + Baseline With *PIK3CA* Mutation (n=20)**




| | Placebo (n=10) | Ribociclib (n=10) |
|---|---|---|
| Events, No. (%) | 10 (100) | 8 (80) |
| Median (months) (95% CI) | **2.74** (2.66-3.12) | **2.56** (2.45-8.65) |
| HR (95% CI) | 1.02 (0.39-2.68) | |

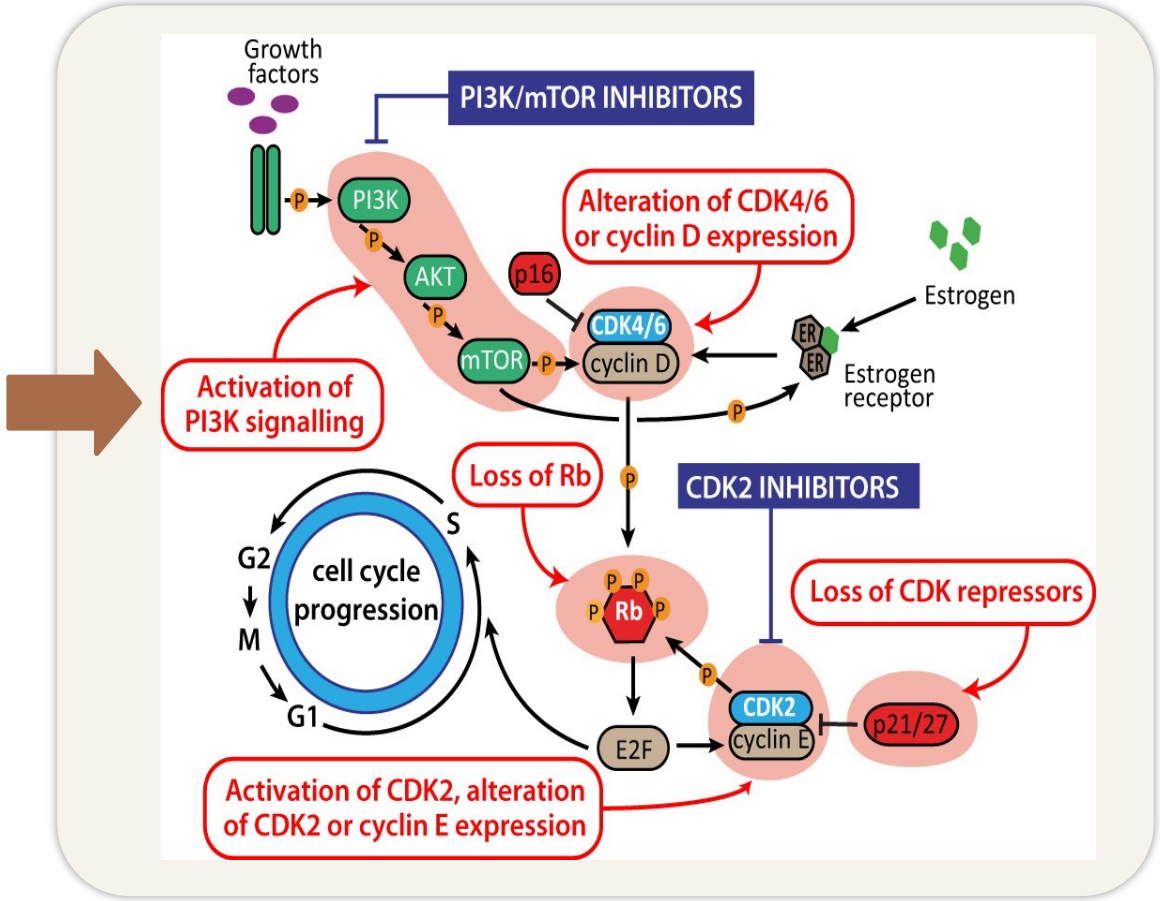
Hortobagyi. Annals of Oncology 2018. Kalinsky. J Clin Oncol 2023.

# Treatment after Progression on 1L CDK4/6i

Progression on 1L CDK4/6i → NGS Testing → Targetable Mutations

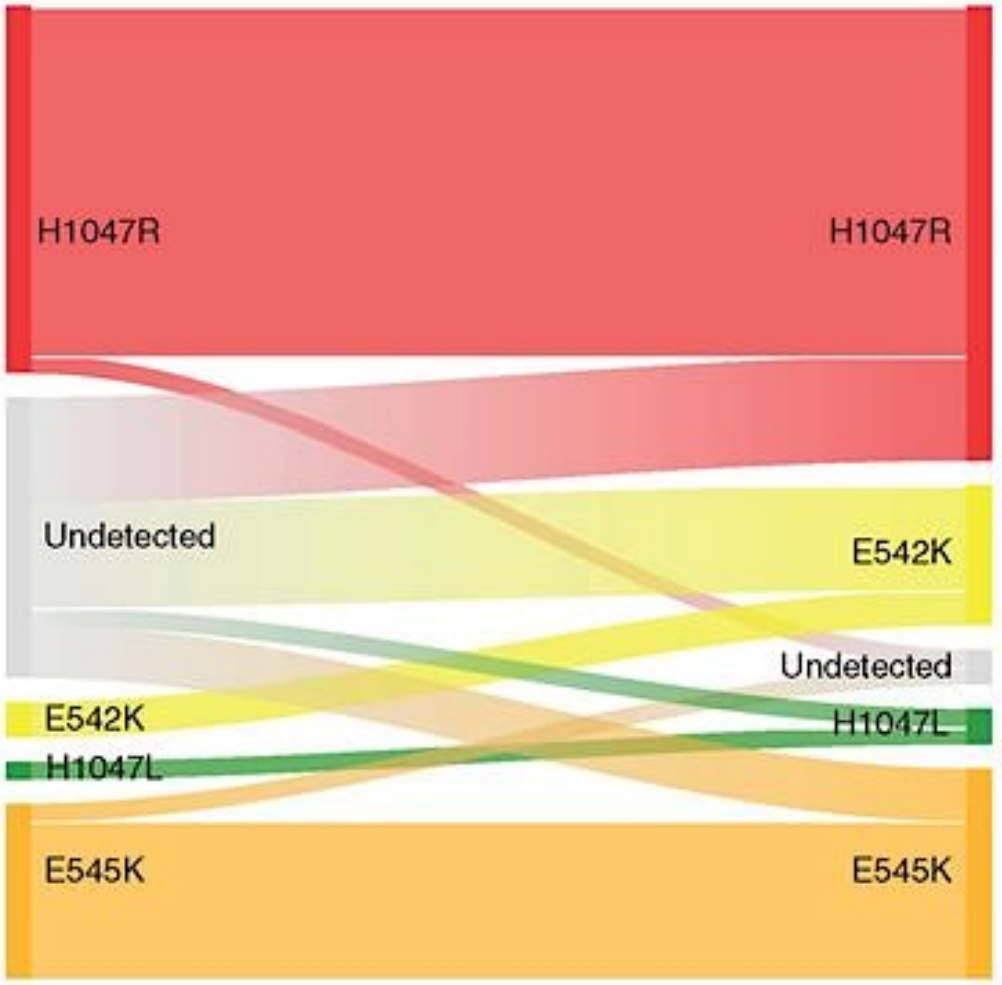
NGS Testing → No Targetable Mutations

# PI3K Pathway Through the Course of CDK4/6i Treatment




Portman. Endocr Relat Cancer 2019.

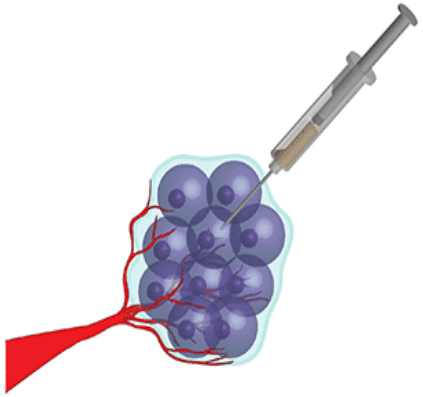
## MONALEESA-2 PIK3CA Mutations




O'Leary. Cancer Discov 2018.

# NGS Testing to Guide 2L Therapy

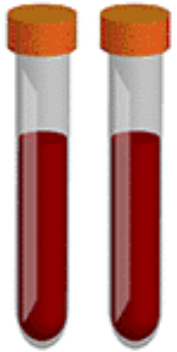
## Tissue Biopsy



| Pros |
| --- |
| - Can use archival samples<br>- Histology/molecular profiling |

| Cons |
| --- |
| - Invasive<br>- Limited insights into tumor heterogeneity |

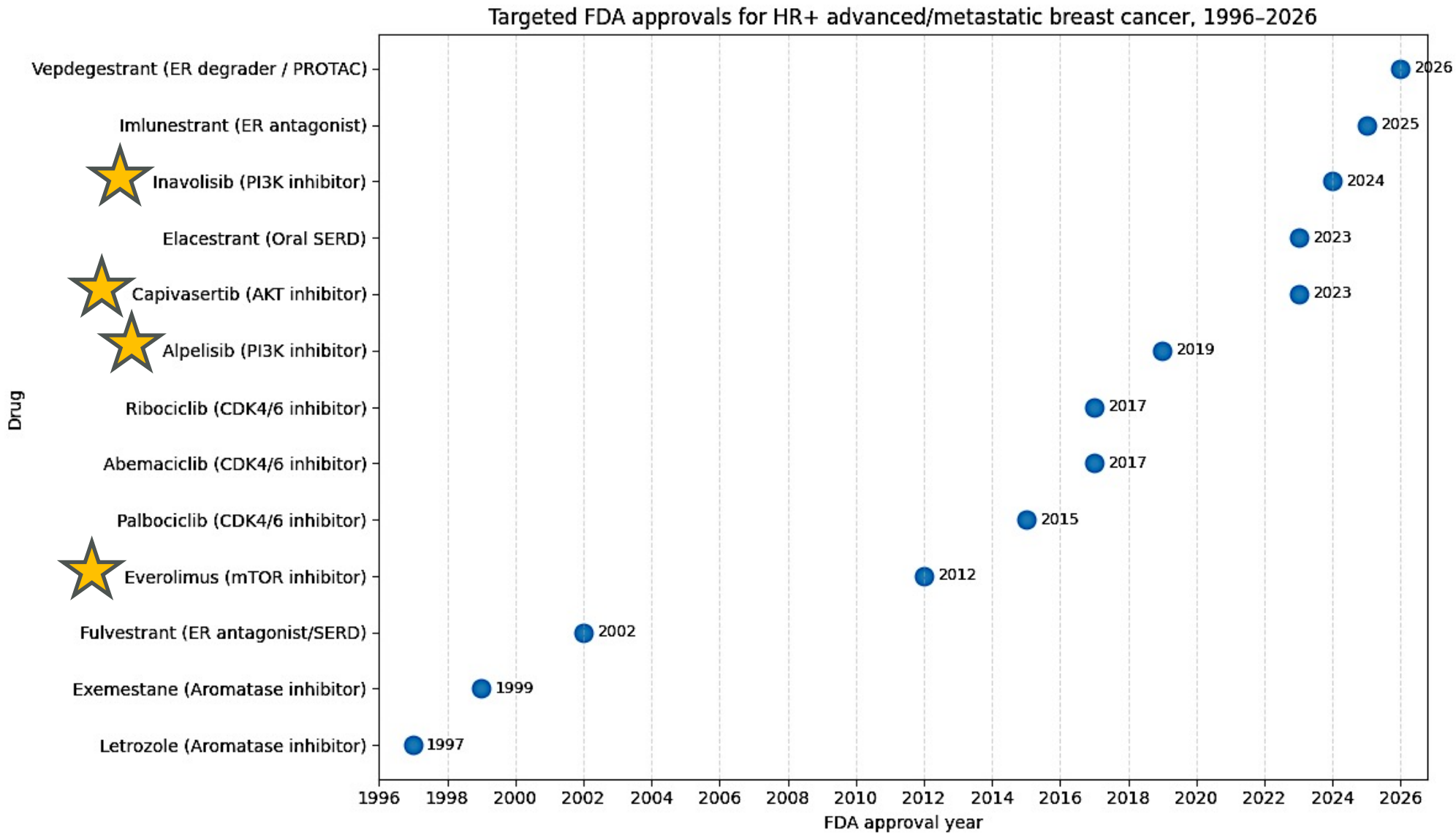
## Liquid Biopsy



| Pros |
| --- |
| - Non-invasive blood test<br>- Reflects tumor heterogeneity<br>- Real-time sequencing |

| Cons |
| --- |
| - False positives from clonal hematopoiesis<br>- Lower sensitivity |

# FDA Approvals of Targeted Therapies for HR+ Advanced Breast Cancer over the Years



# Case Presentation

# Case Presentation

Patient is a 62 yo F with no significant PMH who presents with L breast mass and worsening R hip pain

- She is diagnosed with HR+/HER2- MBC with disease in the hip and spine
- She is started on 1L therapy with letrozole + ribociclib + denosumab
- She does well for approximately 2 years
- Recently, she was found to have progression of her disease with new liver metastases
- Change in therapy is planned
- What should you do to guide 2L therapy?

NGS testing to guide next-line therapy. Can test archival tissue biopsy (if not already done) and/or send liquid biopsy.

# Take Home Points

- Alterations in the PI3K pathway are prevalent in HR+ metastatic breast cancer
  - ~40% have PIK3CA mutation
- PI3K pathway activation is associated with worse clinical outcomes
- There are a growing number of agents targeting the PI3K pathway
- Timely sequencing for identification of patients for pathway-directed therapy is important

# Discussion Questions

**How do you approach testing for alterations in the PI3K/AKT/mTOR pathway in your own practice? What role can oncology nurses play in facilitating appropriate testing?**

# Agenda

**Introduction:** Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway

**Module 1: Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)**

**Module 2:** Strategies to Prevent and Manage Hyperglycemia

**Module 3:** Clinical Utility of Capivasertib for HR-Positive mBC

**Module 4:** Mitigation and Management of Gastrointestinal Adverse Events

**Module 5:** Management of Dermatologic Adverse Events

**Module 6:** Potential Role of Gedatolisib in the Management of HR-Positive mBC

**Module 7:** Monitoring and Management of Cytopenias

RTP
RESEARCH
TO PRACTICE

Mass General Brigham
Mass General Cancer Center

# Role of Inavolisib in HR+ Metastatic Breast Cancer

**Oncology Nursing Society Annual Meeting – May 2026**
**PI3K/AKT/mTOR Pathway in HR+ Metastatic Breast Cancer Symposium**
**Research to Practice**

**Seth A. Wander, MD, PhD**
**Director of Precision Medicine, Termeer Center for Targeted Therapies**
**Director of Translational Research, Breast Oncology Program**
**Assistant Professor of Medicine, Harvard Medical School**
**Massachusetts General Hospital**

**swander@mgh.harvard.edu**

# Regional Targets for Various PI3K Inhibitors

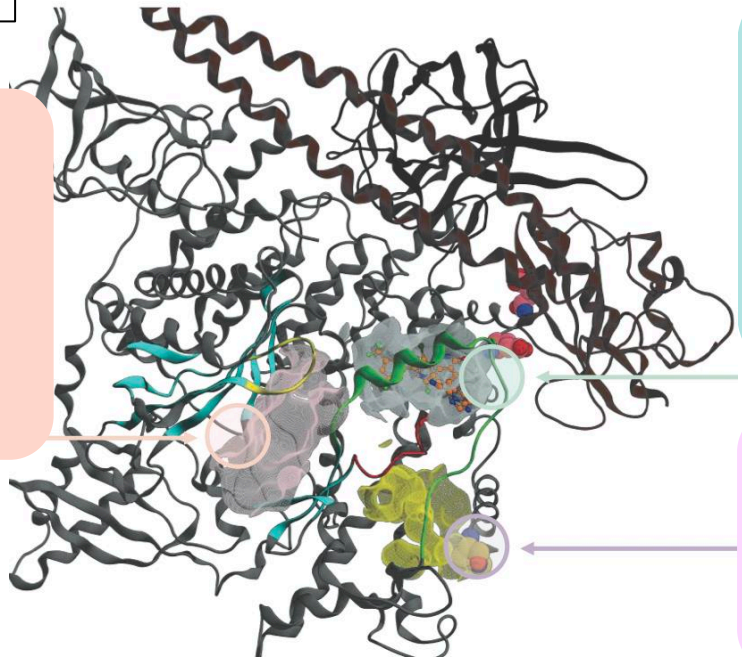
**Non-Mutant Selective**
**Bind orthosteric (active) site**
**Inhibit WT and mutant PI3Ka**

**ATP Binding Site**

Alpelisib

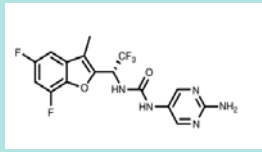
Inavolisib

TOS-358

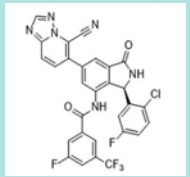


**Pan-Mutant Selective**

STX-478



RLY-2608

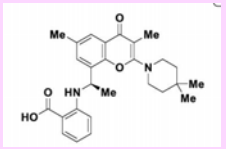


RLY-5836

ETX-636

**H1047R-Mutant Selective**

LOXO-783



OKI-219

CGT-6297

**Pan-Mutant Selective**
**Bind novel allosteric site**
**Inhibits multiple mutant PI3Ka**

**Downstream Inhibitors**
**Block pathway elements**
**AKTi, mTORi, etc**

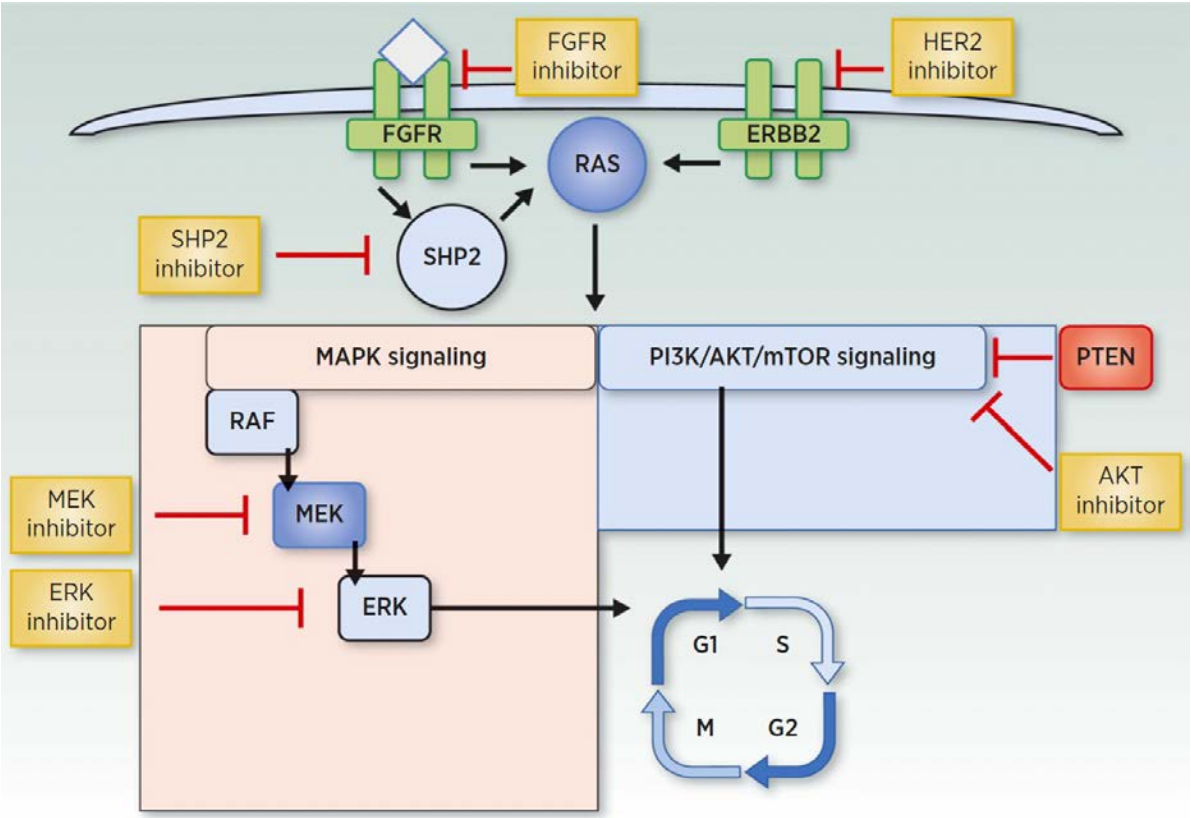
**Single Mutant Selective**
**Bind hotspot mutant site**
**Inhibits only one mutant PI3Ka**

**Slide modified courtesy of Dr. A Varkaris**

# Resistance Drivers Define New Therapeutic Targets

**Oncogenic growth signaling mediators**

Receptor tyrosine kinases
RAS / MAPK pathway
PI3K/AKT/mTOR pathway




RTKs @ cell surface + external ligands

PI3K >>>>>> Activated PI3K

*Alpelisib*
*Inavolisib*

Gedatolisib

AKT

*Capivasertib*

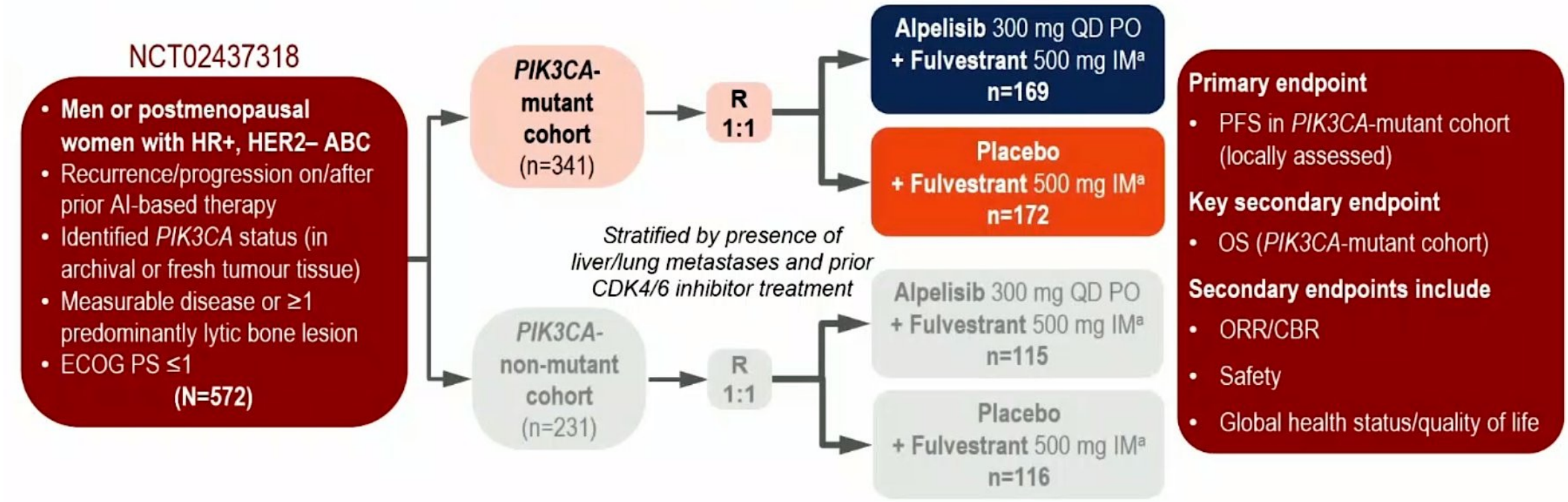
*Everolimus*

mTOR::

Cellular Growth
Survival + Division
Motility + Metastasis

Lloyd MR et al CCR 2022

# SOLAR-1: 1st Generation PI3K inhibition in HR+ MBC

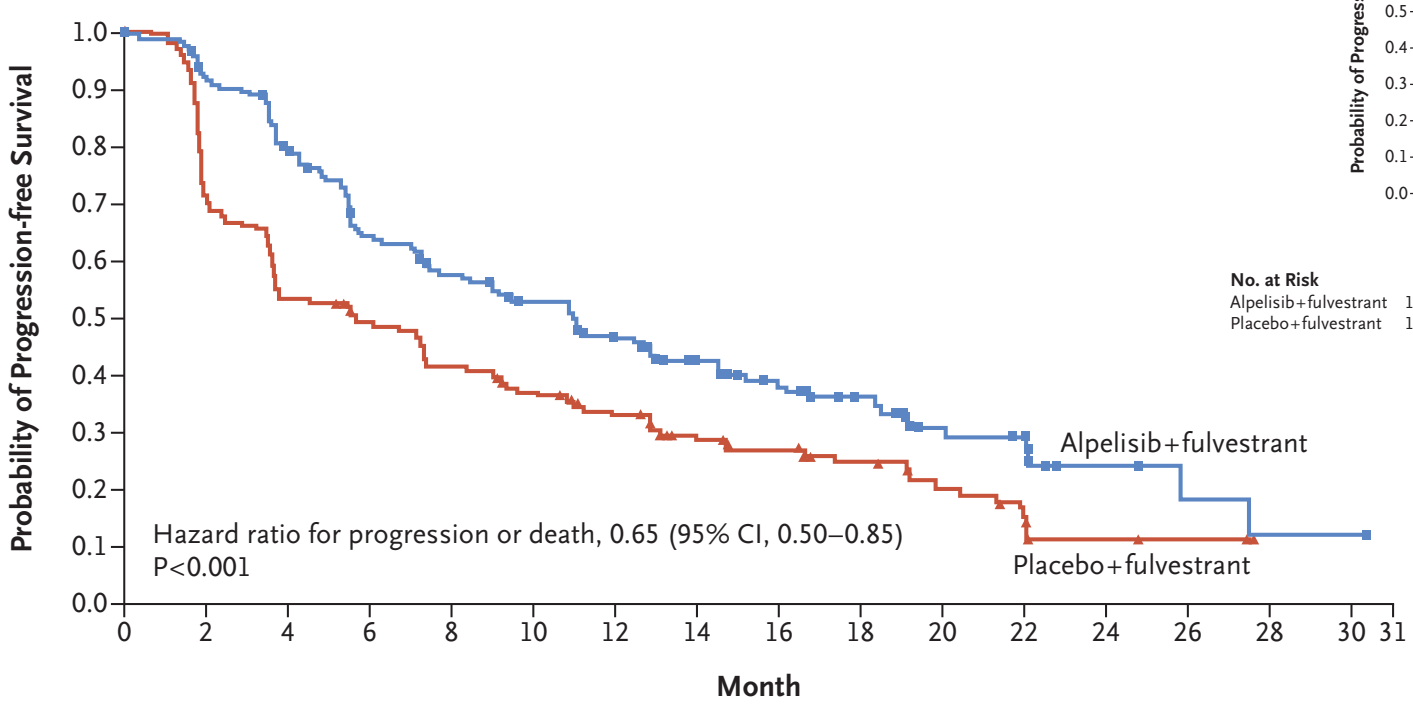



Andre F et al NEJM 2019

# SOLAR-1: Alpelisib Clinical Outcomes

**Median PFS 5.7m > 11.0m**
**HR 0.65 (95% CI 0.50-0.85), p<0.001**

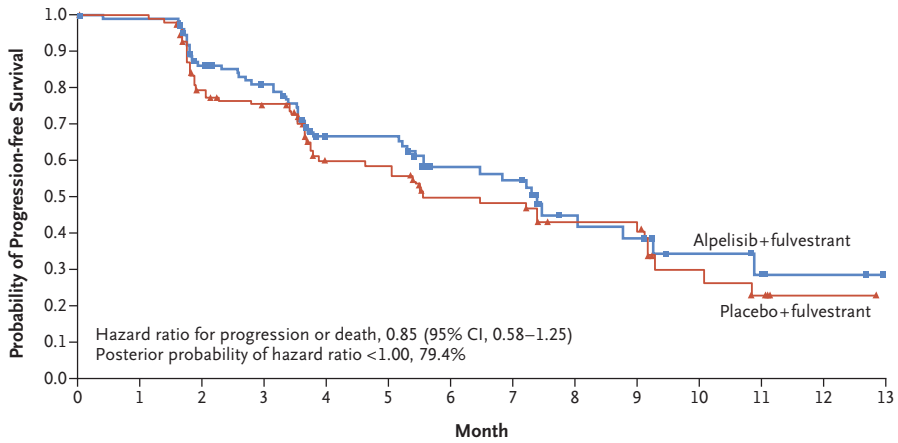
**A** Cohort with *PIK3CA*-Mutated Cancer




**No. at Risk**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alpelisib+fulvestrant | 169 | 145 | 123 | 97 | 85 | 75 | 62 | 50 | 39 | 30 | 17 | 14 | 5 | 3 | 1 | 1 | 0 |
| Placebo+fulvestrant | 172 | 120 | 89 | 80 | 67 | 58 | 48 | 37 | 29 | 20 | 14 | 9 | 3 | 2 | 0 | 0 | 0 |

**B** Cohort without *PIK3CA*-Mutated Cancer




**No. at Risk**

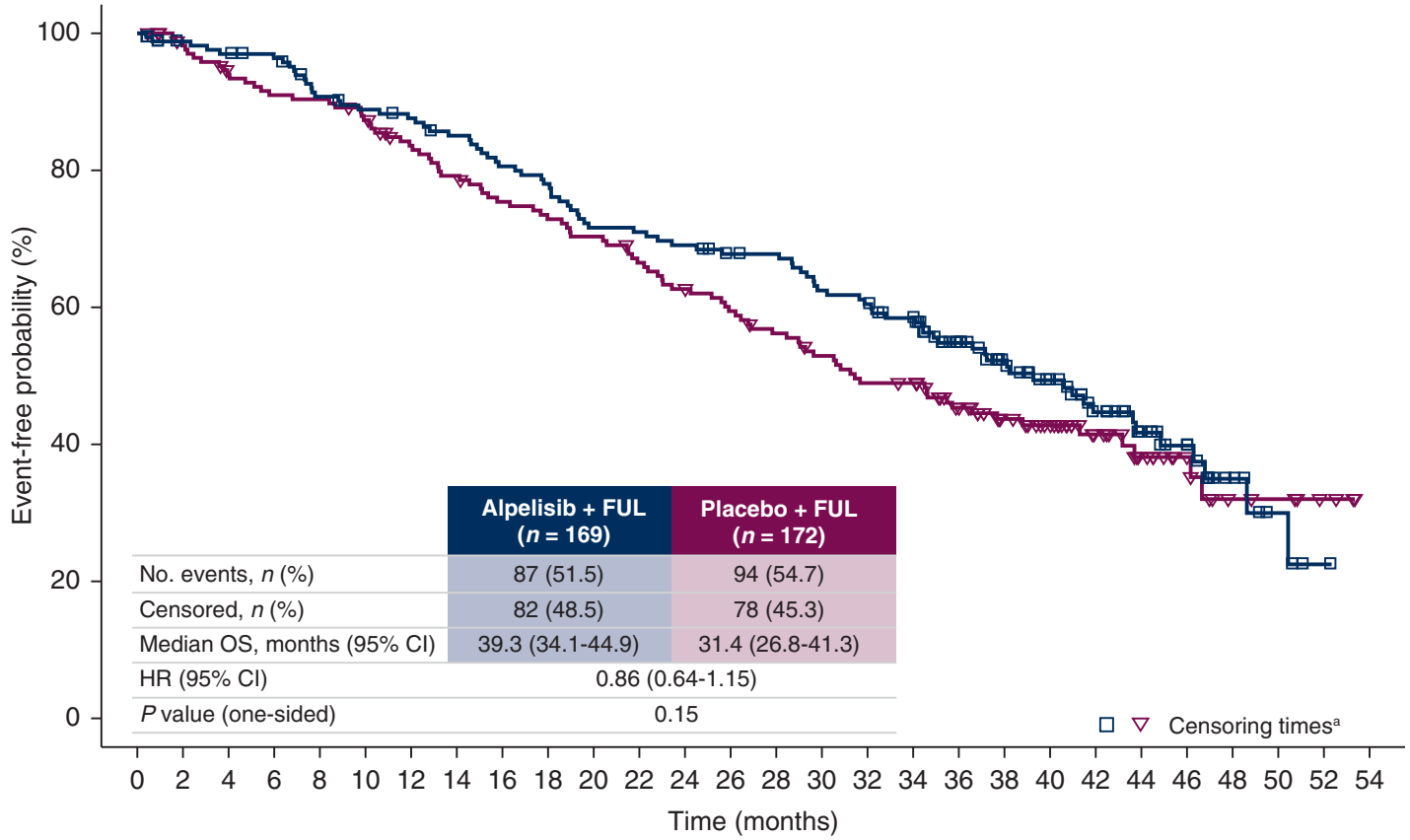
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alpelisib+fulvestrant | 115 | 110 | 86 | 76 | 48 | 48 | 31 | 29 | 14 | 12 | 7 | 5 | 3 | 0 |
| Placebo+fulvestrant | 116 | 110 | 79 | 72 | 43 | 42 | 31 | 30 | 20 | 20 | 8 | 5 | 1 | 0 |

**Andre F et al NEJM 2019; Andre F et al Ann Onc 2020**

# SOLAR-1: Alpelisib Clinical Outcomes

**Median OS 31.4m > 39.3m**

**HR 0.86 (95% CI 0.64-1.15), p=0.15**




| | Alpelisib + FUL (*n* = 169) | Placebo + FUL (*n* = 172) |
|---|---|---|
| No. events, *n* (%) | 87 (51.5) | 94 (54.7) |
| Censored, *n* (%) | 82 (48.5) | 78 (45.3) |
| Median OS, months (95% CI) | 39.3 (34.1-44.9) | 31.4 (26.8-41.3) |
| HR (95% CI) | 0.86 (0.64-1.15) | |
| *P* value (one-sided) | 0.15 | |

Number of patients still at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Alpelisib + FUL** | 169 | 162 | 159 | 156 | 145 | 141 | 138 | 133 | 126 | 122 | 112 | 111 | 108 | 103 | 102 | 94 | 91 | 85 | 68 | 56 | 47 | 35 | 26 | 19 | 9 | 4 | 1 | 0 |
| **Placebo + FUL** | 172 | 164 | 155 | 150 | 149 | 143 | 133 | 126 | 119 | 115 | 111 | 104 | 98 | 92 | 86 | 80 | 74 | 73 | 60 | 49 | 42 | 29 | 20 | 13 | 7 | 6 | 3 | 0 |

**Andre F et al NEJM 2019; Andre F et al Ann Onc 2020**

# SOLAR-1: Alpelisib Toxicity

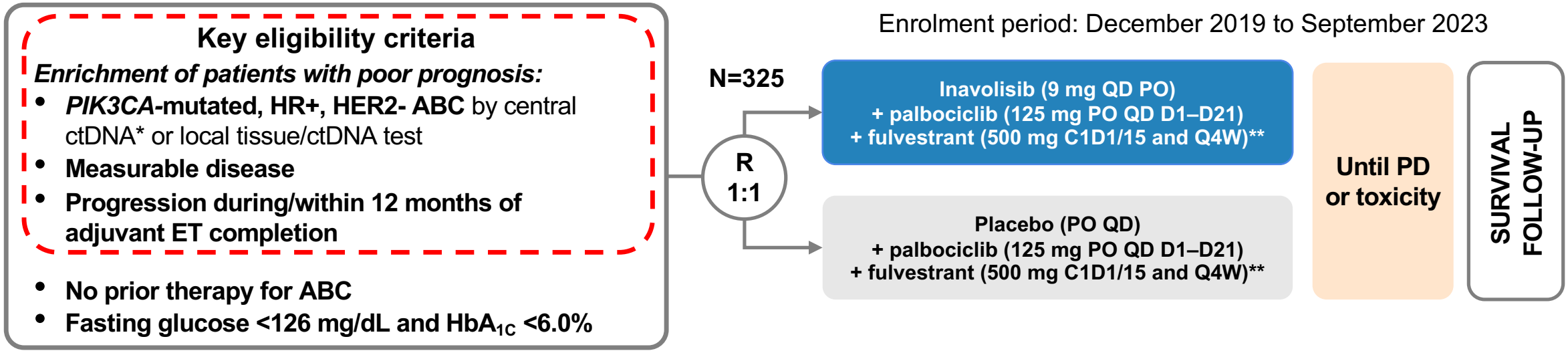
**Table 3. Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.***

| Adverse Event | Alpelisib–Fulvestrant Group (N = 284) | | | Placebo–Fulvestrant Group (N = 287) | | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| | *number of patients (percent)* | | | | | |
| Any adverse event | 282 (99.3) | 183 (64.4) | 33 (11.6) | 264 (92.0) | 87 (30.3) | 15 (5.2) |
| Hyperglycemia† | 181 (63.7) | 93 (32.7) | 11 (3.9) | 28 (9.8) | 1 (0.3) | 1 (0.3) |
| Diarrhea‡ | 164 (57.7) | 19 (6.7) | 0 | 45 (15.7) | 1 (0.3) | 0 |
| Nausea‡ | 127 (44.7) | 7 (2.5) | 0 | 64 (22.3) | 1 (0.3) | 0 |
| Decreased appetite | 101 (35.6) | 2 (0.7) | 0 | 30 (10.5) | 1 (0.3) | 0 |
| Rash§ | 101 (35.6) | 28 (9.9) | 0 | 17 (5.9) | 1 (0.3) | 0 |
| Vomiting‡ | 77 (27.1) | 2 (0.7) | 0 | 28 (9.8) | 1 (0.3) | 0 |
| Weight loss | 76 (26.8) | 11 (3.9) | 0 | 6 (2.1) | 0 | 0 |
| Stomatitis | 70 (24.6) | 7 (2.5) | 0 | 18 (6.3) | 0 | 0 |
| Fatigue | 69 (24.3) | 10 (3.5) | 0 | 49 (17.1) | 3 (1.0) | 0 |
| Asthenia | 58 (20.4) | 5 (1.8) | 0 | 37 (12.9) | 0 | 0 |
| Alopecia | 56 (19.7) | 0 | 0 | 7 (2.4) | 0 | 0 |
| Mucosal inflammation | 52 (18.3) | 6 (2.1) | 0 | 3 (1.0) | 0 | 0 |
| Pruritus | 51 (18.0) | 2 (0.7) | 0 | 16 (5.6) | 0 | 0 |
| Headache | 50 (17.6) | 2 (0.7) | 0 | 38 (13.2) | 0 | 0 |
| Dysgeusia | 47 (16.5) | 0 | 0 | 10 (3.5) | 0 | 0 |
| Arthralgia | 32 (11.3) | 1 (0.4) | 0 | 47 (16.4) | 3 (1.0) | 0 |

A1c < 6.4%
Discontinuation Rate: 25%

**Andre F et al NEJM 2019**

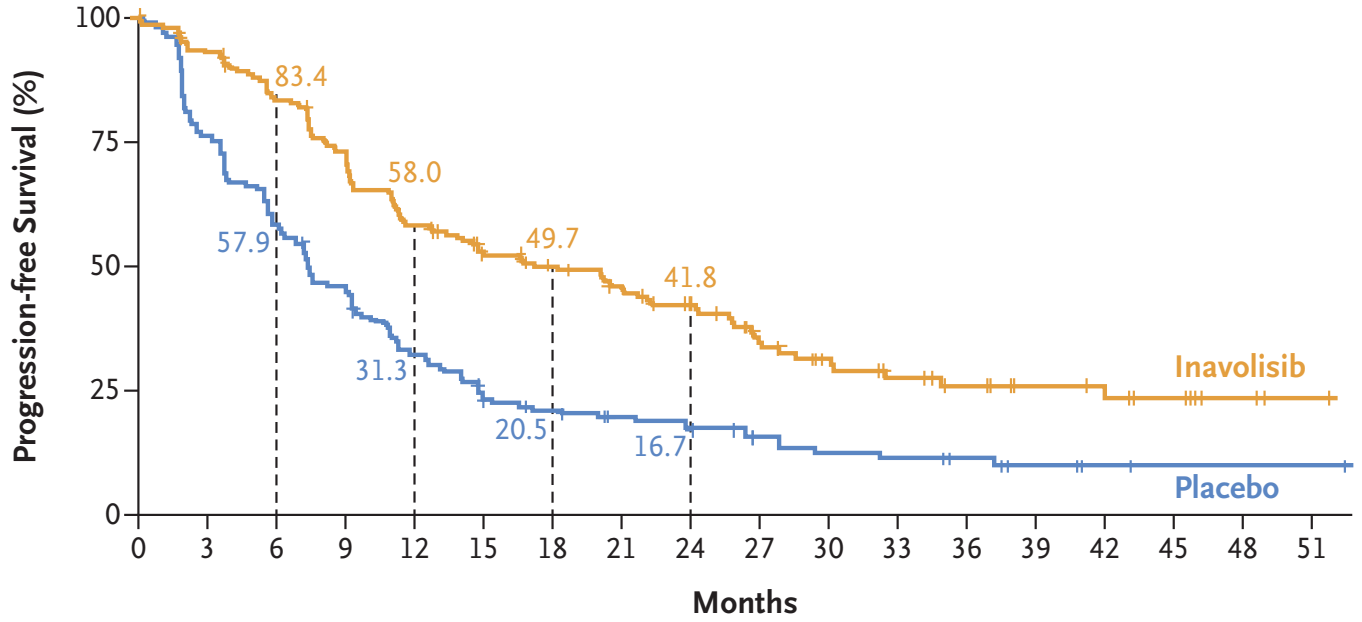
# INAVO120: Inavolisib Triplet in ET-Refractory HR+ MBC




Turner NC et al NEJM 2024

# INAVO120: Inavolisib Clinical Outcomes

**PFS:**
**Median PFS 7.3m > 17.2m**
**HR 0.42 (95% CI 0.32-0.55)**




| No. at Risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inavolisib | 161 | 146 | 129 | 112 | 89 | 73 | 65 | 57 | 46 | 32 | 25 | 19 | 15 | 11 | 10 | 7 | 3 | 1 |
| Placebo | 164 | 125 | 95 | 74 | 50 | 34 | 30 | 24 | 21 | 14 | 11 | 10 | 8 | 4 | 2 | 1 | 1 | 1 |

| | No. of Patients with Event (%) | Median Progression-free Survival (95% CI) |
|---|---|---|
| | | *mo* |
| **Inavolisib (N=161)** | 103 (64.0) | 17.2 (11.6–22.2) |
| **Placebo (N=164)** | 141 (86.0) | 7.3 (5.9–9.2) |

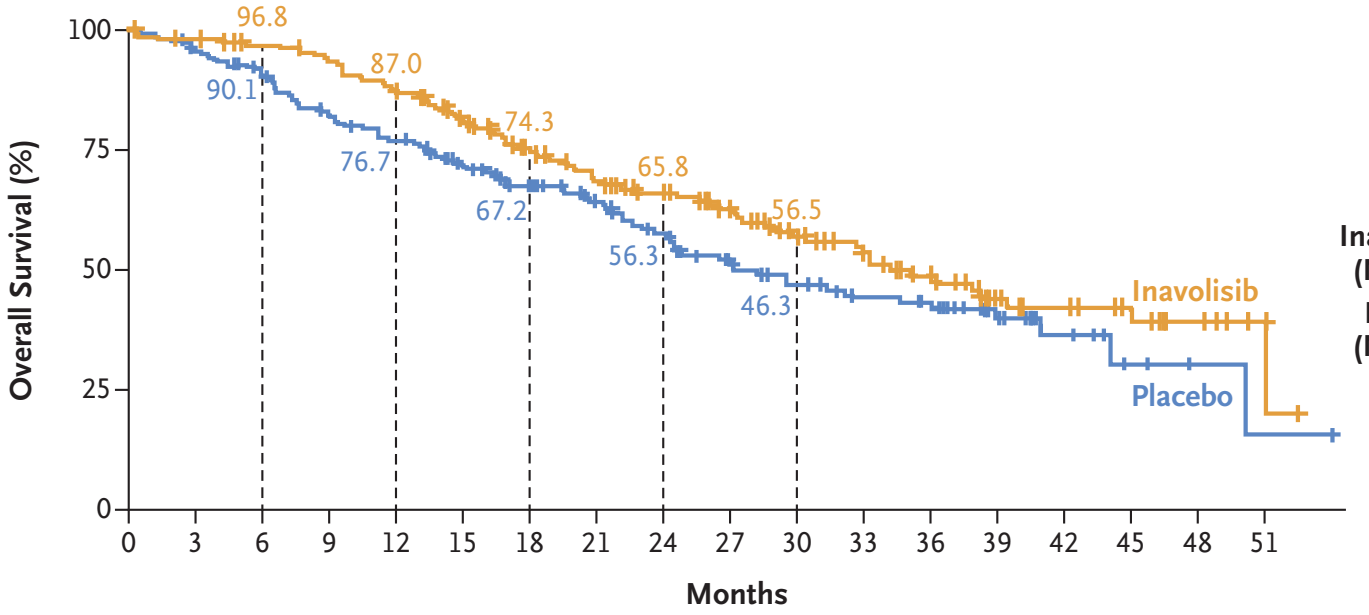
Stratified hazard ratio for disease progression or death, 0.42 (95% CI, 0.32–0.55)

Jhaveri KL et al NEJM 2025

# INAVO120: Inavolisib Clinical Outcomes

**OS:**
**Median OS 27m > 34m**
**HR 0.67 (95% CI 0.48-0.94, p=0.02)**

**Overall Survival in the Full Analysis Population**




| | No. of Deaths (%) | Median Overall Survival (95% CI) |
|---|---|---|
| | | *mo* |
| Inavolisib (N=161) | 72 (44.7) | 34.0 (28.4–44.8) |
| Placebo (N=164) | 82 (50.0) | 27.0 (22.8–38.7) |

Stratified hazard ratio for death, 0.67 (95% CI, 0.48–0.94)
P=0.02

**No. at Risk**

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inavolisib | 161 | 155 | 149 | 142 | 131 | 114 | 99 | 88 | 78 | 67 | 54 | 43 | 34 | 22 | 19 | 13 | 7 | 1 |
| Placebo | 164 | 155 | 142 | 127 | 119 | 104 | 90 | 77 | 63 | 48 | 42 | 36 | 32 | 18 | 10 | 4 | 2 | 1 |

Jhaveri KL et al NEJM 2025

# INAVO120: Toxicity Experience

**Table 2. Adverse Events.***

| Adverse Event | Inavolisib (N = 162) | | Placebo (N = 162) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| Neutropenia | 144 (88.9) | 130 (80.2) | 147 (90.7) | 127 (78.4) |
| Thrombocytopenia | 78 (48.1) | 23 (14.2) | 73 (45.1) | 7 (4.3) |
| Stomatitis and mucosal inflammation | 83 (51.2) | 9 (5.6) | 43 (26.5) | 0 |
| Anemia | 60 (37.0) | 10 (6.2) | 59 (36.4) | 3 (1.9) |
| Hyperglycemia | 95 (58.6) | 9 (5.6) | 14 (8.6) | 0 |
| Diarrhea | 78 (48.1) | 6 (3.7) | 26 (16.0) | 0 |
| Nausea | 45 (27.8) | 1 (0.6) | 27 (16.7) | 0 |
| Rash | 41 (25.3) | 0 | 28 (17.3) | 0 |
| Decreased appetite | 38 (23.5) | 0 | 14 (8.6) | 0 |
| Fatigue | 38 (23.5) | 0 | 21 (13.0) | 2 (1.2) |
| Covid-19 | 37 (22.8) | 3 (1.9) | 17 (10.5) | 1 (0.6) |
| Headache | 34 (21.0) | 0 | 22 (13.6) | 0 |
| Leukopenia | 28 (17.3) | 11 (6.8) | 40 (24.7) | 17 (10.5) |
| Ocular toxic effects | 36 (22.2) | 0 | 21 (13.0) | 0 |

A1c < 6%
Discontinuation Rate: 6.8%

Turner NC et al NEJM 2024

# Key Toxicity Experience Across PAM Pathway Inhibitors

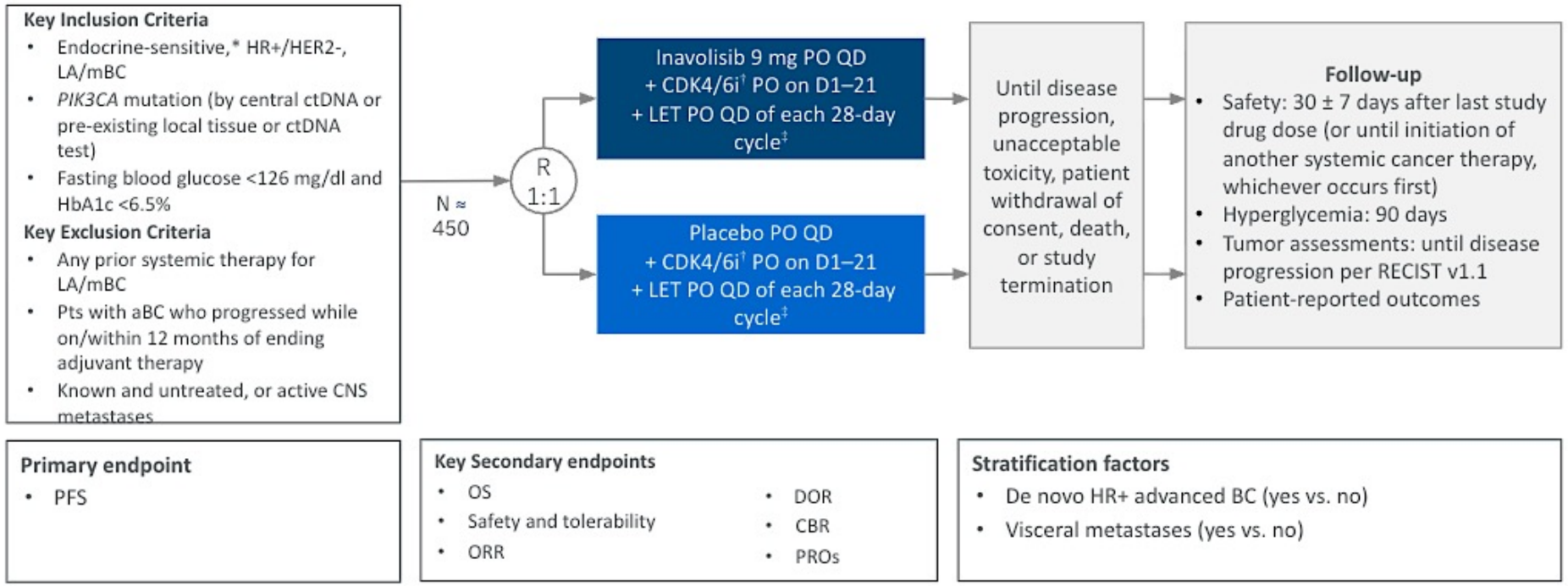
| | SOLAR-1 | | INAVO120 | | Capitello291 | | VIKTORIA-1 | |
|---|---|---|---|---|---|---|---|---|
| | Alpelisib | | Inavolisib | | Capivasertib | | Gedatolisib | |
| | All Grade | Grade 3+ | All Grade | Grade 3+ | All Grade | Grade 3+ | All Grade | Grade 3+ |
| Hyperglycemia | 63.7% | 36.6% | 58.6% | 5.6% | 16.3% | 2.3% | 9.2% | 2.3% |
| Diarrhea | 57.7% | 6.7% | 48.1% | 3.7% | 72.4% | 9.3% | 16.9% | 1.5% |
| Mucositis | 24.6% | 2.5% | 51.2% | 5.6% | 14.6% | 2.0% | 69.2% | 19.2% |
| Rash | 35.6% | 9.9% | 25.3% | 0.0% | 38.0% | 12.1% | 27.7% | 4.6% |
| | Inclusion A1c <6.4% | | Inclusion A1c <6% | | Inclusion A1c <8% | | Inclusion A1c <6.4% | |

Andre F et al NEJM 2019
Turner NC et al NEJM 2024
Turner NC et al NEJM 2023
Hurvitz SA et al ESMO 2025

# INAVO123: Triplet Therapy in the 1L Metastatic Setting

Phase 3 Study of 1L Inavolisib or Placebo + CDK4/6 inhibitor + Letrozole in endocrine-sensitive, HR+/HER2–, *PIK3CA*-mut Advanced BC

## INAVO123 STUDY DESIGN




* De novo or relapsed after at least 2 years of standard neoadjuvant/adjuvant endocrine therapy. † Palbociclib is the only option currently. Additional CDK4/6i options may be available in the future. ‡ Pre- and perimenopausal women, and men will receive an LHRH agonist for the duration of the study treatment.

aBC, advanced breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; D, day; DOR, duration of response; HR, hormone receptor; IM, intramuscularly; LA, locally advanced; LET, letrozole; mBC, metastatic breast cancer; mut, mutated; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PRO, patient-reported outcome; QD, once daily; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; RECIST v1.1. 1. Cortés J et al. Presented at the European Society for Medical Oncology (ESMO) Breast Cancer Annual Congress. Munich, Germany. May 14-17, 2025. #408TiP. 2. NIH. Available at: NCT06790693. Accessed on August 28, 2025.

# Case Presentation

# Case Presentation: Inavolisib

52yo post-menopausal woman with HTN and HLD (A1c WNL)
Prior pT2N1 HR+/HER2- breast cancer diagnosed 4 years prior: treated with bilateral mastectomy (BRCA-WT), adjuvant TC, ovarian suppression and letrozole (good adherence)

New back and hip pain > imaging concerning for multifocal lytic osseous disease and several liver lesions up to 2.3cm (normal LFTs)

Liver biopsy: metastatic breast cancer, ER/PR+, HER2 IHC 1+
NGS (MGH Snapshot): PIK3CA H1047R (VAF 35%), TP53 SNV, TMB 7, MSS
ctDNA (Guardant): PIK3CA H1047R (VAF 26%), TP53 SNV, TMB 4

1st line therapy initiated with ***fulvestrant, palbociclib and inavolisib*** > ongoing response x14m

# Discussion Questions

**For which patients are you prioritizing the triplet regimen of inavolisib/palbociclib/fulvestrant in the front-line setting?**

**What side effects can occur with inavolisib? What are the top things that you would tell a patient who is to going receive inavolisib/palbociclib/fulvestrant about potential toxicities?**

# Agenda

**Introduction:** Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway

**Module 1:** Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)

**Module 2: Strategies to Prevent and Manage Hyperglycemia**

**Module 3:** Clinical Utility of Capivasertib for HR-Positive mBC

**Module 4:** Mitigation and Management of Gastrointestinal Adverse Events

**Module 5:** Management of Dermatologic Adverse Events

**Module 6:** Potential Role of Gedatolisib in the Management of HR-Positive mBC

**Module 7:** Monitoring and Management of Cytopenias

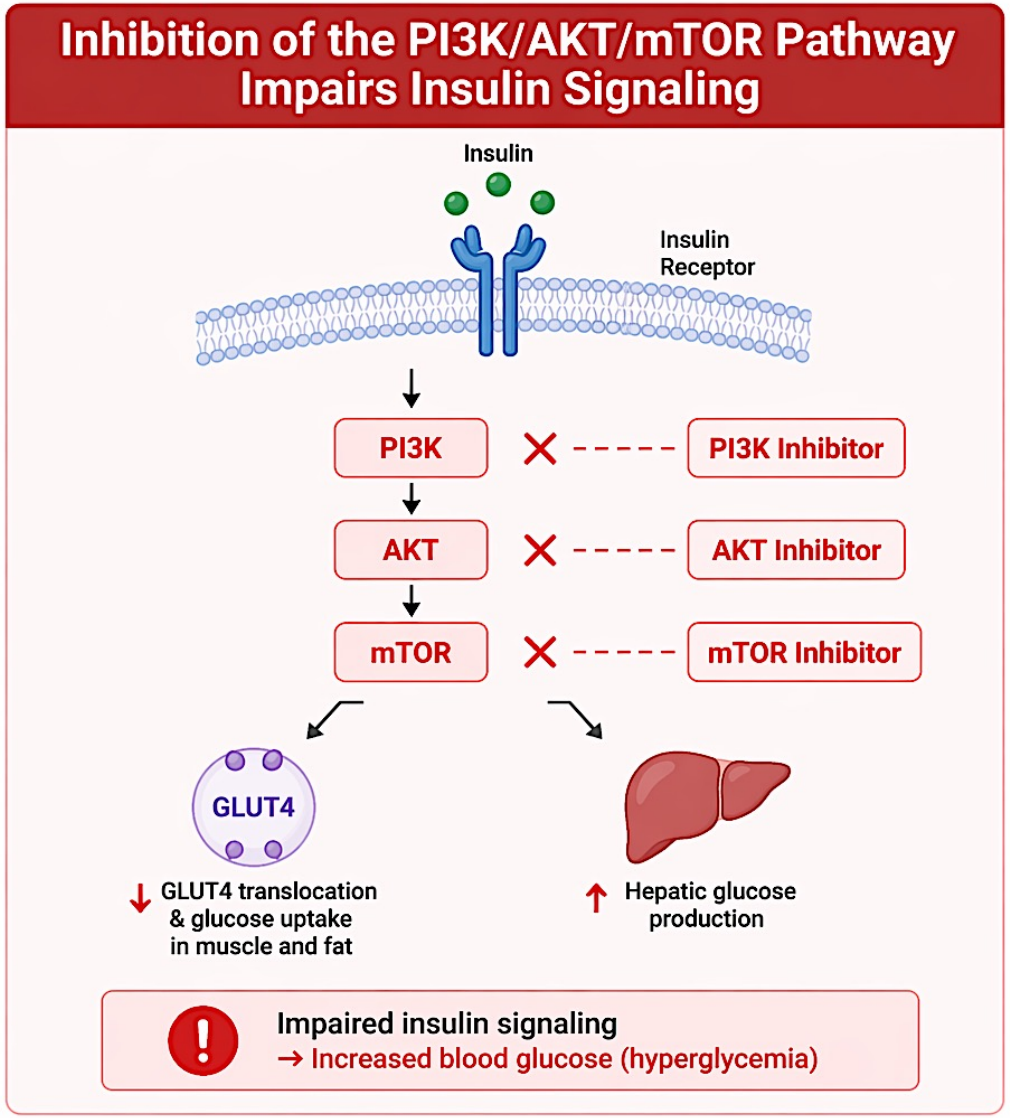
RTP
RESEARCH
TO PRACTICE

# Hyperglycemia Associated with Agents Targeting the PI3K/AKT/mTOR Pathway

**Melissa Rikal, FNP-BC, AOCNP**
Nurse Practitioner
Sarah Cannon Research Institute
Nashville, Tennessee

# Mechanism of hyperglycemia with PI3K/AKT/mTOR pathway inhibitors

- Inhibition of the PI3K/AKT/mTOR pathway impairs insulin signaling
- ↓ Glucose uptake in muscle and adipose tissue
- ↑ Hepatic glucose production→ elevated blood glucose



# Risk Factors for Hyperglycemia with PI3K/AKT/mTOR Inhibitors

- **Patient-Related Risk Factors:**
  - Pre-existing Type 2 Diabetes or prediabetes
  - Obesity (↑ insulin resistance)
  - Advanced age
  - Family history of diabetes
  - Sedentary lifestyle
- **Treatment-Related Risk Factors:**
  - Use of potent PI3K inhibitors (e.g., Alpelisib)
  - Higher drug doses or combination regimens
  - Concurrent use of corticosteroids
  - Longer duration of therapy
- **Laboratory/Clinical Risk Indicators:**
  - Elevated baseline fasting plasma glucose
  - High HbA1c prior to treatment
  - Insulin resistance markers (e.g., high fasting insulin)

# Comparative Hyperglycemia with PI3K/AKT/mTOR Pathway Inhibitors

**1. Incidence (All-grade hyperglycemia)**

- **Inavolisib**: ~58–85% (highest among approved agents)
- **Alpelisib**: ~60–65%
- **Capivasertib**: ~16–37% (lower vs PI3K inhibitors)
- **Gedatolisib** (investigational): ~9-11%

***Key pattern:** PI3Kα inhibitors > AKT inhibitors in frequency

**2. Severity (Grade ≥3 hyperglycemia)**

- **Alpelisib**: ~33–37% (highest severity burden)
- **Inavolisib**: ~5–6% (lower severe rate despite high incidence)
- **Capivasertib**: ~2–3%
- **Gedatolisib**: ~2%

- ***Key pattern:** Severity highest with alpelisib

**3. Timing of Onset**

- **Alpelisib**: rapid onset; median ~15 days (often within 1–2 weeks)
- **Inavolisib**: early onset
- **Capivasertib**: generally later and less abrupt
- **Gedatolisib**: limited published timing; likely early but variable

***Key pattern:**

PI3K inhibitors → early, rapid onset

AKT inhibitors → less abrupt, less frequent

# Optimal Monitoring of Fasting Glucose & HbA1c
## in Patients on PI3K/AKT/mTOR Pathway Inhibitors

### 1 BASELINE ASSESSMENT

**Fasting Plasma Glucose (FPG)**

**HbA1c**

**Risk Stratification**

- Pre-existing diabetes
- Obesity / metabolic syndrome
- Corticosteroid use

### 2 MONITORING SCHEDULE

**Fasting Plasma Glucose (FPG)**

- **Weekly** for the first 2–4 weeks
- Then **every 2–4 weeks**
- **More frequent** if elevated

**HbA1c**

- Every **3 months**
- Consider **earlier** if persistent hyperglycemia

Adjust monitoring frequency based on individual risk factors, glucose levels, and clinical judgment.

# Appropriate Strategies to Prevent and Manage Hyperglycemia with Agents Targeting the PI3K/AKT/mTOR Pathway

## 1 PREVENTION & LIFESTYLE STRATEGIES

### Medical Nutrition Therapy

- Emphasize complex carbohydrates, fiber, lean protein, healthy fats
- Limit refined sugars and simple carbs

### Physical Activity

- Aim for ≥150 minutes of moderate intensity exercise per week
- Reduce sedentary time

### Weight Management

- Achieve and maintain a healthy weight
- Even modest weight loss improves insulin sensitivity

### Self-Monitoring & Education

- Educate on glucose monitoring, symptoms of hyperglycemia
- Encourage adherence to lifestyle plan and medications

## 2 INDICATIONS FOR ANTIDIABETIC MEDICATIONS

| Fasting Plasma Glucose (FPG) | Indication | Suggested Approach |
|---|---|---|
| **<100 mg/dL** (Normal) | No medication indicated | Continue lifestyle and routine monitoring |
| **100–125 mg/dL** (Impaired Fasting Glucose) | Pharmacologic therapy not routinely required | Intensify lifestyle modifications and close monitoring |
| **≥126 mg/dL** (Diabetes range) | Antidiabetic medication indicated | Initiate metformin (if appropriate) Add/adjust therapy as needed |
| **≥160 mg/dL** | Requires treatment intensification | Optimize/add antidiabetic therapy (consider insulin) |
| **>250 mg/dL** | Severe hyperglycemia | Urgent treatment intensification (often insulin) and hydration |

**First-line therapy:**

- Metformin (if eGFR ≥30 mL/min/1.73m² and no contraindications)
- Add agents (SGLT2i, DPP-4i, GLP-1 RA, insulin) based on patient factors, cancer therapy, and glycemic control

## 3 DOSE MODIFICATIONS OF PI3K/AKT/mTOR PATHWAY INHIBITORS BASED ON HYPERGLYCEMIA SEVERITY

| Fasting Plasma Glucose (FPG) | Action on PI3K/AKT/mTOR Inhibitor |
|---|---|
| **≤160 mg/dL** | No dose modification – Continue treatment; optimize glycemic management |
| **>160 to ≤250 mg/dL** | Consider dose reduction – If persistent despite optimal medical therapy |
| **>250 mg/dL (persistent)** | Hold treatment – Resume at same or reduced dose once FPG ≤160 mg/dL and stable on therapy |
| **Severe symptoms / DKA / HHS** | Hold treatment – Manage per standard protocols; resume when stable |

### When to Reassess and Resume

- Reassess glucose control frequently
- Resume at same or reduced dose once glucose is ≤160 mg/dL and stable on therapy

# Case Presentation

# Case Study: Metastatic ER+ / HER2-Negative Breast Cancer Complicated by Alpelisib-Induced Hyperglycemia

**Patient:** 58-year old Caucasian female with HR+ HER2- metastatic breast cancer. She works as a high school art teacher, lives alone in a suburban area. Divorced, one adult daughter living out of state. Actively involved in a local community theater group where she designs costumes. The patient has a strong creative identity and values independence. She is hesitant to “burden” her daughter and often underreports symptoms to avoid worrying others. She also relies heavily on comfort foods during periods of stress and is overweight as a result.

**History:** Prior early breast cancer, ER-positive, PR-positive, HER2-negative; s/p lumpectomy, adjuvant chemo and radiation. Completed 5 years of adjuvant AI, 2 years later develops back pain and imaging revealed bone metastases (spine, pelvis); Biopsy confirmed metastatic ER+/HER2-negative disease. 1st line CDK4/6 inhibitor + letrozole with zoledronic acid, Achieved stable disease for ~18 months, then surveillance scans show PD to liver. NGS liquid biopsy performed showing PIK3CA mutation.

**Current Treatment:** alpelisib + fulvestrant

# Case continued

Risk Factors Identified prior to starting Alpelisib.

- Overweight (BMI ~29)
- Sedentary periods during grading seasons
- Stress-related dietary habits (high refined carbohydrate intake)
- Possible baseline insulin resistance- fasting glucose 110 mg/dL and Hgb A1c 5.6% pre-diabetes (though not previously diagnosed)

# Case continued

- Approximately 3 weeks after initiating alpelisib, the patient reports:
  - Increased thirst
  - Frequent urination
  - Fatigue (which she initially attributes to work stress)
  - She delayed reporting symptoms for a week, assuming they were “just side effects” she should tolerate.
  - You bring her in for evaluation and lab check, fasting glucose is 198 mg/dL.
- Management:
  - Initiate metformin 500mg BID
  - Discuss lifestyle changes w/ practical, low-effort meals due to her schedule but with a focus on reduction in refined sugars, short walks after work or during planning periods.
  - Lay out clear plan to monitor glucose weekly until consistently well controlled

# Case continued

- 2 week follow up: Fasting glucose remains elevated at 165 mg/dL. Decision to keep metformin at same dose to avoid diarrhea w/ work schedule and lack of home support. Dapagliflozin 5mg once daily added. Endocrinology consult ordered. Discussion of treatment hold if remains >160 mg/dL in one week.
- 3 week follow up: Fasting glucose improving at 125 mg/dL, home glucose monitoring initiated to reduce frequent clinic lab checks moving forward. Recommend she keep record of levels in her sketch book which she always has with her.
- 4 week follow up: Fasting glucose maintains at 120mg/dL and consistently in 110-130mg/dL range with home monitoring. Transition to 2 week monitoring given stability, upcoming endocrinologist visit

# Case continued

- Week 6 update: Reports her endocrinologist visit went well. No changes were made given current glucose control. She reports improved sense of control. Opens up more to her daughter after a care team discussion about support systems. Continues working and participating in theater, which remains a major protective factor for her mental health.
- Key Takeaways:
  - Alpelisib-associated hyperglycemia is common
  - Early monitoring (especially in first 2–4 weeks) is critical
  - Management requires a multidisciplinary approach (oncology + endocrinology + nutrition)
  - Psychosocial factors strongly influence symptom reporting and adherence
  - Treatment can often be continued successfully with proactive glucose control

# Agenda

**Introduction:** Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway

**Module 1:** Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)

**Module 2:** Strategies to Prevent and Manage Hyperglycemia

**Module 3: Clinical Utility of Capivasertib for HR-Positive mBC**

**Module 4:** Mitigation and Management of Gastrointestinal Adverse Events

**Module 5:** Management of Dermatologic Adverse Events

**Module 6:** Potential Role of Gedatolisib in the Management of HR-Positive mBC

**Module 7:** Monitoring and Management of Cytopenias

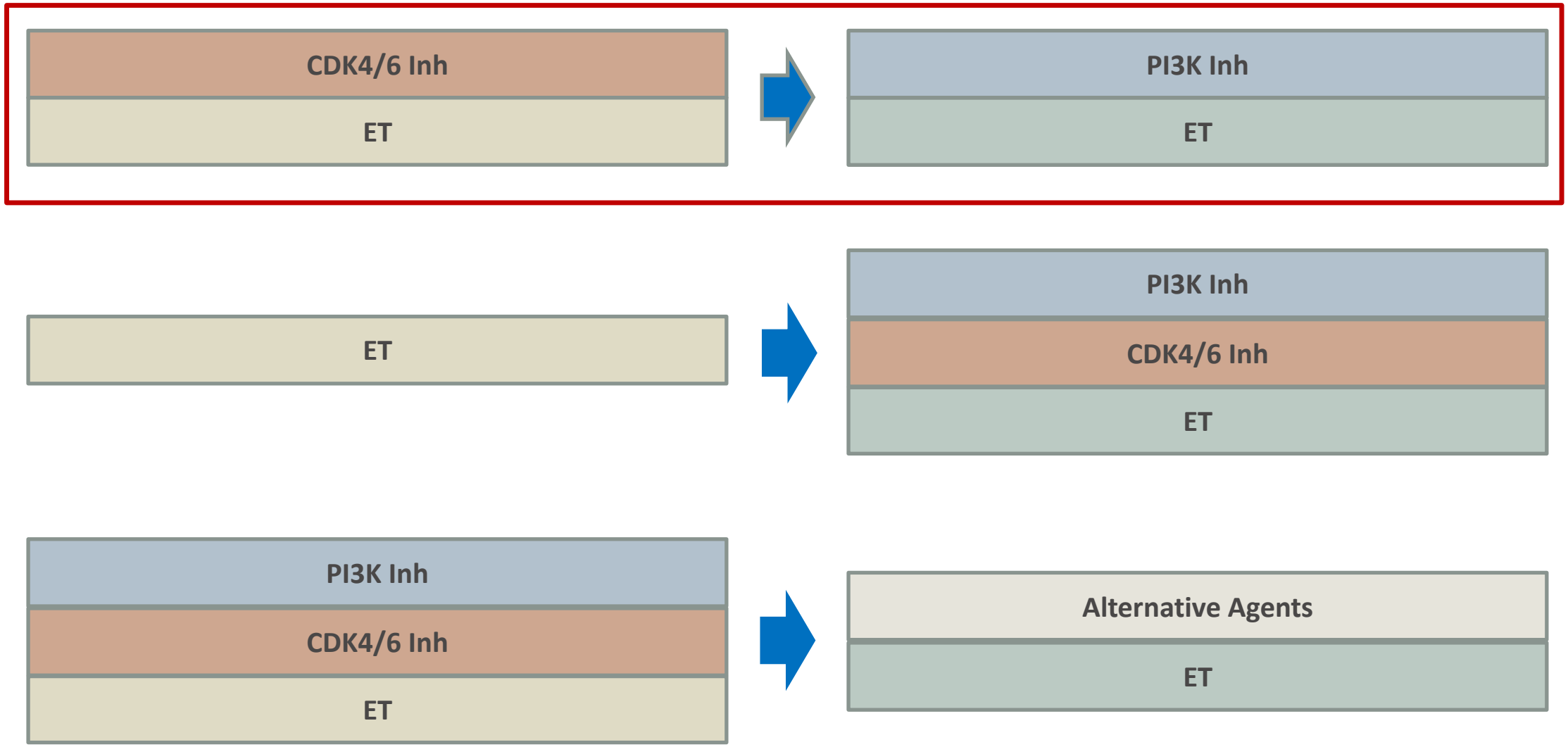
RTP RESEARCH TO PRACTICE

Ellison
Medical
Institute

# The Role of Capivasertib in HR-Positive mBC

Reva Basho, MD
Associate Professor of Medicine
Chief Medical Officer
Ellison Medical Institute

# Sequencing Therapy in HR+ Metastatic Breast Cancer



# SOLAR-1: Alpelisib + Fulvestrant in HR+ MBC After AI

**Alpelisib is an $\alpha$-specific PI3K inhibitor**

Men and postmenopausal women with HR+ ABC; prior AI

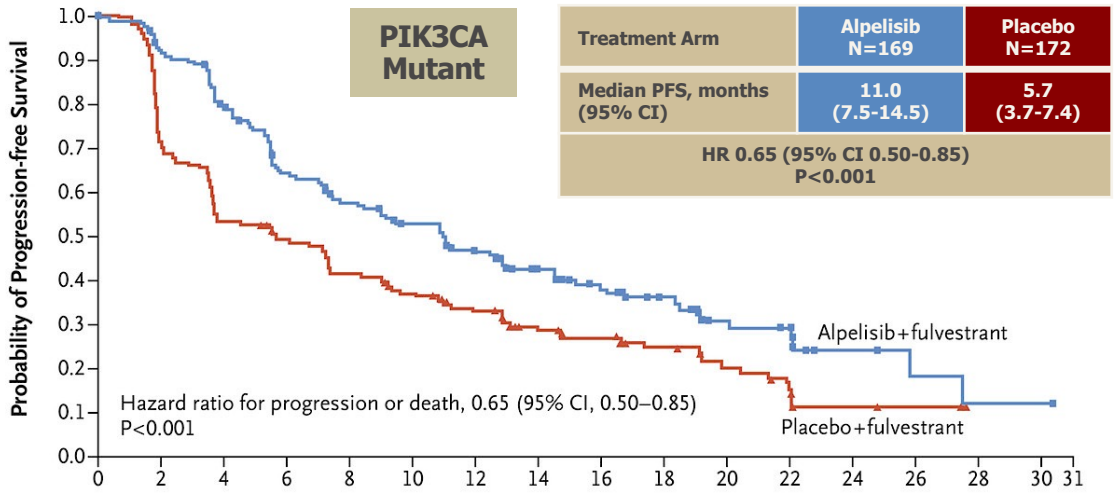
PIK3CA Mutant

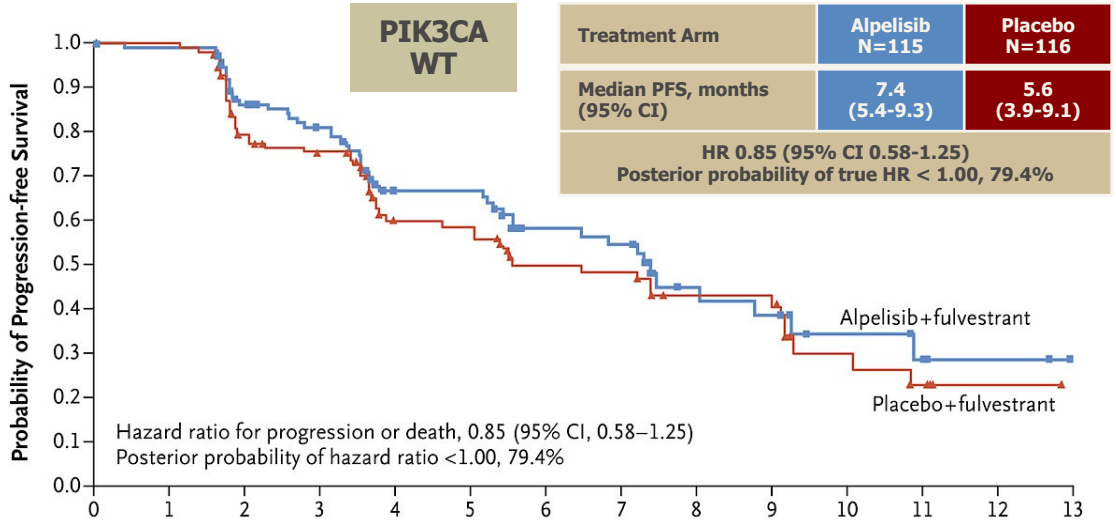
PIK3CA WT

**Randomization (1:1)**

**Stratification Factors:**
- Presence of liver and/or lung metastases
- Prior treatment with CDK 4/6 inhibitors

| Alpelisib + Fulvestrant N=169 | Placebo + Fulvestrant N=172 | Alpelisib + Fulvestrant N=115 | Placebo + Fulvestrant N=116 |
|---|---|---|---|




Andre NEJM 2019.

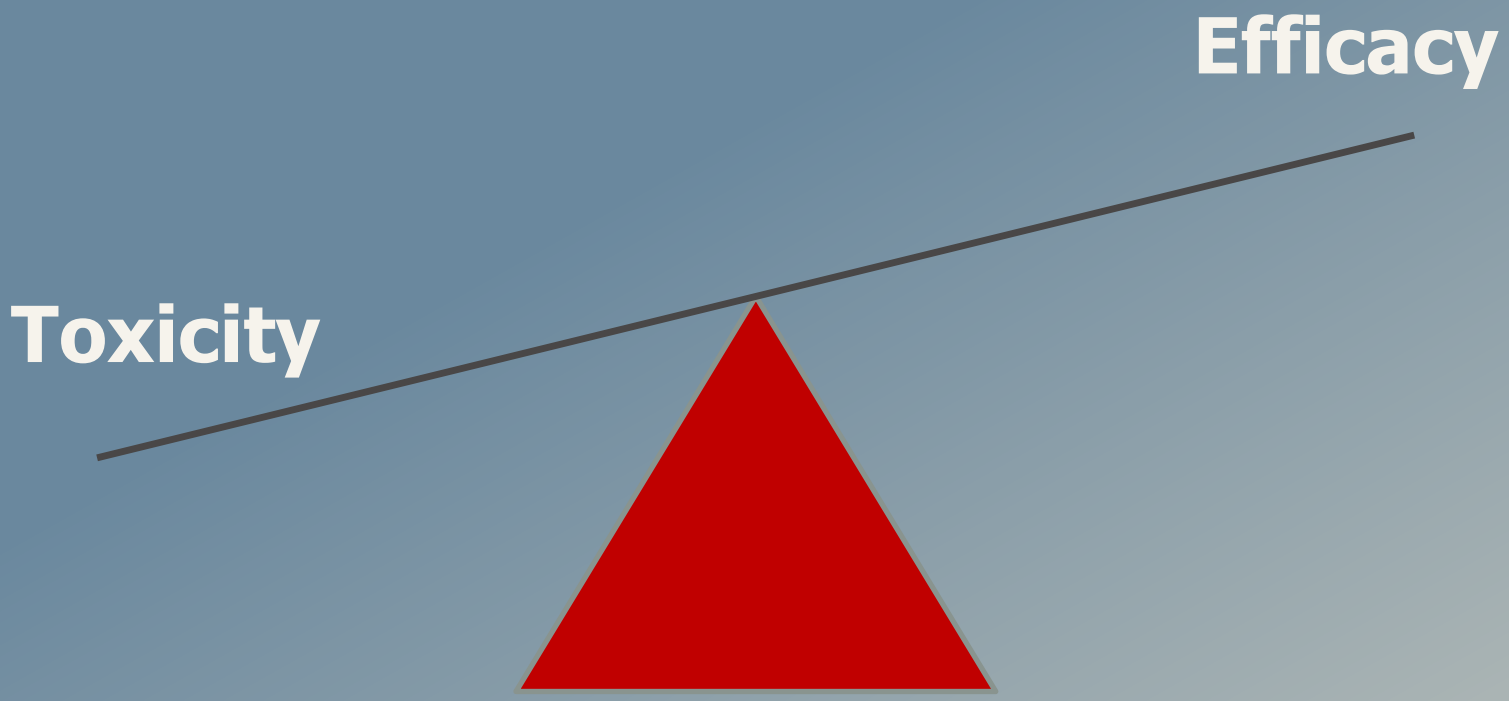
# SOLAR-1: AEs

| Grade 3/4 AEs ≥ 5%<br>N (%) | Alpelisib + Fulvestrant<br>N=284 | Placebo + Fulvestrant<br>N=287 |
|---|---|---|
| Any | 216 (76.0) | 102 (35.5) |
| Hyperglycemia | 104 (36.6) | 2 (0.7) |
| Rash | 57 (20.1) | 1 (0.3) |
| Diarrhea | 19 (6.7) | 1 (0.3) |

**Alpelisib discontinued in 25%**

Most frequent AEs leading to the discontinuation: hyperglycemia (6.3%) & rash (3.2%)

Andre NEJM 2019.


Efficacy
Toxicity

# CAPItello-291: Capivasertib + Fulvestrant After an Aromatase Inhibitor

## Phase 3, randomised, double-blind, placebo-controlled study (NCT04305496)

**Patients with HR-positive/HER2-negative* ABC**

- Men and pre-/post-menopausal women
- Recurrence or progression while on, or <12 months from end of, adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6i allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumour sample from the primary/recurrent cancer available for retrospective central molecular testing

**R1:1 (N=708)**

**Stratification factors:**
- Liver metastases (yes/no)
- Prior CDK4/6i (yes/no)
- Region†

| | |
|---|---|
| Capivasertib | 400 mg twice daily, 4 days on, 3 days off |
| Fulvestrant | 500 mg: Cycle 1, Days 1 & 15; then every 4 weeks |
| Placebo | Twice daily, 4 days on, 3 days off |
| Fulvestrant | 500 mg: Cycle 1, Days 1 & 15; then every 4 weeks |

**Primary DCO**

**Dual primary endpoints**
- PFS by investigator assessment in:
  - *PIK3CA*/*AKT1*/*PTEN*-altered
  - Overall population

**Final DCO**

**Key secondary endpoint**
- OS

**Secondary endpoints**
- PFS2
- Safety

**Exploratory endpoints**
- TTFSC
- OS in patients who had received prior CDK4/6i

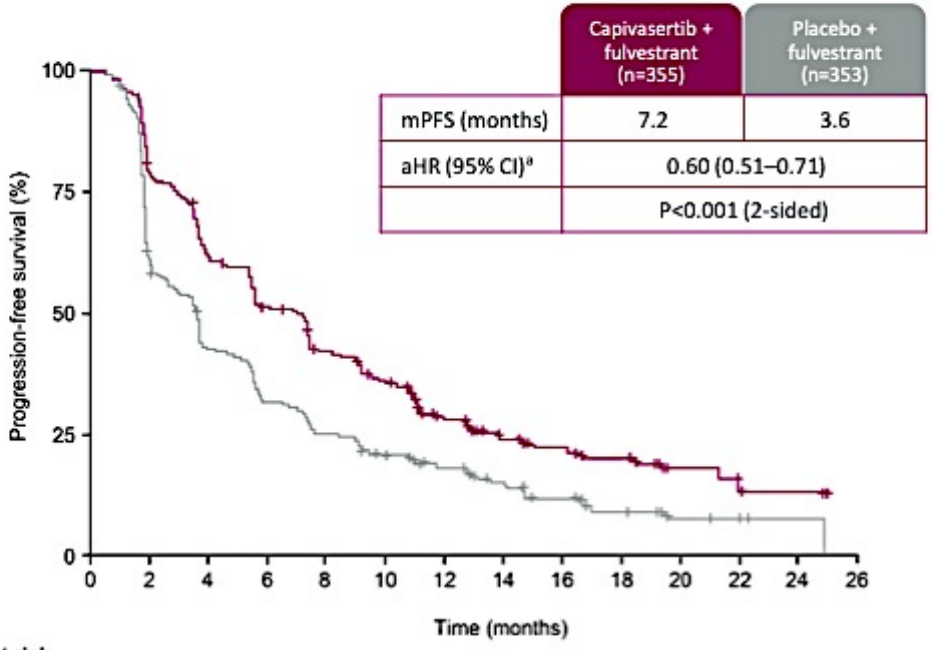
**All listed endpoints assessed in:**
- *PIK3CA*/*AKT1*/*PTEN*-altered
- Overall population

Pre- or peri-menopausal women also received a luteinising hormone-releasing hormone agonist for the duration of the study treatment. *HER2-negative was defined as IHC 0 or 1+, or IHC 2+/ISH–. †Region 1: United States, Canada, Western Europe, Australia and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia. AI, aromatase inhibitor; DCO, data cut-off; FFPE, formalin-fixed paraffin-embedded; IHC, immunohistochemistry; ISH, *in situ* hybridisation; mTOR, mechanistic target of rapamycin; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation until second progression or death due to any cause; R, randomised; SERD, selective oestrogen receptor degrader; TTFSC, time to first subsequent chemotherapy.

Rugo ESMO Breast 2026. Turner NEJM 2023.

# CAPItello-291: PFS

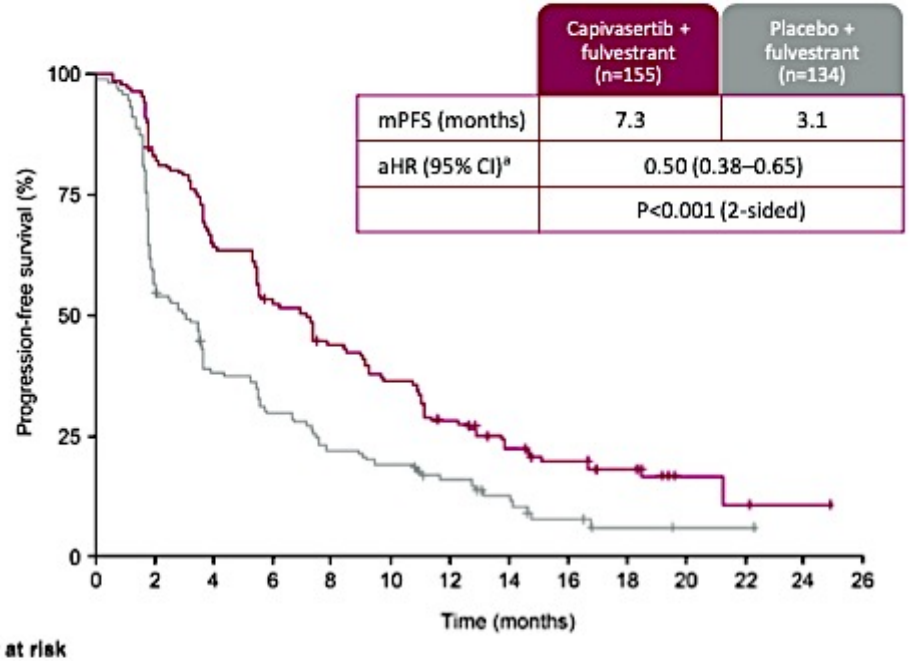
## Overall population




**Number at risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Capivasertib + fulvestrant | 355 | 266 | 207 | 172 | 138 | 115 | 78 | 55 | 43 | 25 | 8 | 5 | 2 | 0 |
| Placebo + fulvestrant | 353 | 207 | 142 | 106 | 83 | 66 | 51 | 33 | 23 | 11 | 4 | 3 | 1 | 0 |

## *PIK3CA/AKT1/PTEN*-altered population



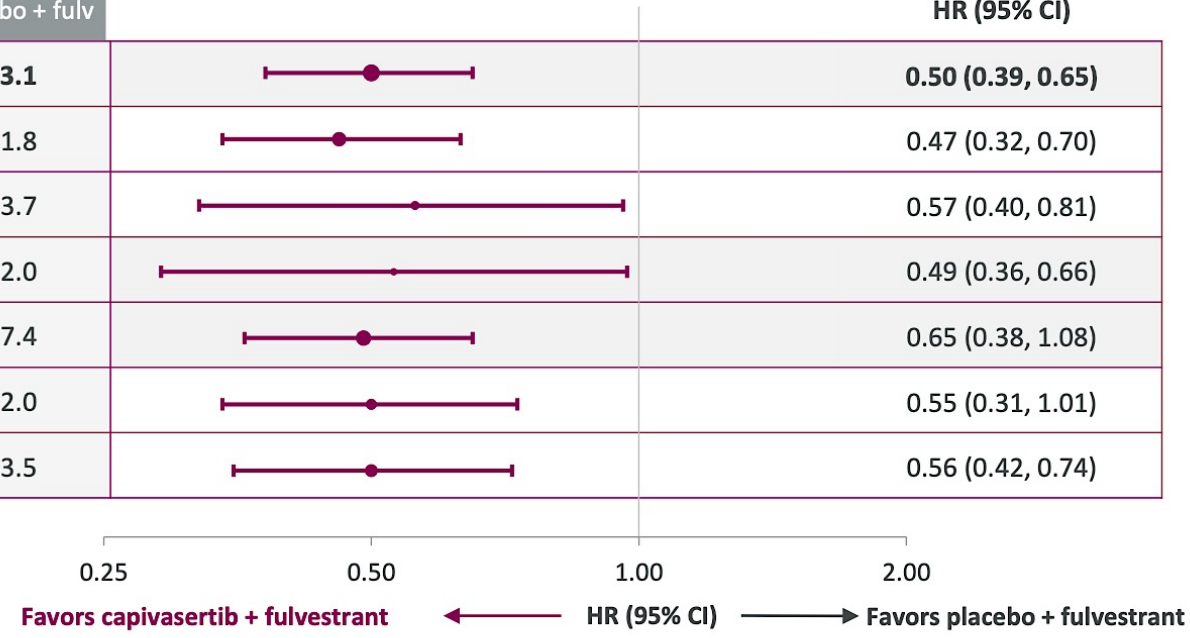

**Number at risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Capivasertib + fulvestrant | 155 | 127 | 99 | 80 | 65 | 54 | 38 | 26 | 21 | 12 | 3 | 2 | 1 | 0 |
| Placebo + fulvestrant | 134 | 77 | 48 | 37 | 28 | 24 | 17 | 11 | 6 | 2 | 1 | 1 | 0 | 0 |

Turner SABCS 2022. Turner NEJM 2023.

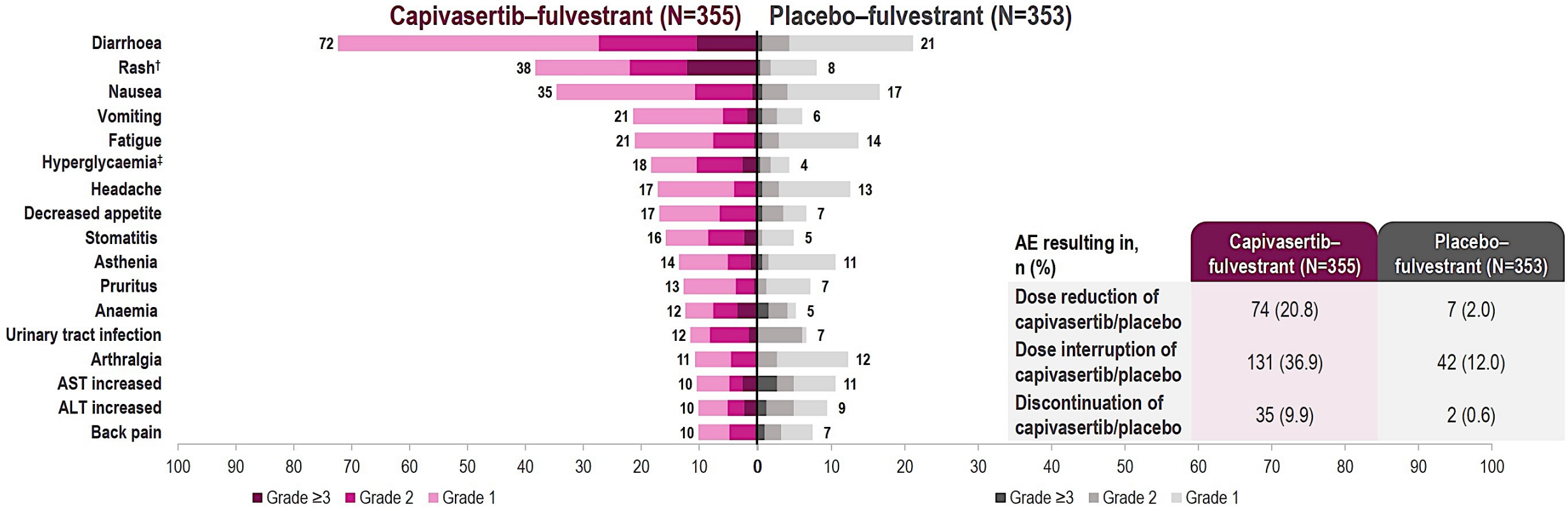
# CAPItello-291: PFS in Key PIK3CA/AKT1/PTEN-Altered Subgroups

| | | Number of patients | mPFS (months) Capi + fulv | mPFS (months) Placebo + fulv | HR (95% CI) |
|---|---|---|---|---|---|
| **All patients** | | **289** | **7.3** | **3.1** | **0.50 (0.39, 0.65)** |
| **Liver metastases at baseline** | Yes | 123 | 5.5 | 1.8 | 0.47 (0.32, 0.70) |
| | No | 166 | 9.1 | 3.7 | 0.57 (0.40, 0.81) |
| **Prior use of CDK4/6is** | Yes | 208 | 5.5 | 2.0 | 0.49 (0.36, 0.66) |
| | No | 81 | 11.0 | 7.4 | 0.65 (0.38, 1.08) |
| **Prior chemotherapy for aBC** | Yes | 53 | 4.0 | 2.0 | 0.55 (0.31, 1.01) |
| | No | 236 | 7.4 | 3.5 | 0.56 (0.42, 0.74) |




Oliveira ESMO Breast 2023.

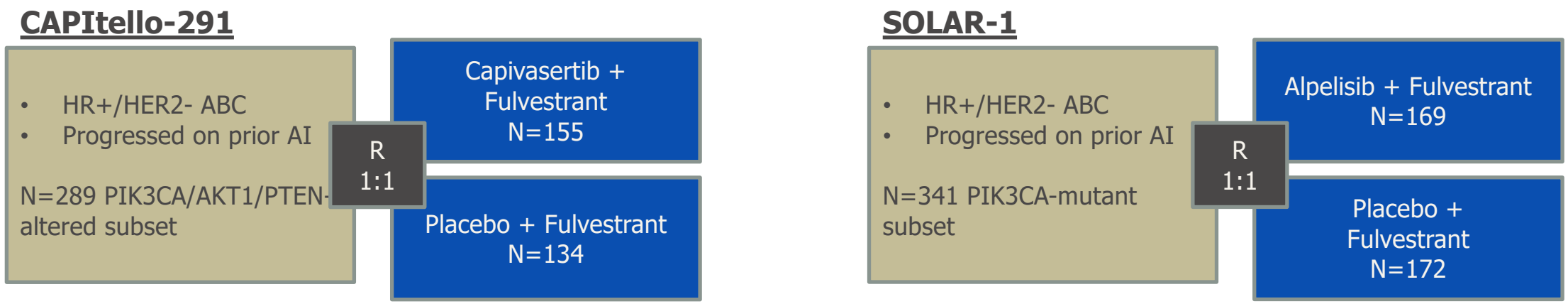
# CAPItello-291: Safety




| AE resulting in, n (%) | Capivasertib–fulvestrant (N=355) | Placebo–fulvestrant (N=353) |
|---|---|---|
| Dose reduction of capivasertib/placebo | 74 (20.8) | 7 (2.0) |
| Dose interruption of capivasertib/placebo | 131 (36.9) | 42 (12.0) |
| Discontinuation of capivasertib/placebo | 35 (9.9) | 2 (0.6) |

Turner SABCS 2022. Rugo ESMO Breast 2026.

# Targeting the PI3K Pathway in the 2nd Line




| | CAPItello-291 | | SOLAR-1 | |
|---|---|---|---|---|
| | PIK3CA/AKT1/PTEN-Altered | | PIK3CA-Mutant | |
| | Capivasertib (N=155) | Placebo (N=134) | Alpelisib (N=169) | Placebo (N=172) |
| Median PFS, Months | 7.3 | 3.1 | 11.0 | 5.7 |
| HR (95% CI) | HR 0.50 (0.38-0.65) | | HR 0.65 (0.50-0.85) | |
| P-value | **P<0.001** | | **P<0.001** | |

Turner NEJM 2023. Andre NEJM 2019.

# CAPItello-292: Capivasertib + CDK4/6i + Fulvestrant after AI

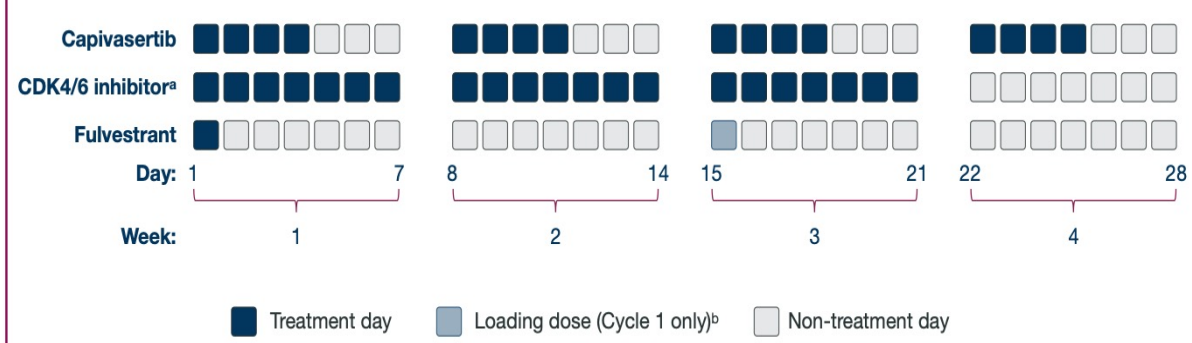
## Key inclusion criteria

- Adults ≥18 years of age with metastatic or locally advanced breast cancer
- Histologically confirmed HR-positive/HER2-negative breast cancer determined from the most recent tumor sample (primary or metastatic) per the American Society of Clinical Oncology and College of American Pathologists guideline[12,13]
  - Breast cancer cells must express ER with or without co-expression of PgR
  - HER2-negative is defined as IHC 0, or 1+ or IHC2+/ISH–
- Prior treatment with a (neo)adjuvant ET (single agent or in combination) and radiologic evidence of breast cancer recurrence or progression while on, or within 12 months of the end of, (neo)adjuvant ET (tamoxifen, AI, or oral SERD)

**R1:1 (N≈628)**

**Capivasertib** — Orally twice daily (4 days on, 3 days off) + **CDK4/6 inhibitor[a]** — Orally once daily (for 21 days of each 28-day cycle) + **Fulvestrant** — 500 mg IM (every 28 days; loading dose on Cycle 1, Day 15)

**Dosing schedule**




**CDK4/6 inhibitor[a]** — Orally once daily (for 21 days of each 28-day cycle) + **Fulvestrant** — 500 mg IM (every 28 days; loading dose on Cycle 1, Day 15)

Enrollment in the Phase 3 study has begun with the palbociclib combination RP3D[c]. The inclusion of ribociclib as an investigator's choice of CDK4/6 inhibitor in Phase 3 will be initiated after the combination RP3D has been established in Phase 1b.

Clinical Study Protocol version 5.0

[a]Investigator's choice of CDK4/6 inhibitor: palbociclib or ribociclib; [b]As per standard administration schedule; [c]Palbociclib combination RP3D: capivasertib 400 mg + palbociclib 125 mg + fulvestrant 500 mg.

Rugo. SABCS 2023.

# Case Presentation

# Case Presentation

Patient is a 53 yo F with a history of previously treated HR+/HER2- breast cancer. She presents with new onset cough. Imaging is suspicious for metastatic disease in the lungs + bones. Lung biopsy confirms HR+/HER2- metastatic breast cancer; PIK3CA H1047R mutation is found

- She is started on 1L therapy with letrozole + ribociclib + denosumab
- She does well for approximately 1.5 years
- Recently, she was found to have progression of her disease in her lungs
- Liquid biopsy again demonstrates PIK3CA H1047R mutation
- What therapies are available to this patient?
  - What would you choose and why?

Fulvestrant + alpelisib and fulvestrant + capivasertib are both options

-Toxicity profiles differ

# Take Home Points

- Alterations in the PI3K pathway are prevalent in HR+ metastatic breast cancer
  - ~40% have PIK3CA mutation
- Alpelisib is an alpha-specific inhibitor of PI3K
  - SOLAR-1: Addition of alpelisib to fulvestrant resulted in a significant improvement in PFS in the 2nd line setting in patients with PIK3CA-mutated disease
  - Grade 3+ AEs in > 75% of patients; 25% discontinued alpelisib
- Capivasertib is an AKT inhibitor
  - CAPItello-291: The addition of capivasertib to fulvestrant resulted in a significant improvement in PFS in the 2nd line setting in patients with PIK3CA/AKT1/PTEN-altered disease
  - Lower rates of grade 3+ AEs

# Discussion Questions

**Are you now prioritizing capivasertib/fulvestrant over alpelisib/fulvestrant for all patients with HR-positive, HER2-negative mBC and a PIK3CA mutation who have experienced disease progression after a CDK4/6 inhibitor and endocrine therapy?**

**Can capivasertib safely be partnered with endocrine agents other than fulvestrant and, if so, which one(s)?**

**What unique pretreatment counseling/education do you offer patients who are going to receive capivasertib versus other agents targeting the PI3K/AKT/mTOR pathway?**

# Agenda

**Introduction:** Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway

**Module 1:** Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)

**Module 2:** Strategies to Prevent and Manage Hyperglycemia

**Module 3:** Clinical Utility of Capivasertib for HR-Positive mBC

**Module 4: Mitigation and Management of Gastrointestinal Adverse Events**

**Module 5:** Management of Dermatologic Adverse Events

**Module 6:** Potential Role of Gedatolisib in the Management of HR-Positive mBC

**Module 7:** Monitoring and Management of Cytopenias

RTP RESEARCH TO PRACTICE

# Gastrointestinal Adverse Events Documented with Agents Targeting the PI3K/AKT/mTOR Pathway

**Kelly Fischer, MSN, FNP-BC**
Family Nurse Practitioner
Dana-Farber Cancer Institute
Boston, Massachusetts

| Adverse Reaction: GI | Capivasertib | Alpelisib | Inavolisib | Gedatolisib |
|---|---|---|---|---|
| Diarrhea | 72% | 57% | 48% | 17% |
| Nausea | 35% | 44% | 28% | 44% |
| Vomiting | 20% | 27% | 15% | 27% |
| Stomatitis | 15% | 25% | 51% | 69% |

# Strategies to mitigate and manage treatment-related GI AEs with agents targeting the PI3K/AKT/mTOR pathway: Diarrhea

- Start over-the-counter loperamide at first sign of diarrhea and take as needed
- Stay hydrated and drink 8-10 glasses of water/clear liquids daily
- Modify diet if needed – limit alcohol and caffeine intake, avoid spicy foods, refrain from lactose-containing food or drink

# Strategies to mitigate and manage treatment-related GI AEs with agents targeting the PI3K/AKT/mTOR pathway: Nausea/Vomiting

- Start antiemetic like ondansetron or prochlorperazine at the first sign of nausea
- Ondansetron can be a bit constipating, so that may be a good first option if patient is also struggling with diarrhea
- Increase fluid intake
- Avoid spicy foods, caffeine, alcohol

# Strategies to mitigate and manage treatment-related GI AEs with agents targeting the PI3K/AKT/mTOR pathway: Stomatitis

- Rinse mouth with warm salt water as needed
- Avoid mouthwash containing alcohol
- Brush teeth with soft bristle toothbrush and floss
- Keep lips moisturized
- Suck on hard candies
- A compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis with Inavolisib

# Role of nutritional counseling and diet modifications during treatment with agents targeting the PI3K/AKT/mTOR pathway

- Referral to nutrition
- All of these agents may cause hyperglycemia, so nutritional counseling should focus on following a low carbohydrate, high fiber diet
- Avoid simple carbs (white breads, white pastas), sweetened beverages/juices
- Focus more on lean proteins, fish, non-starchy vegetables, nuts
- Eat small, frequent meals as opposed to large meals
- For patients experiencing diarrhea, follow a bland diet and eat foods with more soluble fiber (bananas, applesauce)
- Hydration is important

# Case Presentation

# Case Presentation: A 63 y/o female with HR-positive, HER2-negative metastatic breast cancer

- 2000. R breast cancer. BCS for 1.2 cm and 0.8 cm multifocal tumors, grade 2 of 3, with DCIS. 2 of 9 axillary nodes positive.
  - Adjuvant AC x 4, then tamoxifen x 5 years
  - Adjuvant radiation
- February 2022 – Developed new back pain. Scans showed several suspicious vertebral lesions.
- 3/17/2022 – Bone biopsy shows metastatic ER+, PR -, HER2 – breast cancer.
- 3/28/2022 – Starts **letrozole/palbociclib/zoledronic acid**.
- 9/2022 – Hospitalized with neutropenic sepsis and cholecystitis. Stent placed. Palbo held.
- 3/2023 – Scans show PD in bones. Switch to **fulvestrant**/palbo (palbo at DR of 75 mg 3 weeks on, 1 week off post-hospitalization in 9/2022).
- 3/2026 – Scans show PD in bones. Switch to **capivasertib/fulvestrant**. Start capivasertib at dose reduction of 320 mg BID for 4 days on, 3 days off.
  - Genomic testing shows PIK3CA mutation

All Rows

Search

TUMOR MARKERS

| | 2026 4/27/26 06:59 | 4/13/26 10:55 | 3/2/26 07:12 | 2025 12/23/25 06:39 | 11/24/25 07:41 |
|---|---|---|---|---|---|
| CA15-3 | 248 ▲ | 380 ▲ | 589 ▲ | 498 ▲ | 491 ▲ |
| CEA | 11.0 ▲ | 13.5 ▲ | 21.6 ▲ | 16.5 ▲ | 15.5 ▲ |

# Agenda

**Introduction:** Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway

**Module 1:** Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)

**Module 2:** Strategies to Prevent and Manage Hyperglycemia

**Module 3:** Clinical Utility of Capivasertib for HR-Positive mBC

**Module 4:** Mitigation and Management of Gastrointestinal Adverse Events

**Module 5: Management of Dermatologic Adverse Events**

**Module 6:** Potential Role of Gedatolisib in the Management of HR-Positive mBC

**Module 7:** Monitoring and Management of Cytopenias

RTP RESEARCH TO PRACTICE

# Dermatologic Adverse Events Associated with Agents Targeting the PI3K/AKT/mTOR Pathway

**Melissa Rikal, FNP-BC, AOCNP**
Nurse Practitioner
Sarah Cannon Research Institute
Nashville, Tennessee

# Dermatologic Adverse Events Associated with Agents Targeting the PI3K/AKT/mTOR Pathway

- **Most frequent dermatologic AEs across all agents**
  - Maculopapular rash
  - Pruritus
  - Dry skin
- **Alpelisib (PI3Kα inhibitor)**
  - Rash: ~45–64% all grades
  - Grade ≥3 rash: ~2–20% depending on prophylaxis
- **Capivasertib (AKT inhibitor)**
  - Broad cutaneous AEs: 35% all grades
  - Grade ≥3 rash: ~12%
- **Inavolisib (PI3Kα inhibitor)**
  - Rash ~25% all grades
  - Grade ≥ 3: rare
- **Gedatolisib (dual PI3K/mTOR inhibitor)**
  - Eczematous and morbilliform eruptions most common ~27-32% all grades
  - Grade ≥ 3: ~3-4%

# Role of Prophylactic Antihistamines to Mitigate Dermatologic AEs with PI3K/AKT/mTOR Inhibitors

- Rationale for antihistamine use
  - Dermatologic AEs are common and often early-onset (within 2–4 weeks)
  - Likely mediated by immune and inflammatory pathways (histamine release, cytokines)
- Antihistamines help reduce pruritus and rash severity
- Strongest data with alpelisib
  - Prophylactic antihistamines ↓ incidence of all grade rash by 50%
  - Reduction in Grade ≥3 rash by 40% and reduced treatment interruptions
- Recommended Approach
  - Initiate at start of therapy (Day 1)
  - Continue for first 4–8 weeks (highest risk period)
  - Consider longer duration if prior rash
  - Use non-sedating antihistamines when able- fexofenadine, cetirizine, loratadine

# Topical Management of Dermatologic AEs

**1. Emollients**

- Start at treatment initiation and continue throughout therapy
- Thick creams/ointments (ceramide-based preferred)
- ↓ Xerosis and pruritus and supports skin barrier integrity

**2. Topical Corticosteroids**

- At first sign of rash
- Low–moderate potency (e.g., hydrocortisone, triamcinolone) for most areas
- Avoid high potency on face/intertriginous areas
- ↓ Inflammation and erythema,↓ progression to Grade ≥2 rash

**3. Topical Antibiotics**

- Use if signs of secondary infection: crusting, pustules, oozing
- Options: mupirocin, topical clindamycin

**4. Systemic/Oral Corticosteroids**

- Use if Grade 3/Severe Rash in addition to holding treatment and referral to dermatology.

# Thresholds for Dose Modification, Treatment Interruption and Treatment Discontinuation for Dermatologic AEs

## with Agents Targeting the PI3K/AKT/mTOR Pathway

### GRADE 1 (MILD)

Localized, minimal symptoms or asymptomatic

**MANAGEMENT**

- Continue therapy without interruption
- Emollients + low/moderate potency topical corticosteroids

**NO DOSE MODIFICATION**

### GRADE 2 (MODERATE)

More diffuse rash and/or symptomatic (pruritus, discomfort)

**MANAGEMENT – INITIAL APPROACH**

- Continue therapy with close monitoring
- Add topical corticosteroids (moderate–high potency)
- Add oral antihistamines

**ESCALATION CRITERIA**

Persistent >1–2 weeks or worsening despite optimal topical therapy

**INTERRUPT TREATMENT**
until ≤ Grade 1

Resume at same dose or reduced dose

### GRADE 3 (SEVERE)

Extensive rash, significant symptoms, or limiting ADLs

**MANAGEMENT**

- Interrupt treatment immediately
- High-potency topical steroids
- ± Systemic corticosteroids
- Dermatology referral recommended

**INTERRUPT TREATMENT**
until ≤ Grade 1

**RECHALLENGE**
Resume at reduced dose once ≤ Grade 1

Consider permanent discontinuation if recurrent

### GRADE 4 (LIFE-THREATENING)

Severe cutaneous reactions (e.g., SJS, TEN, DRESS)

**MANAGEMENT**

- Permanently discontinue therapy
- Urgent hospitalization
- Specialist care (dermatology ± ICU/burn unit)

**PERMANENTLY DISCONTINUE THERAPY**

### RECURRENT OR INTOLERABLE TOXICITY

Multiple Grade 2–3 recurrences despite optimal management

→ Consider **DOSE REDUCTION**

→ Evaluate **RISK–BENEFIT** of continuation

→ Consider **TREATMENT DISCONTINUATION**

# Case Presentation

# Case: Managing Rash on Capivasertib

**Patient:** 42-year-old female with HR+/HER2- metastatic breast cancer. She is a single parent w/ limited support. She holds an hourly paid job and cannot miss work easily. She has ongoing body image concerns that were initially triggered by alopecia that occurred during adjuvant chemotherapy. She lives far from the outpatient oncology clinic.

**History:**

- Prior early-stage breast cancer (treated with surgery, chemo, endocrine therapy)
- Progressed on first line CDK4/6 inhibitor + AI
- NGS liquid biopsy shows PTEN mutation

**Current Therapy:** Capivasertib + Fulvestrant

# Case continued

- Week 3 on Therapy
  - Patient calls into clinic reporting diffuse pruritic rash (trunk + arms), sleep disruption due to itching.
  - Exam reveals maculopapular rash, grade 2
  - Management
    - Add medium–high potency topical corticosteroids
    - Continue topical emollient
    - Ensure she is taking a non-sedating antihistamine for daytime function
    - Ensure she is scheduled for her week 4 in-person visit for fulvestrant injection, labs and to assess rash in person.

# Case continued

- **Week 4 Update**
  - Rash persists and worsens slightly
  - Still Grade 2 but more symptomatic
  - Patient distressed about her appearance + limited sleep due to pruritus
- **Management**
  - Temporarily interrupt capivasertib
  - Start short course oral corticosteroids
  - Continue topical therapy + antihistamines
  - Add diphenhydramine at bedtime to promote sleep and reduce pruritus
  - Arrange a telehealth follow-up due to work expectations and distance from the clinic.
- **Week 5 Update During Telehealth Visit**
  - Rash has improved to Grade 1
  - Restart capivasertib at dose reduction, continue topical corticosteroids, emollient and oral antihistamines
- **Week 6 Update via telehealth Visit**
  - Rash remains very mild and slowly improving. Patient is happy to have minimal impact on physical appearance. She is sleeping better and reports less pruritus. She is grateful to have not missed any work shifts since this was managed so promptly and follow ups were accommodated with telehealth visits.

# Agenda

**Introduction:** Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway

**Module 1:** Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)

**Module 2:** Strategies to Prevent and Manage Hyperglycemia

**Module 3:** Clinical Utility of Capivasertib for HR-Positive mBC

**Module 4:** Mitigation and Management of Gastrointestinal Adverse Events

**Module 5:** Management of Dermatologic Adverse Events

**Module 6: Potential Role of Gedatolisib in the Management of HR-Positive mBC**

**Module 7:** Monitoring and Management of Cytopenias

RTP RESEARCH TO PRACTICE

Mass General Brigham
Mass General Cancer Center

# Potential Role of Gedatolisib in the Management of HR+ Metastatic Breast Cancer

**Oncology Nursing Society Annual Meeting – May 2026**
**PI3K/AKT/mTOR Pathway in HR+ Metastatic Breast Cancer Symposium**
**Research to Practice**

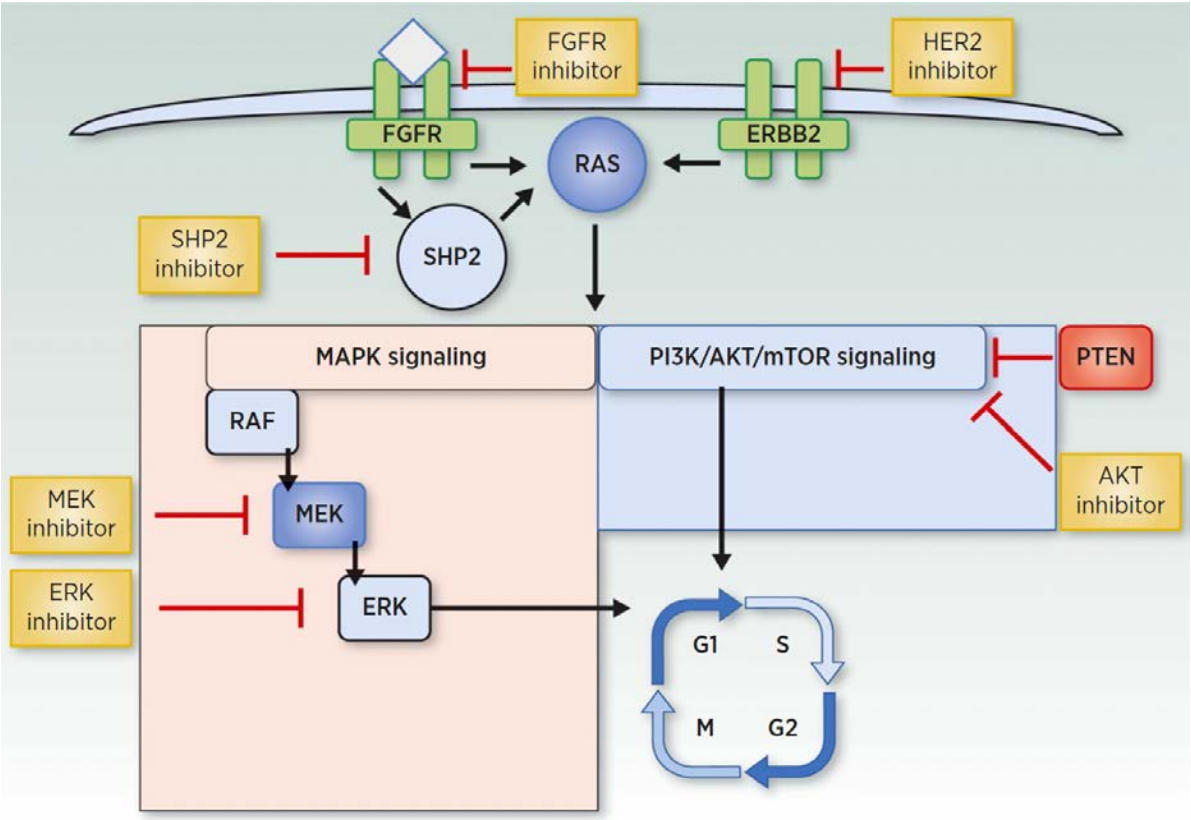
**Seth A. Wander, MD, PhD**
**Director of Precision Medicine, Termeer Center for Targeted Therapies**
**Director of Translational Research, Breast Oncology Program**
**Assistant Professor of Medicine, Harvard Medical School**
**Massachusetts General Hospital**

**swander@mgh.harvard.edu**

# Resistance Drivers Define New Therapeutic Targets

**Oncogenic growth signaling mediators**

Receptor tyrosine kinases
RAS / MAPK pathway
PI3K/AKT/mTOR pathway




Lloyd MR et al CCR 2022

RTKs @ cell surface + external ligands

PI3K >>>>>> Activated PI3K

*Alpelisib*
*Inavolisib*

Gedatolisib

AKT

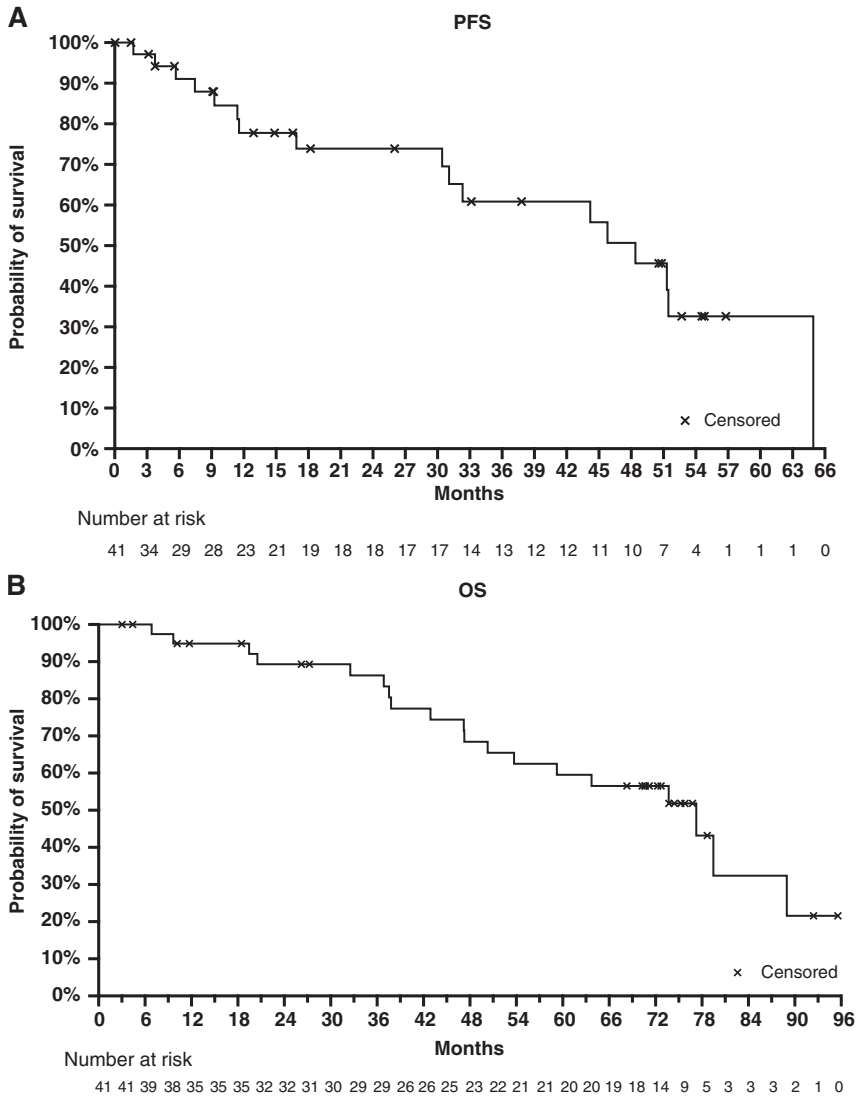
*Capivasertib*

*Everolimus*

mTOR::

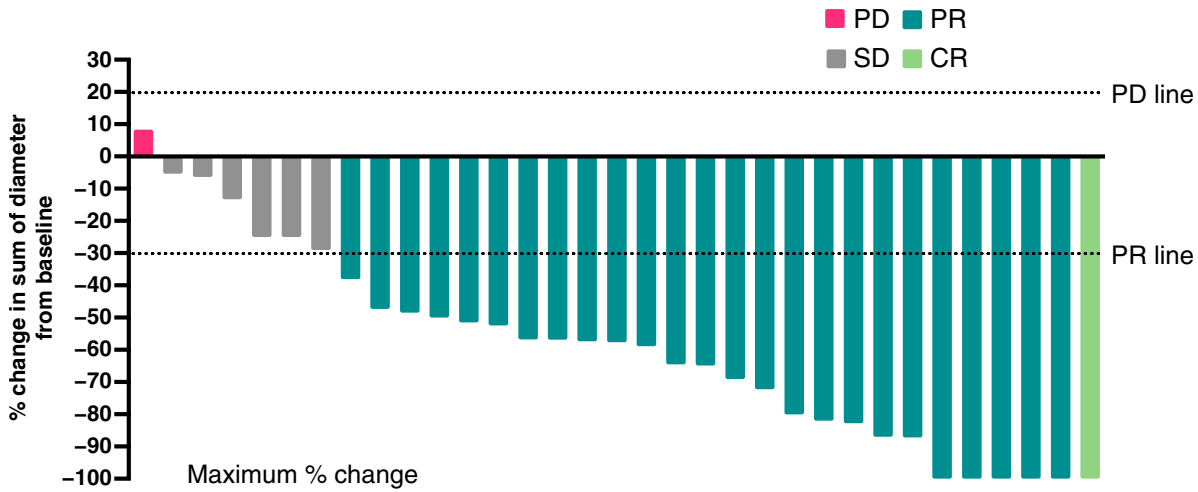
Cellular Growth
Survival + Division
Motility + Metastasis

# Gedatolisib: Phase 1, 1L HR+ MBC Experience



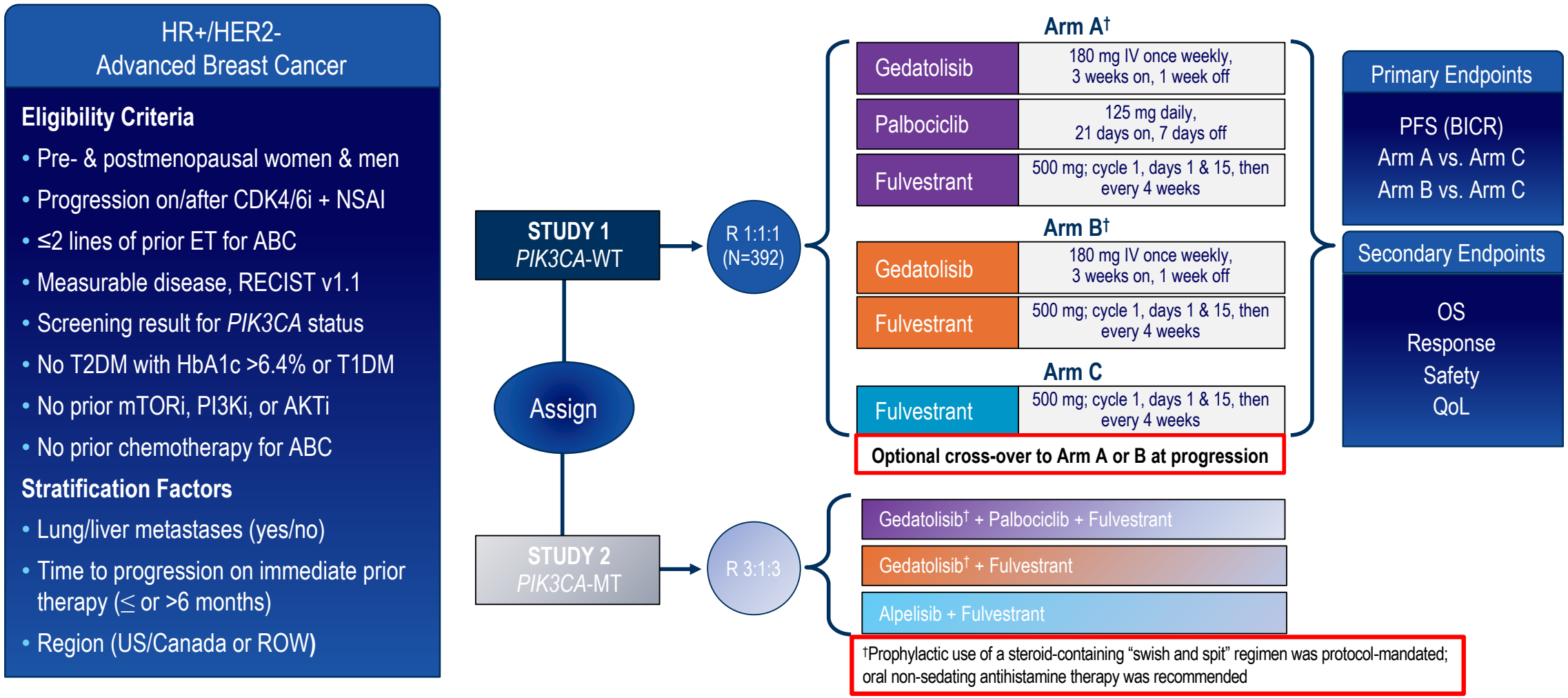

- N= 41 patients; HR+ MBC, treatment naïve
- 22% PIK3CAm
- ORR 79% overall, similar +/- PIK3CA mutations
- Median PFS 48.4 months
- Median OS 77.3 months

| | Response evaluable WT *PIK3CA*[a] (*N* = 25) | Response evaluable mut *PIK3CA* (*N* = 7) | Total response evaluable (*N* = 33) |
|---|---|---|---|
| ORR, *n* (%)[b] | 20 (80%) | 5 (71%) | 26 (79%) |
| Median DOR, months (95% CI)[b] | 48 (24, NR) | 47 (4, NR) | 48 (25, NR) |
| Best overall response, *n* (%) | | | |
| CR | 1 (4%) | 0 | 1 (3%) |
| PR | 19 (76%) | 5 (71%) | 25 (76%) |
| SD | 4 (16%) | 2 (29%) | 6 (18%)[c] |
| PD | 1 (4%) | 0 | 1 (3%) |




Wesolowski et al CCR 2025

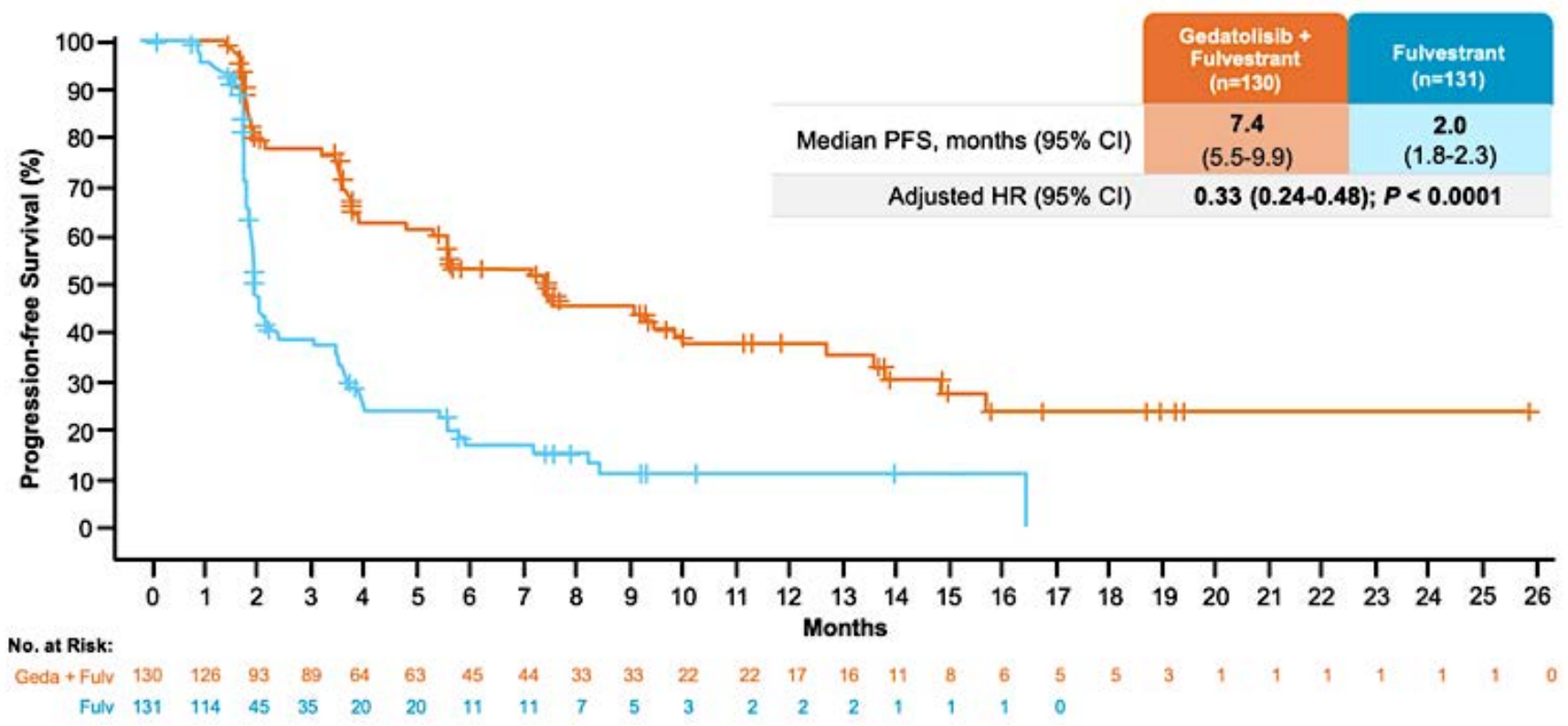
# VIKTORIA-1: Gedatolisib PAM Pathway Inhibitor




Hurvitz SA et al ESMO 2025

# VIKTORIA-1: Doublet Efficacy

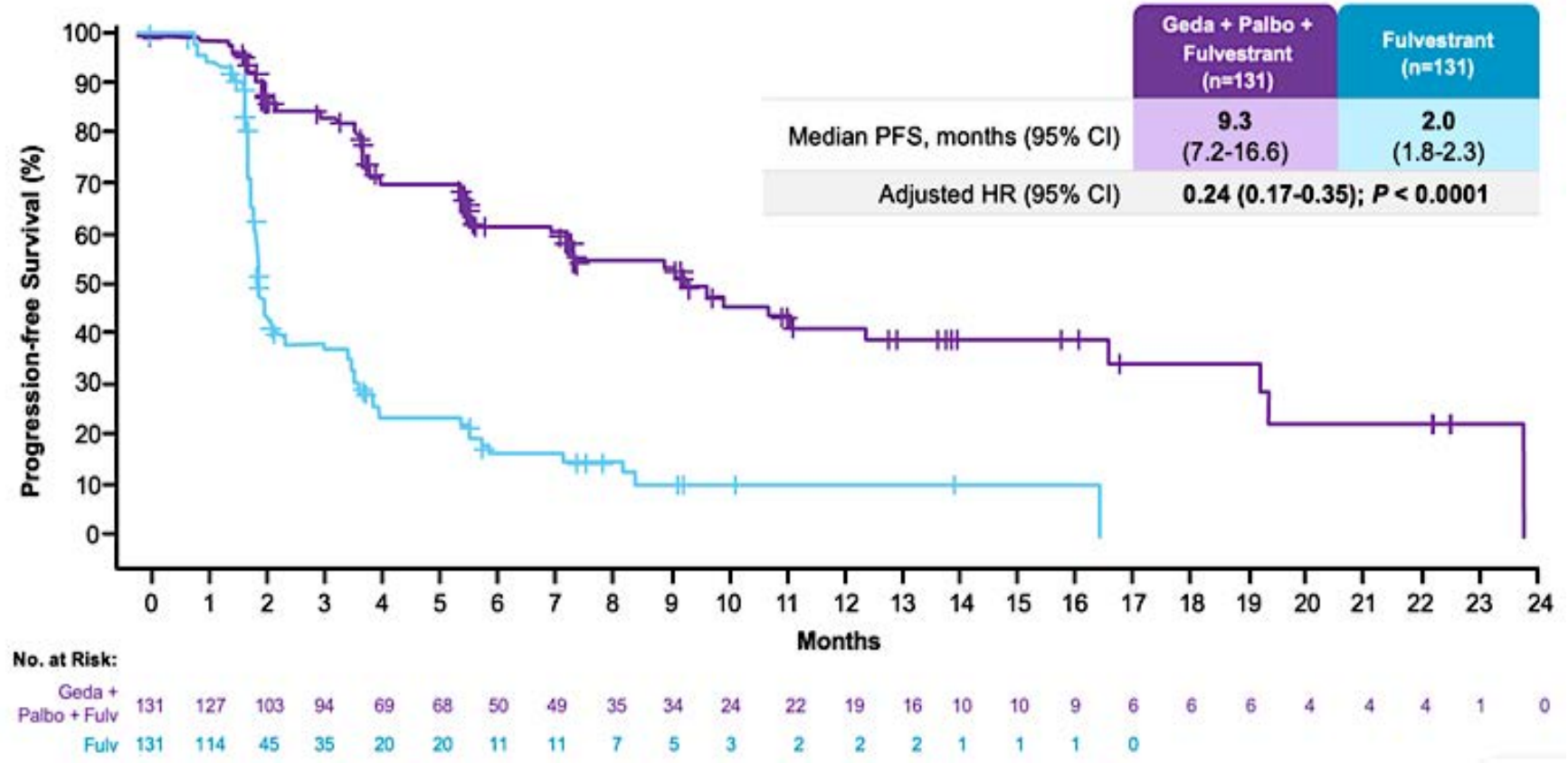
## PFS Gedatolisib Doublet vs. Fulvestrant




Hurvitz SA et al ESMO 2025; *J Clin Oncol* 2026;44:1108-19.

# VIKTORIA-1: Triplet Efficacy

## PFS Gedatolisib Triplet vs. Fulvestrant




Hurvitz SA et al ESMO 2025; *J Clin Oncol* 2026;44:1108-19.

# VIKTORIA-1: Gedatolisib Toxicity

A1c < 6.4%
Discontinuation Rate:
2.3% Triplet
3.1% Doublet

| SAE and discontinuation, n (%) | Gedatolisib + palbociclib + fulvestrant (n=130) | Gedatolisib + fulvestrant (n=130) | Fulvestrant (n=123) |
|---|---|---|---|
| Pts with ≥1 SAE | 14 (10.8) | 12 (9.2) | 1 (0.8) |
| Study treatment D/C due to TRAE | 3 (2.3) | 4 (3.1) | 0 |
| Deaths due to TRAE[†] | 2 (1.5) | 0 | 0 |

| Adverse events, n (%) | Gedatolisib + palbociclib + fulvestrant (n=130) | | | Gedatolisib + fulvestrant (n=130) | | | Fulvestrant (n=123) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| **Stomatitis[‡]** | **90 (69.2)** | **25 (19.2)** | **0** | **74 (56.9)** | **16 (12.3)** | **0** | **0** | **0** | **0** |
| Neutropenia[‡] | 85 (65.4) | 68 (52.3) | 13 (10.0) | 2 (1.5) | 0 | 1 (0.8) | 1 (0.8) | 1 (0.8) | 0 |
| Nausea | 57 (43.8) | 5 (3.8) | 0 | 56 (43.1) | 1 (0.8) | 0 | 4 (3.3) | 0 | 0 |
| **Rash[‡]** | **36 (27.7)** | **6 (4.6)** | **0** | **42 (32.3)** | **7 (5.4)** | **0** | **0** | **0** | **0** |
| Vomiting | 36 (27.7) | 2 (1.5) | 0 | 30 (23.1) | 0 | 0 | 1 (0.8) | 0 | 0 |
| Fatigue | 29 (22.3) | 2 (1.5) | 0 | 27 (20.8) | 1 (0.8) | 0 | 5 (4.1) | 0 | 0 |
| **Diarrhea[§]** | **22 (16.9)** | **2 (1.5)** | **0** | **16 (12.3)** | **1 (0.8)** | **0** | **0** | **0** | **0** |
| **Hyperglycemia[‡,§]** | **12 (9.2)** | **3 (2.3)** | **0** | **15 (11.5)** | **3 (2.3)** | **0** | **0** | **0** | **0** |

**Hurvitz SA et al ESMO 2025; *J Clin Oncol* 2026;44:1108-19.**

# Toxicity Experience Across Current PAM Inhibitors

| | SOLAR-1 | | INAVO120 | | Capitello291 | | VIKTORIA-1 | |
|---|---|---|---|---|---|---|---|---|
| | Alpelisib | | Inavolisib | | Capivasertib | | Gedatolisib | |
| | All Grade | Grade 3+ | All Grade | Grade 3+ | All Grade | Grade 3+ | All Grade | Grade 3+ |
| Hyperglycemia | 63.7% | 36.6% | 58.6% | 5.6% | 16.3% | 2.3% | 9.2% | 2.3% |
| Diarrhea | 57.7% | 6.7% | 48.1% | 3.7% | 72.4% | 9.3% | 16.9% | 1.5% |
| Mucositis | 24.6% | 2.5% | 51.2% | 5.6% | 14.6% | 2.0% | 69.2% | 19.2% |
| Rash | 35.6% | 9.9% | 25.3% | 0.0% | 38.0% | 12.1% | 27.7% | 4.6% |
| | Inclusion A1c <6.4% | | Inclusion A1c <6% | | Inclusion A1c <8% | | Inclusion A1c <6.4% | |

Andre F et al NEJM 2019
Turner NC et al NEJM 2024
Turner NC et al NEJM 2023
Hurvitz SA et al ESMO 2025

# VIKTORIA1: Gedatolisib PAM Pathway Inhibitor

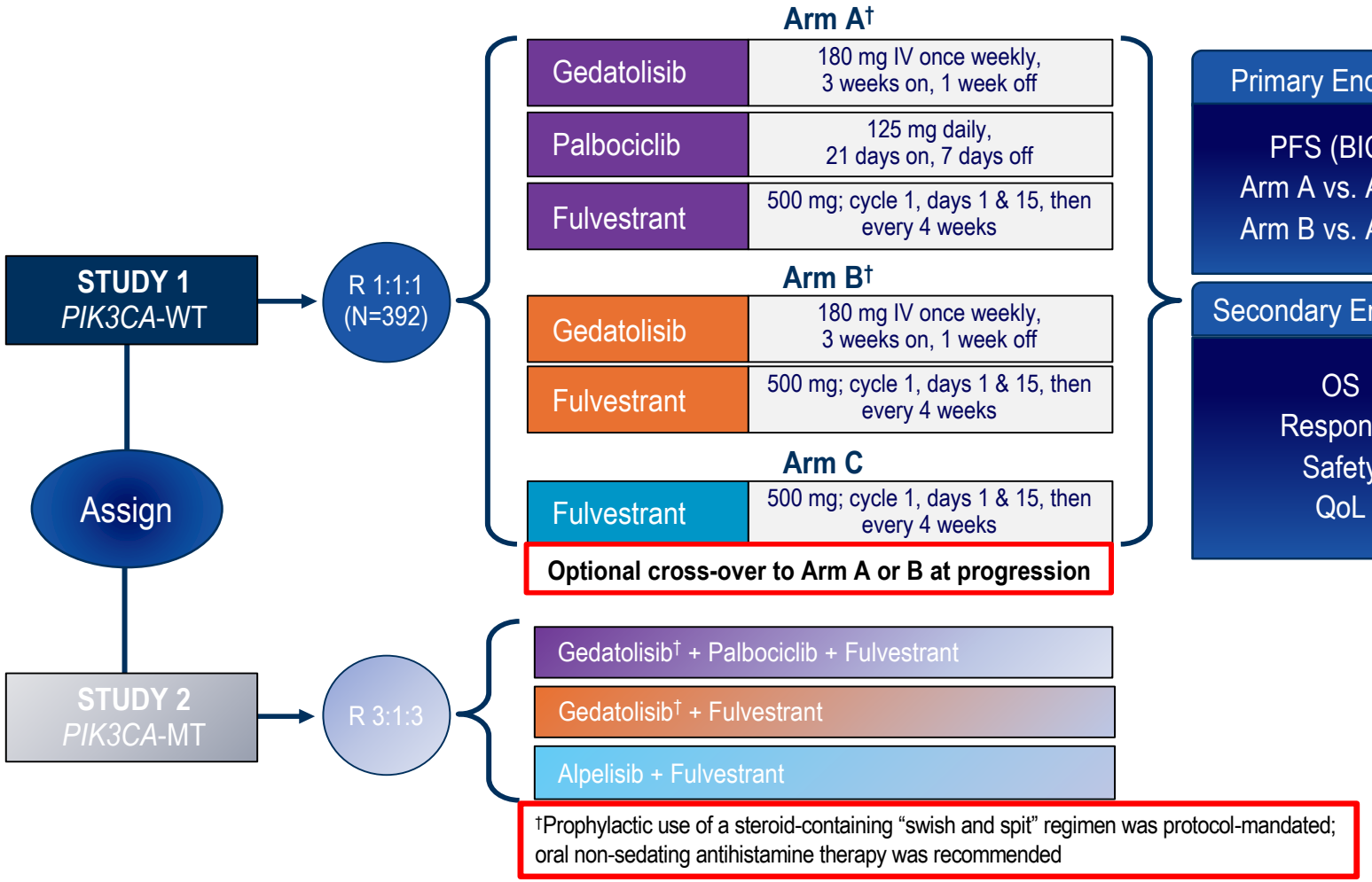
## HR+/HER2- Advanced Breast Cancer

**Eligibility Criteria**

- Pre- & postmenopausal women & men
- Progression on/after CDK4/6i + NSAI
- ≤2 lines of prior ET for ABC
- Measurable disease, RECIST v1.1
- Screening result for *PIK3CA* status
- No T2DM with HbA1c >6.4% or T1DM
- No prior mTORi, PI3Ki, or AKTi
- No prior chemotherapy for ABC

**Stratification Factors**

- Lung/liver metastases (yes/no)
- Time to progression on immediate prior therapy (≤ or >6 months)
- Region (US/Canada or ROW)




Hurvitz SA et al ESMO 2025

# VIKTORIA1: Gedatolisib PAM Pathway Inhibitor

## Phase 3 VIKTORIA-1 Trial Achieves Primary Endpoint With Improvement in Progression-Free Survival in PIK3CA Mutant Cohort

May 1, 2026

### Detailed data for the gedatolisib triplet and doublet regimens will be presented at a late-breaking abstract oral session at the 2026 ASCO Annual Meeting

The primary efficacy analysis of gedatolisib combined with fulvestrant and palbociclib (the “gedatolisib triplet”) demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (“PFS”) compared to alpelisib, a PI3Kα inhibitor, and fulvestrant. The secondary endpoint comparing gedatolisib plus fulvestrant (the “gedatolisib doublet”) versus alpelisib plus fulvestrant, which was not part of the primary efficacy analysis in the hierarchical order, also demonstrated a statistically significant and clinically meaningful improvement in PFS compared to alpelisib and fulvestrant. Both gedatolisib regimens were generally well tolerated, with manageable safety profiles, and no new safety signals.

**Title:** A randomized, open-label, phase 3 study of gedatolisib + fulvestrant ± palbociclib vs standard of care in HR+/HER2−/*PIK3CA*-mutant advanced breast cancer (VIKTORIA-1 Study 2)

**Abstract:** LBA1008

**Session Type/Title:** Oral Abstract Session - Breast Cancer—Metastatic

**Date and Time:** June 2, 2026, 9:45 AM-12:45 PM CDT

# Current and Evolving Therapeutic Landscape: ER+ MBC

1st Line::
AI/OS + CDK4/6i
(Ribociclib)

Fulvestrant + Palbo
+ Inavolisib
(*PIK3CAm*,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib
Antiestrogen + Everolimus
(*NGS Negative*)

Fulvestrant + Alpelisib
(*PIK3CAm*)

Fulvestrant + Capivasertib
(*PIK3CAm, AKTm, PTENm*)

Elacestrant, Imlunestrant,
or Vepdegestrant
(*ESR1m*)

Olaparib
(*BRCAm*)

3rd Line (and beyond)::
Trastuzumab Deruxtecan (ADC, HER2-low)
Chemotherapy (many choices)
Sacituzumab Govitecan (ADC)
Datopotamab Deruxtecan (ADC)

# Current and Evolving Therapeutic Landscape: ER+ MBC

*(+) Phase III Data (not yet approved)*
*Camizestrant Switch via ESR1 ctDNA?*

1st Line::
AI/OS + CDK4/6i
(Ribociclib)

Fulvestrant + Palbo
+ Inavolisib
(*PIK3CAm*,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib
Antiestrogen + Everolimus
(*NGS Negative*)

Fulvestrant + Alpelisib
(*PIK3CAm*)

Fulvestrant + Capivasertib
(*PIK3CAm, AKTm, PTENm*)

Elacestrant, Imlunestrant,
or Vepdegestrant
(*ESR1m*)

Olaparib
(*BRCAm*)

3rd Line (and beyond)::
Trastuzumab Deruxtecan (ADC, HER2-low)
Chemotherapy (many choices)
Sacituzumab Govitecan (ADC)
Datopotamab Deruxtecan (ADC)

**Ongoing clinical trials exploring:
New antiestrogens (KAT6i) and doublets/triplets
New CDK4/2 inhibitors
New targeted agents (PI3K, RAS pathway)
New ADCs

*(+) Phase III Data (not yet approved)*
Doublet/Triplet:
*Imlunestrant + Abemaciclib? NGS agnostic or ESR1m?*
*Giredestrant + Everolimus? ESR1m?*
***Gedatolisib + Fulvestrant +/- Palbociclib**? NGS agnostic?*

# Case Presentation

# Case Presentation: Gedatolisib

61yo woman with DMII (no insulin, A1c <6%) and HLD
No mammograms >5y; presented with progressive fatigue and abdominal discomfort
Imaging with multifocal liver lesions, peritoneal deposits, >4cm R breast mass and regional adenopathy
Liver biopsy > metastatic breast cancer, ER/PR positive, HER2 IHC 0/null
NGS (MGH Snapshot): GATA3 mutation, TP53 mutation, TMB 2, MSS
ctDNA (Guardant): no actionable alterations

1st line therapy with letrozole + ribociclib > stable disease x10 months
New progression in liver and lung (normal LFTs)
Repeat ctDNA again negative

Current options: *Fulvestrant* vs *Fulvestrant/Everolimus* vs *Fulvestrant/Abemaciclib* vs *Chemo*
Future option: ***Fulvestrant/Gedatolisib +/- Palbociclib***?

# Discussion Questions

**In which line of therapy do you envisage using gedatolisib opposite current options for patients with PIK3CA wild-type and PIK3CA-mutant disease?**

**Which patients do you see as the optimal candidates for gedatolisib/fulvestrant/palbociclib versus gedatolisib/fulvestrant?**

**If gedatolisib were to become available, how would your pretreatment counseling/education differ for patients who are going to receive that agent versus others targeting the PI3K/AKT/mTOR pathway?**

# Agenda

**Introduction:** Identification of Appropriate Candidates for Agents Targeting the PI3K/AKT/mTOR Pathway

**Module 1:** Role of Inavolisib in HR-Positive Metastatic Breast Cancer (mBC)

**Module 2:** Strategies to Prevent and Manage Hyperglycemia

**Module 3:** Clinical Utility of Capivasertib for HR-Positive mBC

**Module 4:** Mitigation and Management of Gastrointestinal Adverse Events

**Module 5:** Management of Dermatologic Adverse Events

**Module 6:** Potential Role of Gedatolisib in the Management of HR-Positive mBC

**Module 7: Monitoring and Management of Cytopenias**

RTP RESEARCH TO PRACTICE

# Cytopenias Documented with Agents Targeting the PI3K/AKT/mTOR Pathway

**Kelly Fischer, MSN, FNP-BC**
Family Nurse Practitioner
Dana-Farber Cancer Institute
Boston, Massachusetts

| Adverse Reaction: Cytopenias | Capivasertib | Alpelisib | Inavolisib | Gedatolisib |
|---|---|---|---|---|
| Neutropenia | 23% | - | 89% | 65% |
| Anemia | 45% | 42% | 37% | 42% |
| Thrombocytopenia | 12% | 14% | 48% | 4% |

# Appropriate monitoring of complete blood counts in patients receiving agents targeting the PI3K/AKT/mTOR pathway

More frequent lab monitoring initially is recommended

once every week for the first 4 weeks, then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated

# Thresholds for dose modification, treatment interruption and treatment discontinuation in patients experiencing cytopenias: Inavolisib

| Severity | Dose Modification |
|---|---|
| Grade 1, 2, or 3 | None required |
| Grade 4 | Hold until recover to less than or equal to grade 2<br>Resume at same dose or reduce one dose level |

# Thresholds for dose modification, treatment interruption and treatment discontinuation in patients experiencing cytopenias: Capivasertib

| Severity | Dose Modification |
|---|---|
| Grade 2 | Withhold Capivaertib until recovery to less than or equal to Grade 1<br>Resume Capivasertib at same dose |
| Grade 3 | Withhold Capivasertib until recovery to less than or equal to Grade 1<br>If recovery occurs in less than or equal to 28 days, resume at same dose. If recovery occurs in greater than 28 days, resume at one lower dose |
| Grade 4 | Permanently discontinue |

# Role of other supportive care strategies to manage cytopenias with agents targeting the PI3K/AKT/mTOR pathway

- Usually, first step in managing cytopenias is to interrupt therapy and/or modify dose if needed
- Growth factor support (ie filgrastim) is not usually recommended as a prophylactic measure when starting these therapies
- Can consider transfusions as needed for anemia, thrombocytopenia

# Case Presentation

# Case Presentation: A 54-year-old female with hormone positive, HER2 negative metastatic breast cancer

- March 2023: Diagnosed with left invasive ductal carcinoma, ER+, PR+, HER2- (IHC 1+).
- April 2023: Underwent left mastectomy and SLNB, showed IDC, grade 3, 4 cm, multifocal LVI, 0/3 SLNs involved by malignancy though one with ITCs → pT2N0(i+)(sn). Oncotype 33.
- May-August 2023: ddAC-T (taxol DR for neuropathy).
- October-November 2023: PMRT.
- December 2023: Start anastrozole. Then switch to exemestane in June 2024.
- March 2025: Develops left groin pain.
- June 2025: PET CT shows diffuse avid lytic bone lesions, and a large 9.6 cm lesion in left iliac with non-displaced pathologic fracture.
- June 2025: Bone biopsy confirms metastatic ER+, PR low, HER2- (IHC 0+ aka ultralow) breast cancer.

# Case Presentation: A 54-year-old female with hormone positive, HER2 negative metastatic breast cancer

- June 2025: Palliative RT to left hip.
- July 2025: Started **fulvestrant** + **palbociclib**. Also monthly denosumab.
- August 2025: Found to have **PIK3CA mutation** on NGS. **Inavolisib** added to regimen.
- September 2025: Admitted with hyperglycemia (blood sugar > 600). Inavolisib held for several weeks.
- October-November 2025: RT to cervical spine (pain due to lytic lesion and fracture). Palbo and inavo held during RT.
- October 2025: New baseline re-staging scans show similar mixed sclerotic/lytic osseous lesions.
- December 2025: Re-staging scans show increased sclerosis of osseous lesions, likely treatment effect.
- February 2025: Scans stable.

All Rows

Search

| COMPLETE BLOOD C... | 2026 4/7/26 08:39 | 3/10/26 08:44 | 2/10/26 09:17 | 1/13/26 09:17 | 2025 12/16/25 10:40 | 12/10/25 09:03 | 12/2/25 11:00 | 11/21/25 07:38 | 11/7/25 08:56 | 10/24/25 12:36 |
|---|---|---|---|---|---|---|---|---|---|---|
| WBC | 1.88 ▼ | 1.89 ▼ | 2.04 ▼ | 1.83 ▼ | 3.05 ▼ | 1.70 ▼ | 1.78 ▼ | 6.50 | 5.76 | 2.71 ▼ |
| RBC | 2.60 ▼ | 2.69 ▼ | 2.90 ▼ | 3.02 ▼ | 3.26 ▼ | 3.00 ▼ | 3.65 ▼ | 3.61 ▼ | 3.30 ▼ | 3.37 ▼ |
| Hgb | 9.0 ▼ | 9.2 ▼ | 9.5 ▼ | 9.5 ▼ | 9.9 ▼ | 9.3 ▼ | 11.0 ▼ | 11.4 ▼ | 10.3 ▼ | 10.8 ▼ |
| HCT | 27.0 ▼ | 27.4 ▼ | 28.5 ▼ | 29.0 ▼ | 31.5 ▼ | 27.4 ▼ | 34.2 ▼ | 35.4 ▼ | 32.5 ▼ | 32.0 ▼ |
| MCV | 103.8 ▲ | 101.9 ▲ | 98.3 | 96.0 | 96.6 | 91.3 | 93.7 | 98.1 | 98.5 | 95.0 |
| MCH | 34.6 ▲ | 34.2 ▲ | 32.8 ▲ | 31.5 ▲ | 30.4 | 31.0 | 30.1 | 31.6 ▲ | 31.2 ▲ | 32.0 |
| MCHC | 33.3 | 33.6 | 33.3 | 32.8 | 31.4 ▼ | 33.9 | 32.2 | 32.2 | 31.7 ▼ | 33.8 |
| PLT | 81 ▼ | 82 ▼ | 88 ▼ | 95 ▼ | 211 | 78 ▼ | 39 ▼ | 250 | 253 | 112 ▼ |
| MPV | 10.2 | 10.4 | 10.6 | 10.0 | 9.8 | 10.8 | 10.4 | 9.7 | 9.8 | 10.2 |
| RDW | 15.2 ▲ | 16.6 ▲ | 17.5 ▲ | 17.9 ▲ | 18.4 ▲ | 17.1 ▲ | 16.3 ▲ | 15.6 ▲ | 17.0 ▲ | 18.1 ▲ |
| BLOOD DIFFERENTIA... | | | | | | | | | | |

# Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse

*A Complimentary NCPD Symposium Series Held During the 51st Annual ONS Congress*

# Bispecific Antibodies and Antibody-Drug Conjugates for Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

**Friday, May 15, 2026**

**6:00 PM – 8:00 PM**

## Faculty

**Farrukh T Awan, MD, MS, MBA**
**Robin Klebig, MSN, APRN, CNP, AOCNP**
**Mollie Moran, APRN-CNP, AOCNP**

## Moderator

**Brad S Kahl, MD**

RTP RESEARCH TO PRACTICE

*Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.*

## *To Claim NCPD Credit*

*In-person attendees: Please refer to the program syllabus for the NCPD credit link or QR code.*

*Virtual attendees: The NCPD credit link is posted in the chat room.*

*NCPD/ONCC credit information will be emailed to each participant within 1 to 2 business days.*

RTP
RESEARCH
TO PRACTICE