Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

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

A CME/MOC-Accredited Live Webinar

Wednesday, July 15, 2026

5:00 PM – 6:00 PM ET

Faculty

Virginia Kaklamani, MD, DSc

Hope S Rugo, MD

Moderator

Neil Love, MD

RTP Year in Review 2026

Faculty

Virginia Kaklamani, MD, DSc
Professor of Medicine
Ruth McLean Bowman Bowers Chair in Breast Cancer Research and Treatment
AB Alexander Distinguished Chair in Oncology
Leader, Breast Oncology Program
UT Health San Antonio MD Anderson Cancer Center
San Antonio, Texas

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Hope S Rugo, MD
Director, Women's Cancers Program
Division Chief, Breast Medical Oncology
Professor, Department of Medical Oncology and Therapeutics Research
City of Hope Comprehensive Cancer Center
Duarte, California
Professor Emeritus, UCSF

Commercial Support

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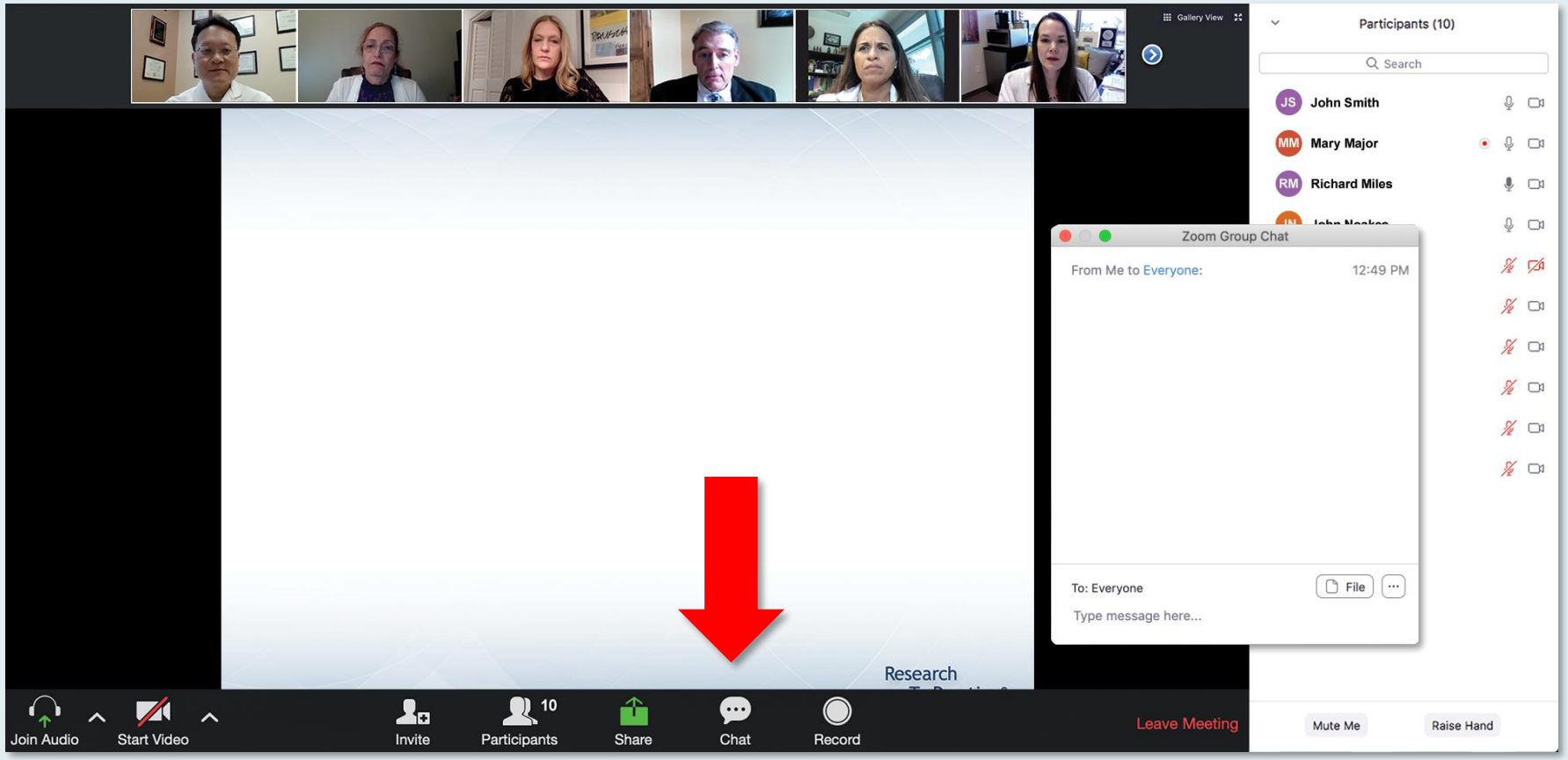

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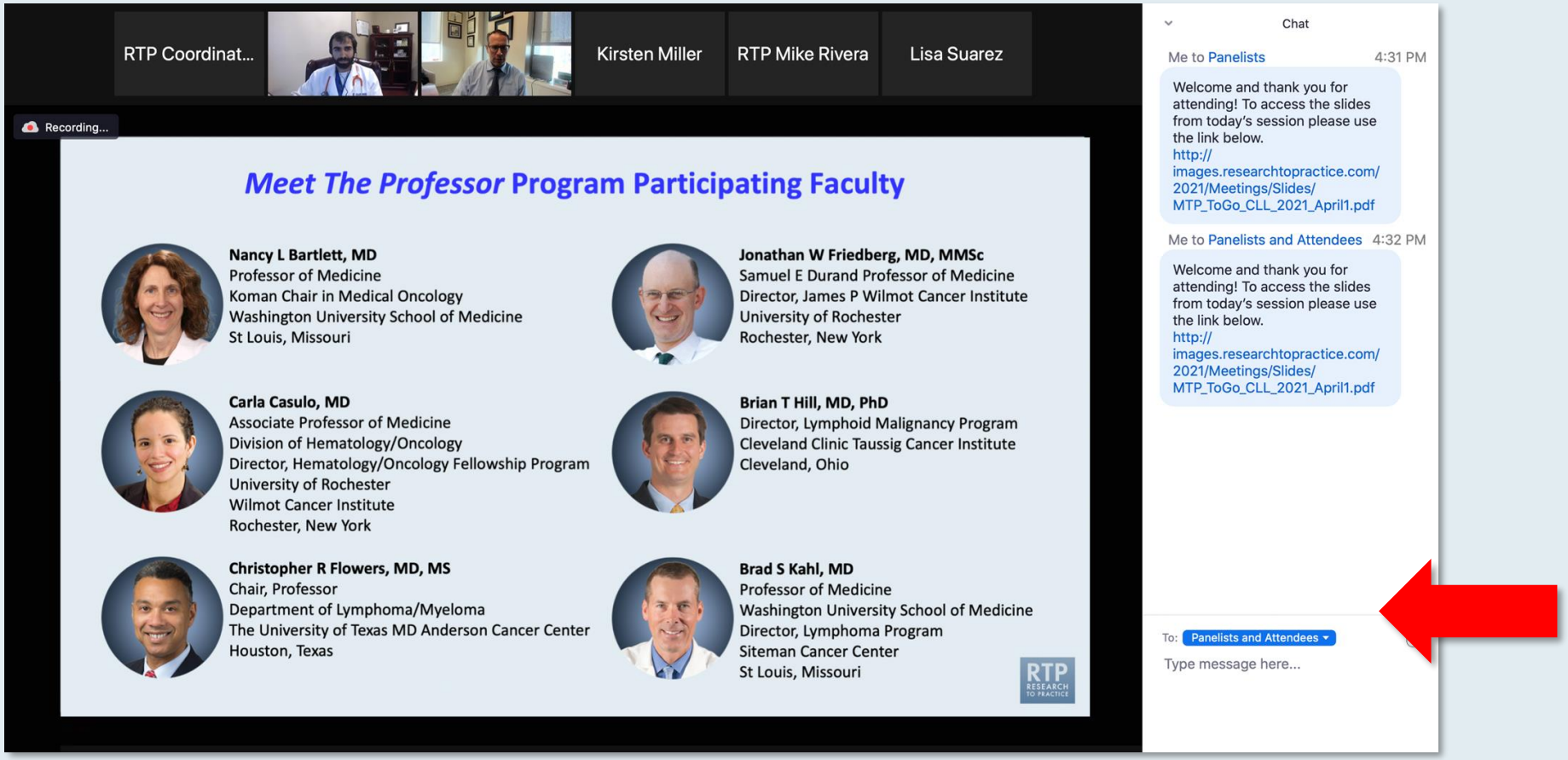

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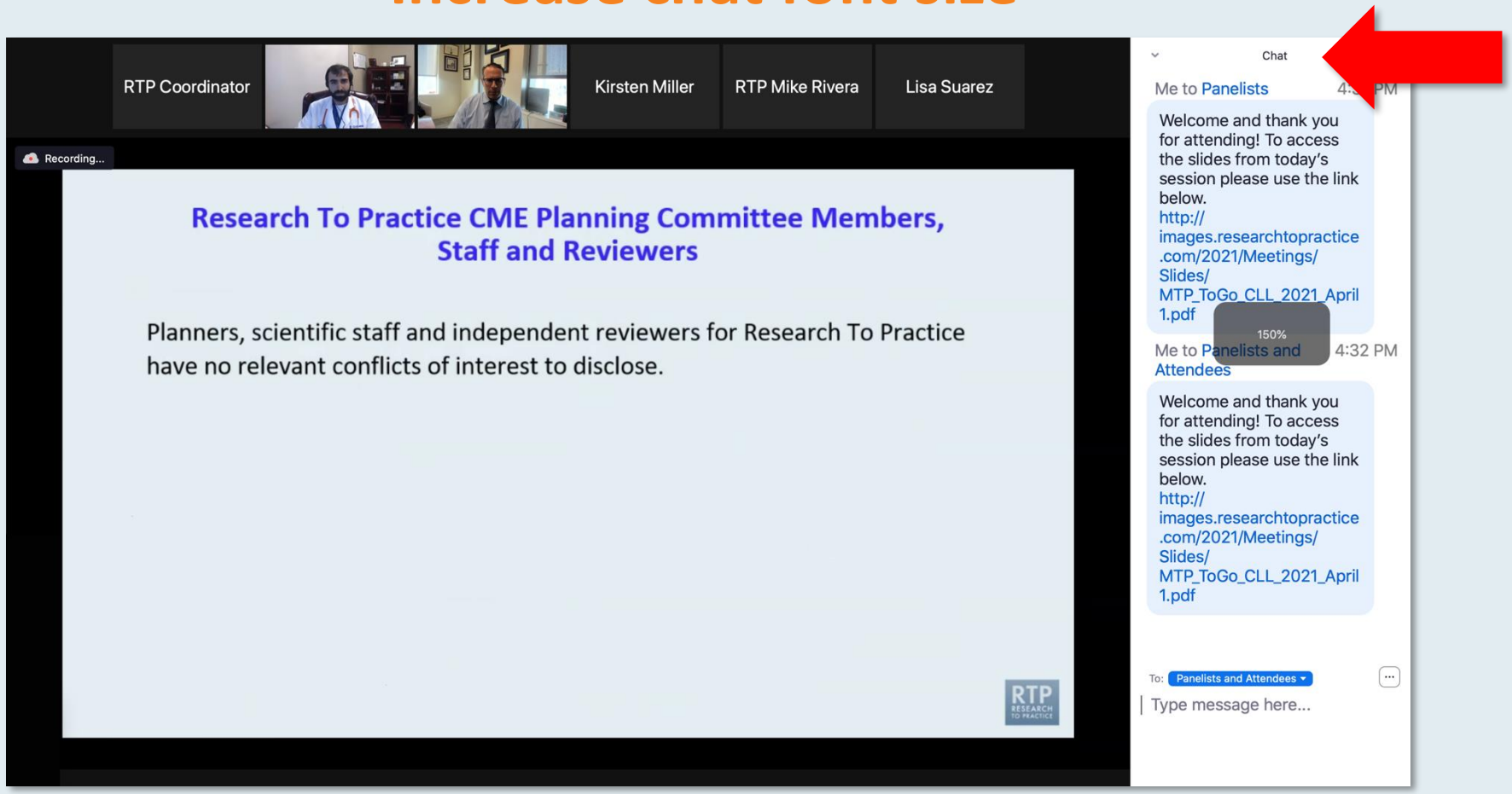

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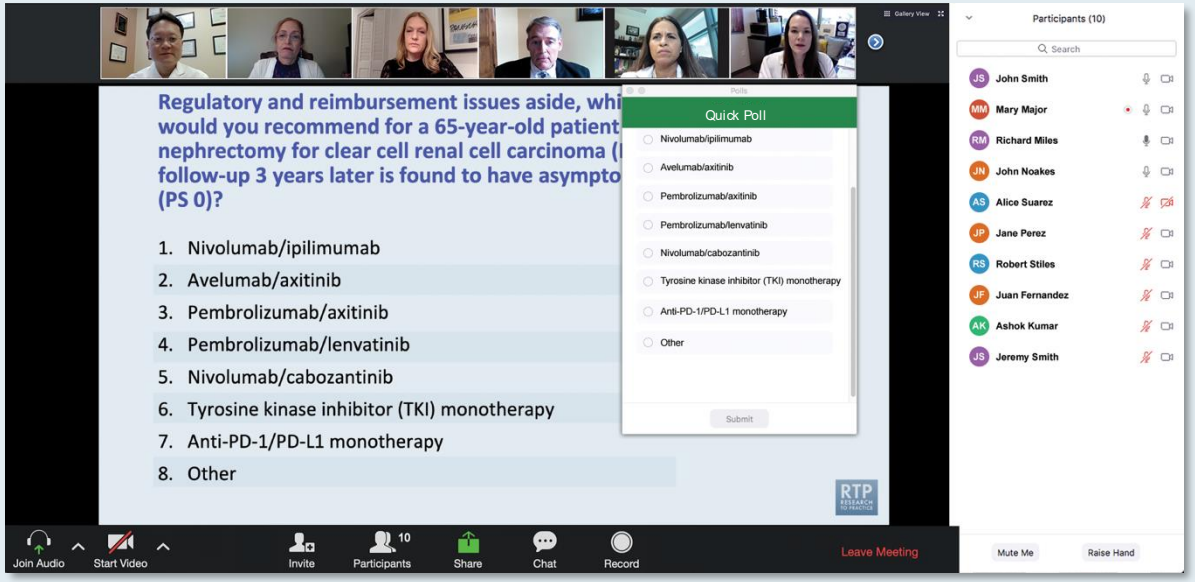

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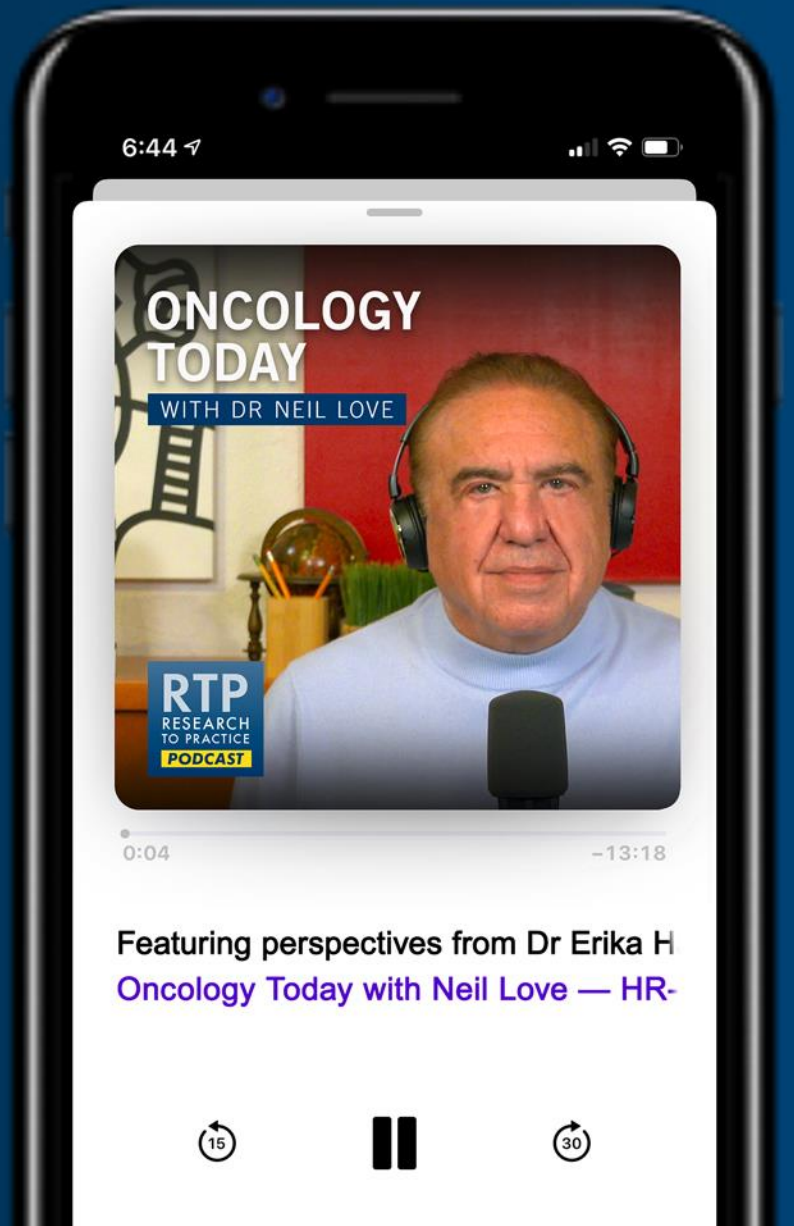

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The Implications of Recent Datasets for the Current and Future Management of Genitourinary Cancers — An ASCO 2026 Review

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RTP RESEARCH TO PRACTICE

Patterns of Care: Exploring How Community Oncologists Manage Metastatic Triple-Negative Breast Cancer

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RTP RESEARCH TO PRACTICE

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Additional faculty to be announced.

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Integrating New Advances into the Care of Patients with Cancer

A Multitumor Symposium in Partnership with the American Oncology Network

Saturday, August 22, 2026

JW Marriott Nashville | Nashville, Tennessee

Chronic Lymphocytic Leukemia
9:00 AM – 9:50 AM CT

Gastroesophageal Cancers
9:50 AM – 10:40 AM CT

Gynecologic Cancers
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Lung Cancer
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INTRODUCTION: San Antonio Memories

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MODULE 2: Capivasertib

MODULE 3: Gedatolisib

MODULE 4: Inavolisib

MODULE 5: New Agents and Ongoing Trials

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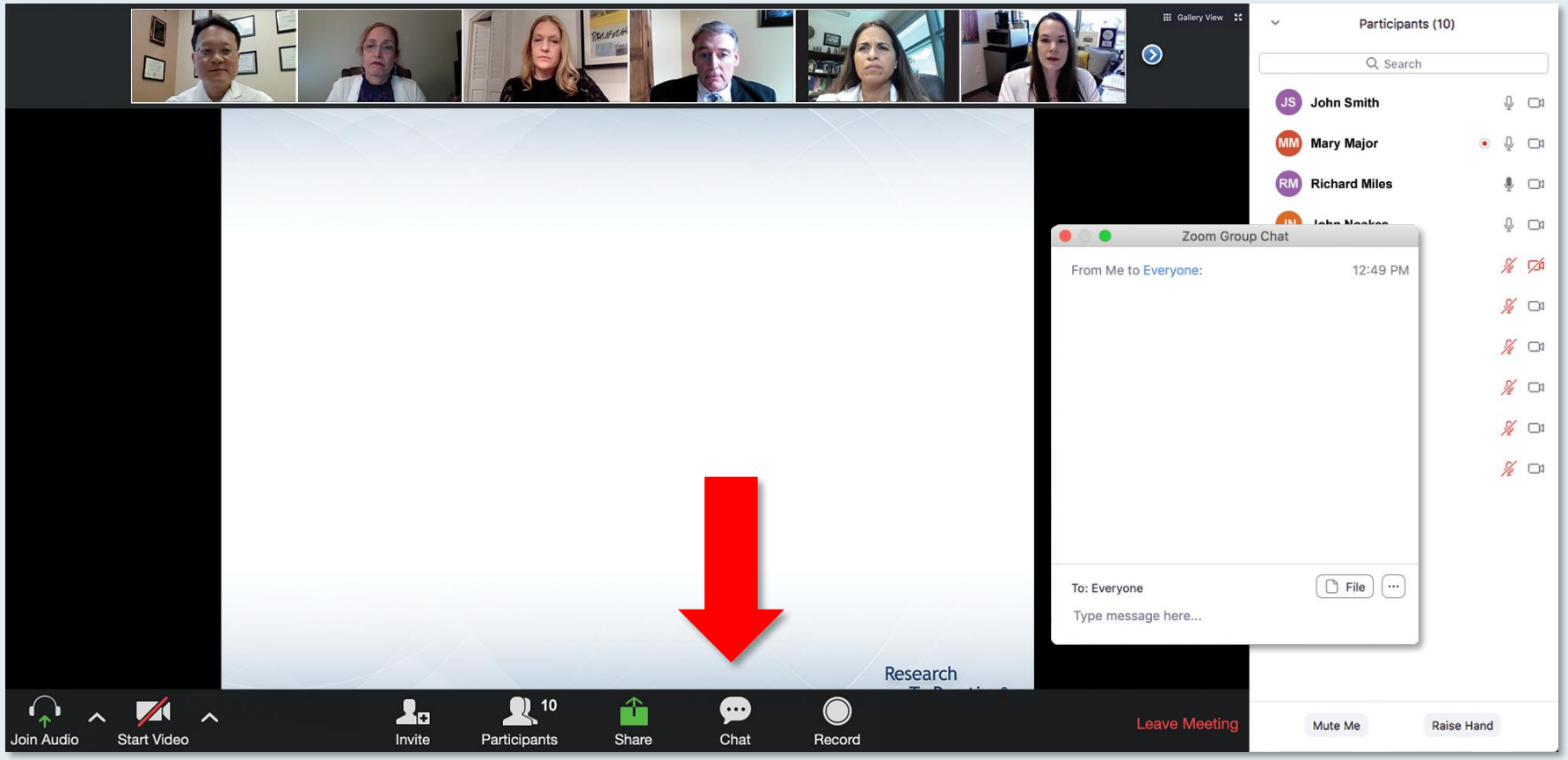

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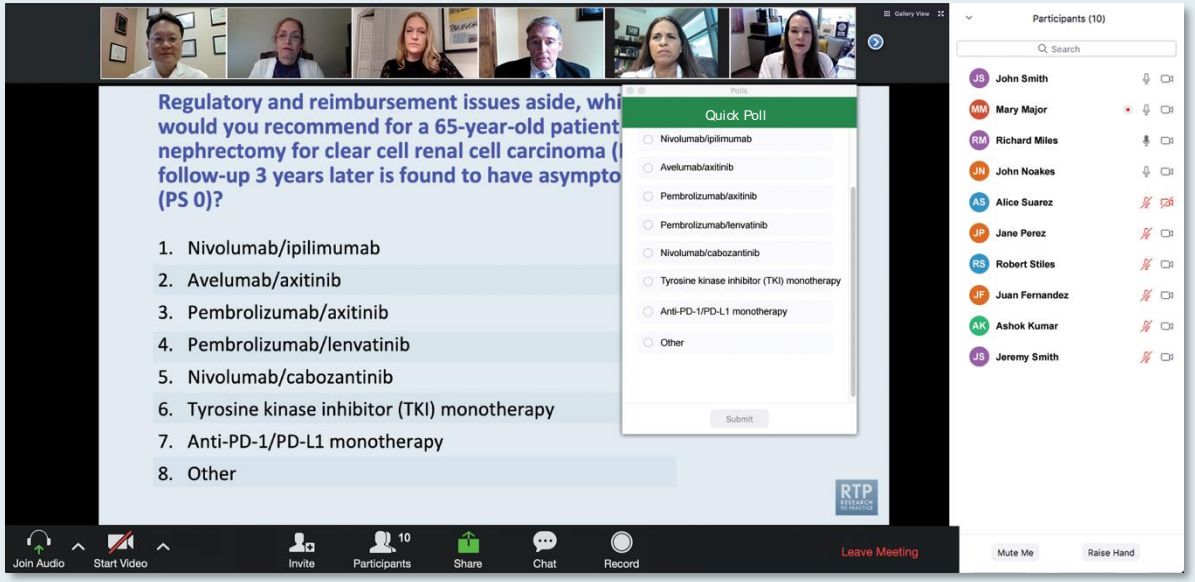

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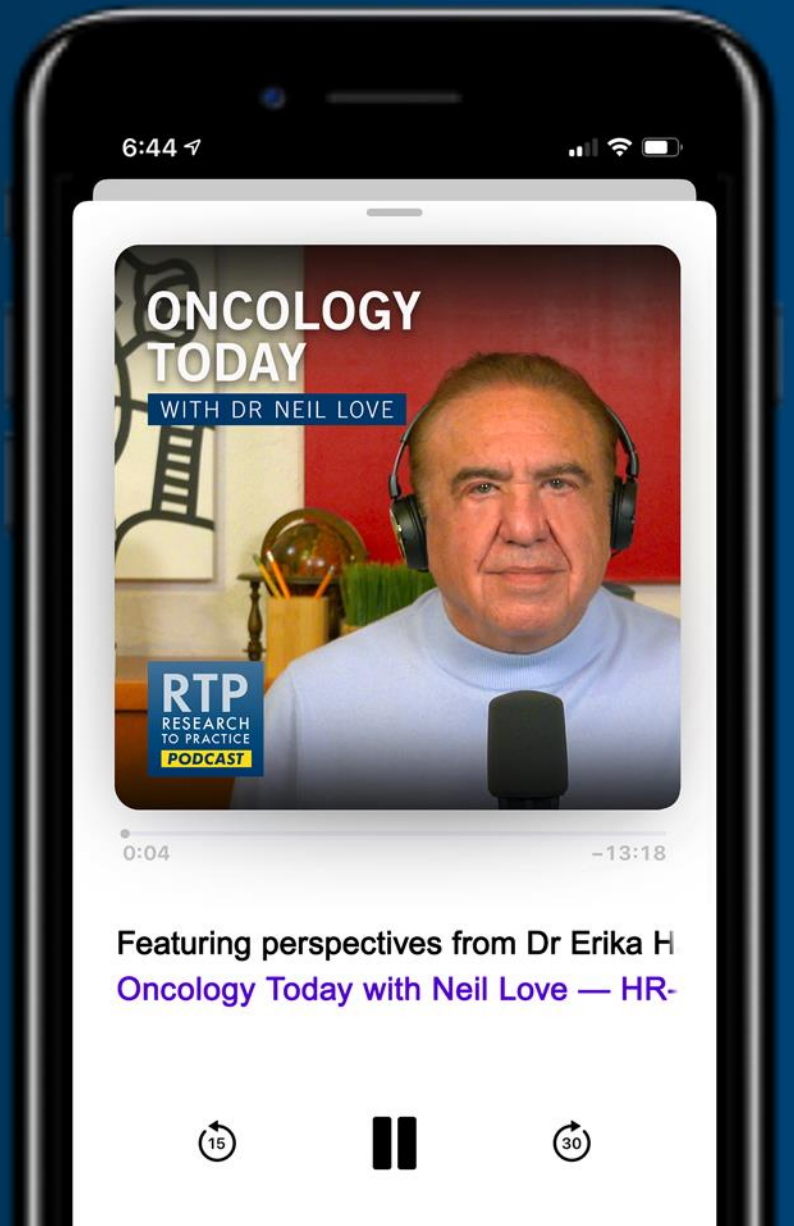

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PI3Ki review

Virginia Kaklamani, MD DSc
Professor of Medicine
Leader, Breast Oncology Program

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

City of Hope

Year in Review
Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR+ mBC

Hope S. Rugo, MD
Director, Women's Cancers Program
Division Chief, Breast Medical Oncology
Professor, Department of Medical Oncology & Therapeutics Research
City of Hope Comprehensive Cancer Center
Professor Emeritus, UCSF

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Key Datasets

Virginia Kaklamani, MD, DSc

- Fernando S et al. PIK3R1 (p85α) alterations define a targetable subset of breast cancer with broad sensitivity to PI3K and AKT inhibitors. San Antonio Breast Cancer Symposium 2025;Abstract RF4-05.
- Kalinsky K et al. Comparative analysis of blood- and tissue-based PIK3CA mutation detection methods in the pivotal phase 3 INAVO120 trial of palbociclib + fulvestrant ± inavolisib in hormone receptor-positive, HER2-negative advanced breast cancer. San Antonio Breast Cancer Symposium 2025;Abstract PS1-10-26.
- Jhaveri KL et al. Overall survival with inavolisib in PIK3CA-mutated advanced breast cancer. *N Engl J Med* 2025;393(2):151-61.
- Turner N et al. Molecular features of response to palbociclib + fulvestrant ± inavolisib in hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer as assessed from baseline circulating tumor DNA in the pivotal phase 3 INAVO120 trial. San Antonio Breast Cancer Symposium 2025;Abstract PD5-09.
- Loibl S et al. Efficacy of inavolisib (INAVO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with PIK3CA-mutated, hormone receptor-positive, HER2-negative (HER2-), endocrine-resistant advanced breast cancer (aBC) with and without hyperglycaemia (HG) in the phase III INAVO120 trial. ESMO Breast Cancer 2026;Abstract 420RO.

Key Datasets

Virginia Kaklamani, MD, DSc (continued)

- Basho R et al. INAVO123: Phase 3 study of first-line inavolisib/placebo + a cyclin-dependent kinase 4/6 inhibitor + letrozole in participants with PIK3CA-mutated, hormone receptor-positive, HER2-negative, endocrine-sensitive advanced breast cancer. San Antonio Breast Cancer Symposium 2025;Abstract PS5-07-27.
- Neven P et al. Capivasertib (C) + ribociclib (R) + fulvestrant (F) in patients (pts) with HR-positive/HER2-negative advanced breast cancer (ABC): CAPItello-292 phase Ib. ESMO Breast Cancer 2025;Abstract 316P.
- Sudhan DR et al. Mechanisms of resistance to capivasertib in combination with CDK4/6 inhibitor (CDK4/6i) plus fulvestrant in patients with hormone receptor-positive/HER2-negative (HR+/HER2−) advanced breast cancer (ABC): Exploratory analysis from the phase 1b CAPItello-292 study. San Antonio Breast Cancer Symposium 2025;Abstract RF4-04.
- Wesolowski R et al. Gedatolisib combined with palbociclib and letrozole in patients with no prior systemic therapy for hormone receptor-positive, HER2-negative advanced breast cancer. *Clin Cancer Res* 2025;31(19):4040-8.
- VIKTORIA-2: A randomized, open-label, phase 3 study evaluating efficacy and safety of gedatolisib with endocrine therapy and palbociclib vs endocrine therapy and ribociclib as first-line treatment in patients with HR-positive and HER2-negative advanced breast cancer. NCT06757634.

Key Datasets

Hope S Rugo, MD

- Rugo HS et al. Capivasertib (C) and fulvestrant (F) for patients (pts) with HR+/HER2- advanced breast cancer (ABC): Final overall survival (OS) results from the phase III CAPItello-291 trial. ESMO Breast Cancer 2026;Abstract 417O.
- Rugo HS et al. Capivasertib plus fulvestrant as first and second-line endocrine-based therapy in PIK3CA/AKT1/PTEN-altered hormone receptor-positive advanced breast cancer: Subgroup analysis from the phase 3 CAPItello-291 trial. ESMO 2025;Abstract 526P.
- Turner NC et al. Capivasertib plus fulvestrant in hormone receptor-positive (HR+) advanced breast cancer (ABC): Exploratory ctDNA analyses from the phase 3 CAPItello-291 trial. San Antonio Breast Cancer Symposium 2025;Abstract RF7-05.
- Vaklavas C et al. Camizestrant in combination with capivasertib for women with ER-positive, HER2-negative advanced breast cancer: Results from SERENA-1. *ESMO Open* 2026;11(2):106049.
- Pistilli B et al. Gedatolisib (Geda), a multitarget PI3K/AKT/mTOR (PAM) inhibitor, plus fulvestrant (Fulv) ± palbociclib (Palbo) for second-line (2L) treatment of patients (Pts) with HR+/HER2-/PIK3CA-wild type (WT) advanced breast cancer (ABC): Updated results from VIKTORIA-1. ESMO Breast Cancer 2026;Abstract 505P.

Key Datasets

Hope S Rugo, MD (continued)

- Hurvitz S et al. A randomized, open-label, phase 3 study of gedatolisib + fulvestrant ± palbociclib vs standard of care in HR+/HER2−/PIK3CA-mutant (MT) advanced breast cancer (VIKTORIA-1 Study 2). ASCO 2026;Abstract LBA1008.
- Jhaveri K et al. A phase 1/2 trial of tersolisib (LY4064809/STX-478), a pan-mutant-selective PI3Kα inhibitor (PI3Kαi), in PIK3CA-mutant advanced solid tumors: Updated results from PIKALO-1. ASCO 2026;Abstract 1072.
- A phase 3, randomized, double-blind, placebo-controlled study of LY4064809 combined with a CDK4/6 inhibitor and endocrine therapy in adults with HR+, HER2- advanced breast cancer with a PIK3CA mutation who received no prior treatment for advanced breast cancer (PIKALO-2). NCT07174336.
- Saura C et al. Efficacy of mutant-selective PI3Kα inhibitor RLY-2608 in combination with fulvestrant in patient (pt) subset populations, including pts with PIK3CA-mutant HR+/HER2- advanced breast cancer (BC) pre-treated with fulvestrant or other SERD. San Antonio Breast Cancer Symposium 2025;Abstract PD10-07.
- Rugo H et al. ReDiscover-2, a phase 3 study of zovegalisib (zovega, RLY-2608) + fulvestrant (fulv) versus capivasertib (capi) + fulv as treatment for locally advanced or metastatic PIK3CA-mutant HR+/HER2- breast cancer following recurrence or progression on or after treatment with a CDK4/6 inhibitor. ASCO 2026;Abstract TPS1148.

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INTRODUCTION: San Antonio Memories

MODULE 1: PI3K/AKT/PTEN Alterations and Therapies

MODULE 2: Capivasertib

MODULE 3: Gedatolisib

MODULE 4: Inavolisib

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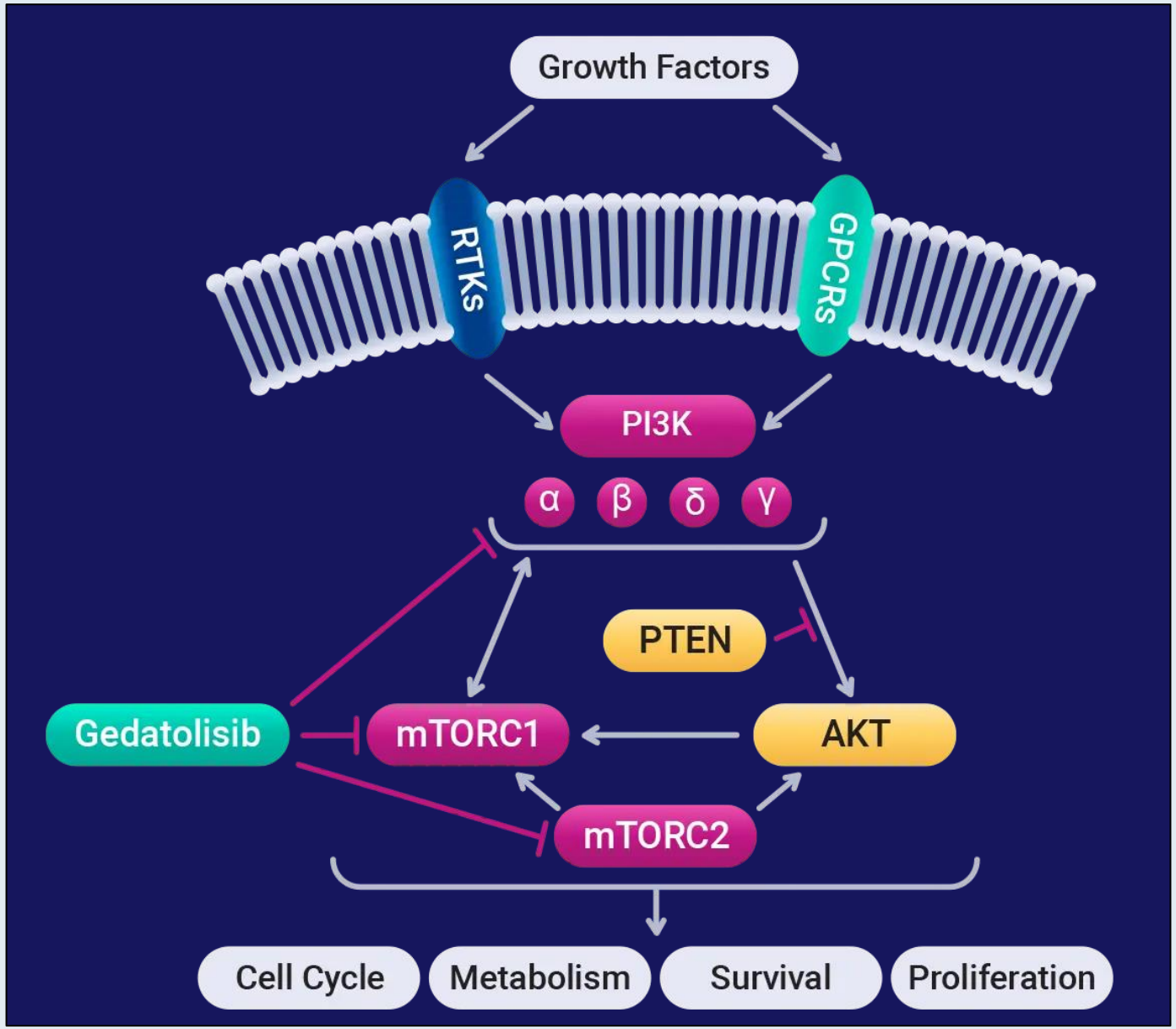
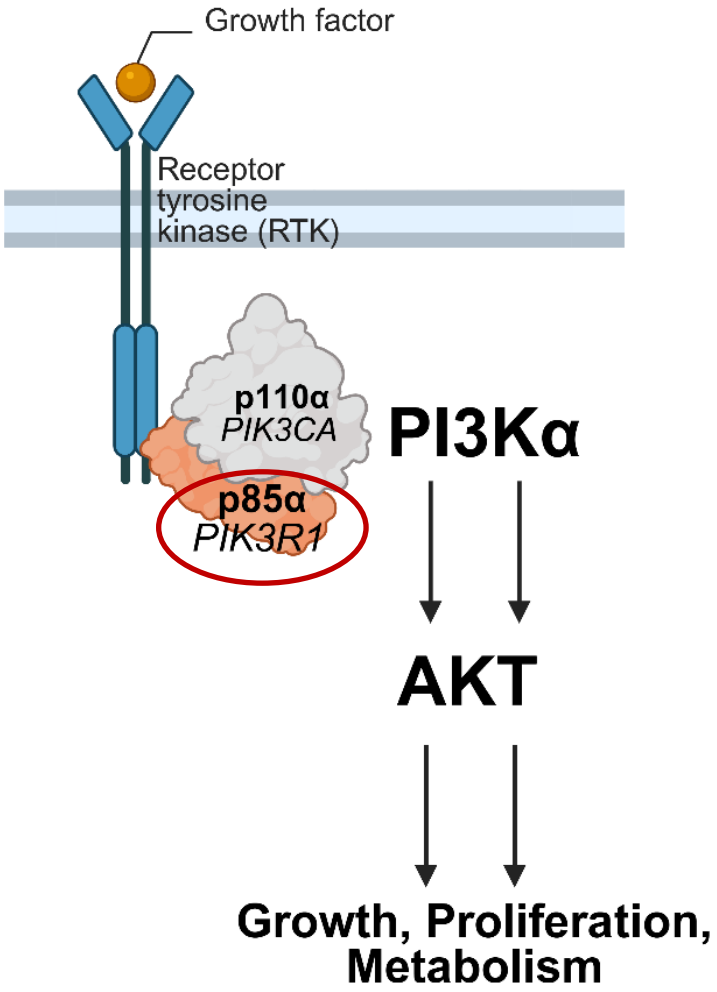
Gedatolisib Mechanism of Action

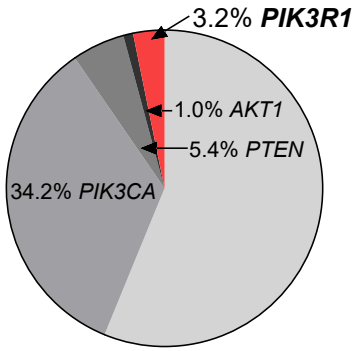


[From the manufacturer's website]

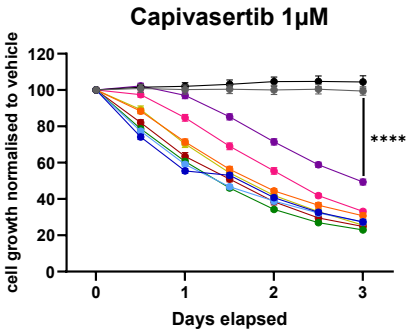
PIK3R1 (p85α) alterations define a targetable subset of breast cancer with broad sensitivity to PI3K and AKT inhibitors

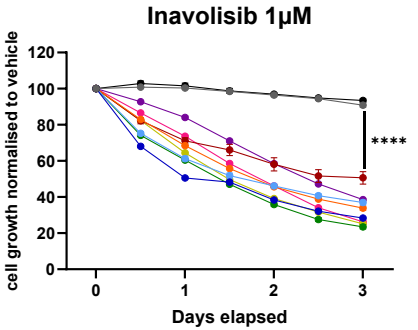


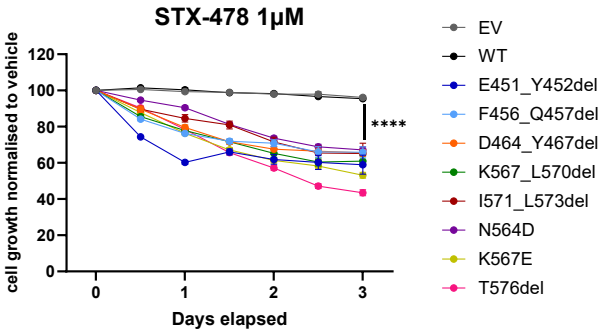
PIK3R1 alterations are found in 3.2% of BC



Breast cancer N = 51,574







PIK3R1 alterations predict sensitivity to AKTi, PI3Ki and mutant-selective PI3Ki

Fernando SABCS 2025;Abstract RF4-05

Next Steps in Targeting the PI3K/AKT/mTOR Pathway

- **Targeting PIK3CA with triplet therapy**
  - **Endocrine sensitive disease in the 1st line setting:**
    - INAVO123 (invavolisib, NCT06790693)
    - VIKTORIA-2 (gedatolisib, NCT06757634)
    - **PIKALO-2 (tersolisib, NCT07174336)**
  - **Endocrine resistant disease in the 1st line setting:**
    - CAPItello-292 (capivasertib, NCT04862663)
    - VIKTORIA-2 (gedatolisib, NCT06757634)
    - **PIKALO-2 (tersolisib; NCT07174336)**
- **Targeting PIK3CA in the >1st line setting**
  - **Re-discover**
    - **RLY-2608-102 (zovegalisib; NCT06982521)**

Year in Review:
PI3K/AKT/mTOR Pathway in
HR-Positive Metastatic Breast Cancer

INTRODUCTION: San Antonio Memories

MODULE 1: PI3K/AKT/PTEN Alterations and Therapies

MODULE 2: Capivasertib

MODULE 3: Gedatolisib

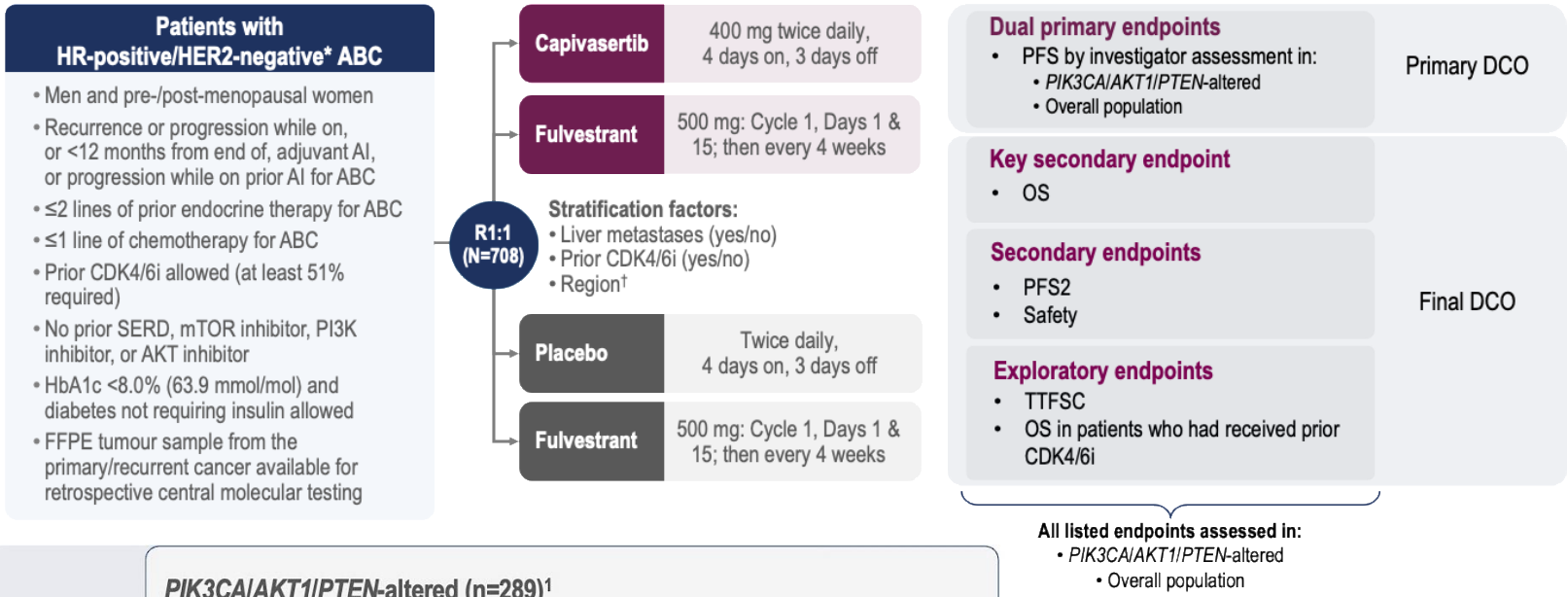
MODULE 4: Inavolisib

MODULE 5: New Agents and Ongoing Trials

RTP Year in Review 2026

Capivasertib and Fulvestrant for HR+/HER2– MBC: Final OS Results from the Phase 3 CAPItello-291 Trial

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



PFS	***PIK3CA/AKT1/PTEN*-altered (n=289)[1]** **7.3 months** vs 3.1 months, hazard ratio **0.50** (95% CI 0.38–0.65); p<0.001 **Overall (n=708)[1]** **7.2 months** vs 3.6 months, hazard ratio **0.60** (95% CI 0.51–0.71); p<0.001 • PFS benefit observed regardless of *ESR1* alterations detected in ctDNA, including those who received prior first-line AI + CDK4/6i[2]
Other endpoints	• Meaningful, sustained treatment benefit via PFS2 (secondary) and TTFSC (exploratory)[3] • Safety profile compared favourably with that of other agents targeting the same pathway[1–3]

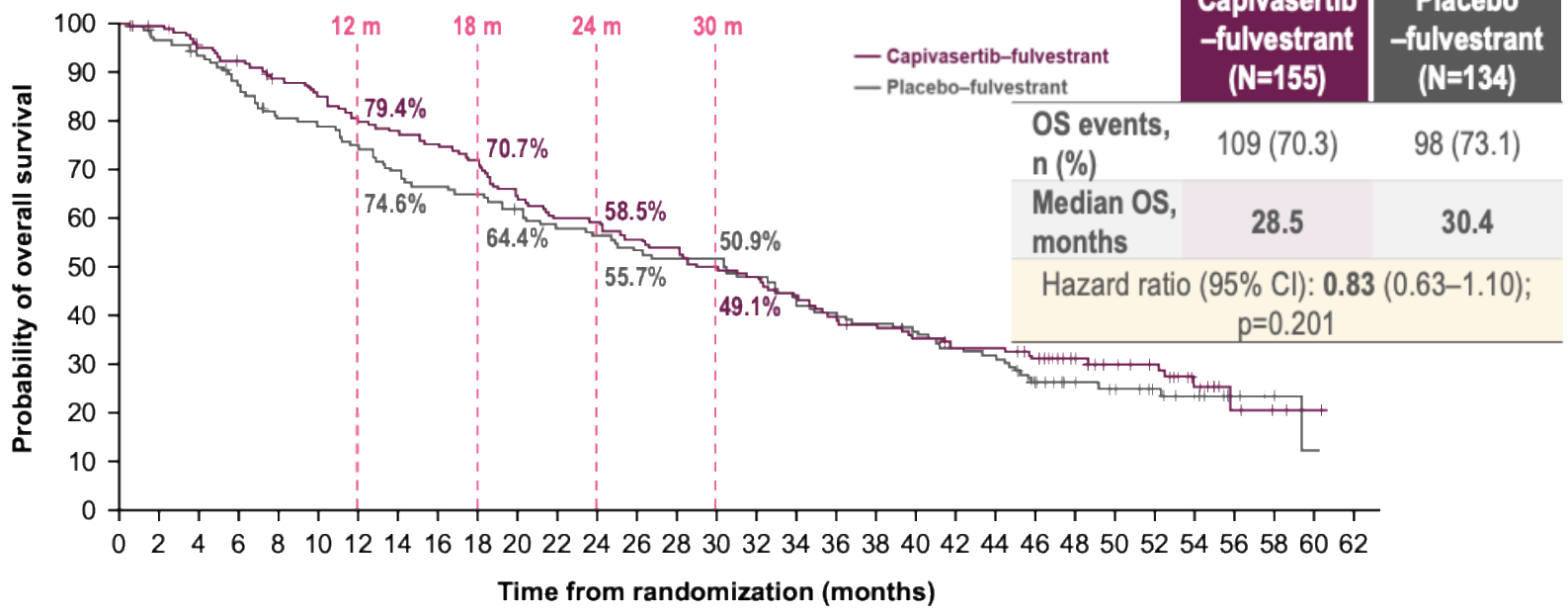
Trial population

- 70% CDK4/6i
- 40% 1° end resistance
- Med 1 line prior Rx
- 19% prior chemo for advanced disease

The study was designed with 90% power to detect a difference in OS between arms in the overall population, **but was underpowered in the altered population with only 53% power**

Rugo et al, ESMO Breast 2026;Abstract 417O

Results: Altered Population



	Capivasertib–fulvestrant (N=155)	Placebo–fulvestrant (N=134)
OS events, n (%)	109 (70.3)	98 (73.1)
Median OS, months	28.5	30.4
Hazard ratio (95% CI): **0.83** (0.63–1.10); p=0.201		

Number of patients at risk

Capivasertib–fulvestrant	155	153	144	139	131	126	118	115	111	105	94	88	87	82	79	73	70	64	57	54	50	46	46	41	33	26	21	13	4	2	1	0
Placebo–fulvestrant	134	127	122	113	102	100	95	88	84	82	77	72	70	66	64	64	59	52	49	47	44	40	38	27	21	18	14	10	5	2	1	0

Final DCO: 16 June 2025. Data maturity: 71.6%.

PFS2

	Capivasertib–fulvestrant (N=155)	Placebo–fulvestrant (N=134)
PFS2 events, n	134	118
Median PFS2, months	15.9	11.1
Hazard ratio (95% CI): **0.68** (0.53–0.88)		

Time to 1st Chemo

	Capivasertib–fulvestrant (N=155)	Placebo–fulvestrant (N=134)
TTFSC events, n	137	123
Median TTFSC, months	11.0	6.0
Hazard ratio (95% CI): **0.62** (0.48–0.80)		

Significant imbalance in subsequent therapy

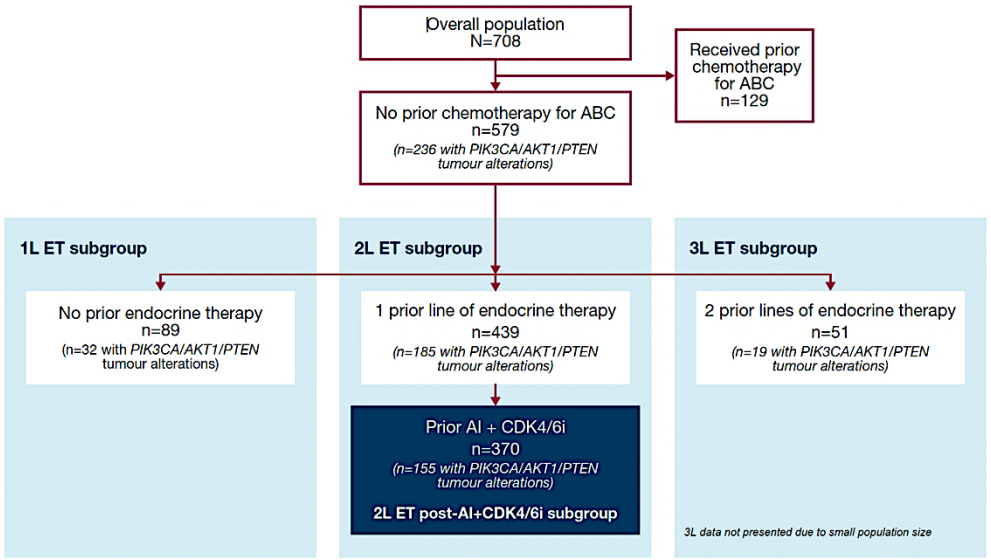
- Targeted therapy in subsequent Rx
  - 25.8% (Capi)
  - 42.5% (Pla)

Prior CDK4/6i

	Capivasertib–fulvestrant (N=114)	Placebo–fulvestrant (N=94)
OS events, n	83	74
Median OS, months	28.1	21.2
Hazard ratio (95% CI): **0.78** (0.57–1.07)		

Rugo et al, ESMO Breast 2026;Abstract 417O

Capi/Fulv as 1st and 2nd Line ET in PIK3CA/AKT1/PTEN-altered HR+ MBC: Subgroup analysis from the CAPItello-291



- In patients with PIK3CA/AKT1/PTEN altered, HR+ MBC:
  - Capi and Fulv demonstrated a consistent PFS benefit in either the 1L (PD <12 months after adjuvant ET) or as 2L setting in patients without prior chemotherapy
- The numbers are too small for definitive conclusions but diarrhea and rash were less frequent in the 1st line population

Figure 2A. PFS in all chemotherapy-naive patients with *PIK3CA/AKT1/PTEN* alterations (n=236)

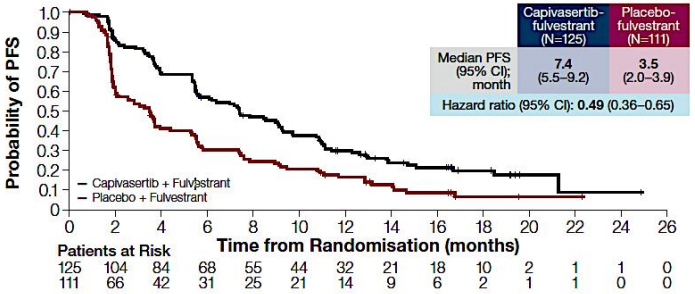


Figure 2B. PFS in chemotherapy-naive 1L ET patients with *PIK3CA/AKT1/PTEN* alterations (n=32)

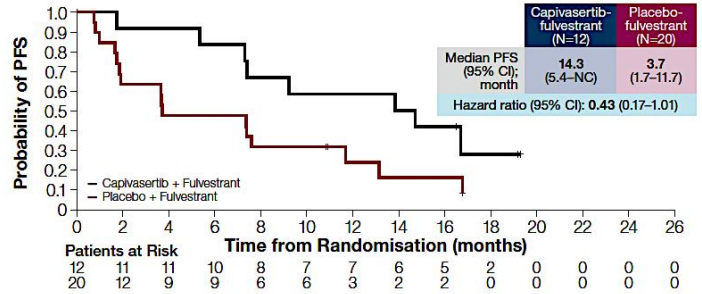


Figure 2C. PFS in chemotherapy-naive 2L ET patients with *PIK3CA/AKT1/PTEN* alterations (n=185)

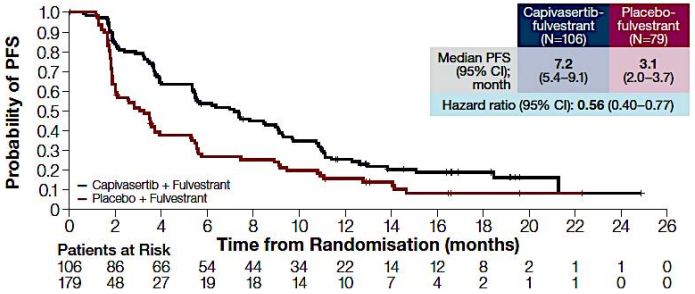
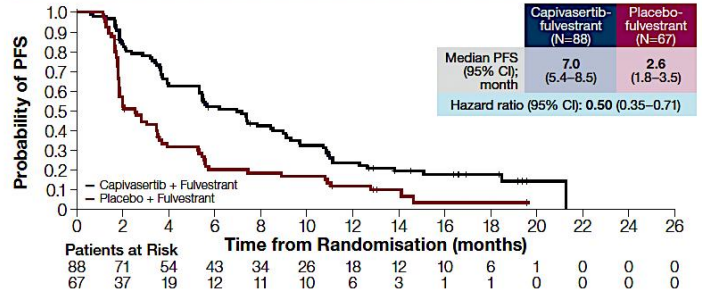


Figure 2D. PFS in chemotherapy-naive 2L ET (post AI+CDK4/6i) patients with *PIK3CA/AKT1/PTEN* alterations (n=155)



Rugo et al, ESMO 2025;Abstract 526P

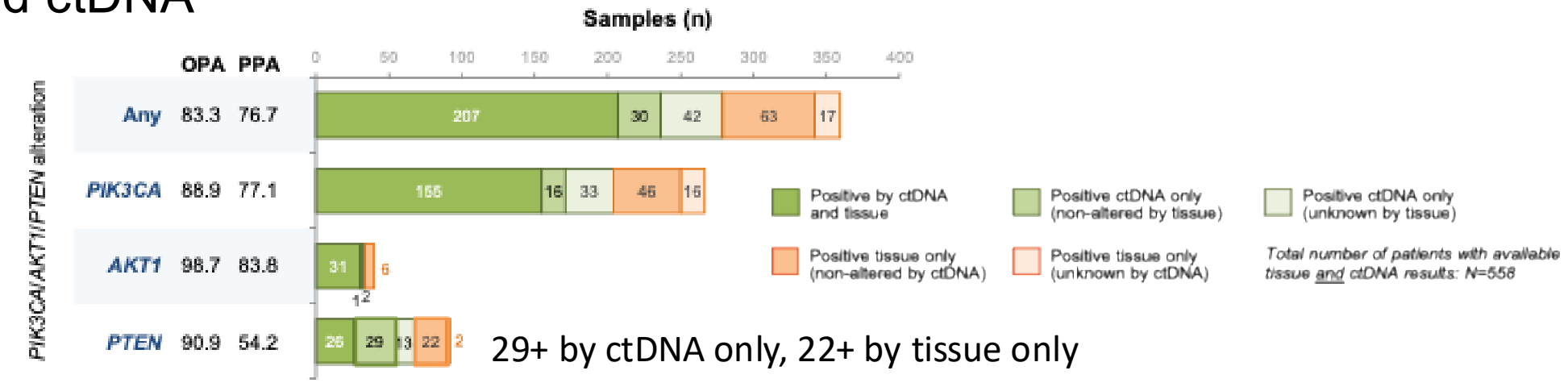
Conclusions and Take-Home Message

- Capivasertib–fulvestrant in the 2nd line setting for patients with *PIK3CA/AKT1/PTEN*-altered HR+/HER2- MBC resulted in:
  - Statistically significant, clinically meaningful PFS benefits, improved PFS2, and delayed time to first subsequent chemotherapy
- The OS hazard ratio (0.83) indicated a numerical trend in favour of capi/fulv in the altered population, but was not significant
  - As a key secondary endpoint with 53% power, the study was underpowered to detect a benefit in OS for the altered population
  - Marked imbalance in post-progression therapy likely confounded OS
  - In *PIK3CA/AKT1/PTEN*-altered patients with prior CDK4/6i Rx, the OS hazard ratio was 0.78
- Safety remained consistent and manageable with no new safety signals

Capivasertib–fulvestrant provides lasting treatment benefit vs placebo–fulvestrant, with manageable safety; OS interpretation is limited by study power and post-progression treatment confounding

Capivasertib/Fulvestrant in HR+ *PIK3CA/AKT1/PTEN*-altered ABC: Exploratory ctDNA analyses from CAPItello-291

- Guardant Infinity assay
  - Large genomic (750+ genes) and epigenomic panel with dense probe coverage for certain genes, including *PTEN* & methylation-based tumor DNA tumor fraction
- 658/708 ctDNA samples; 279 pathway alteration, 149/279 co-occurring ESR1m
  - Alterations detected by ctDNA only in 72/700 pts (10.3%)
    - Detection of PTEN alterations was the most discordant between tissue and ctDNA

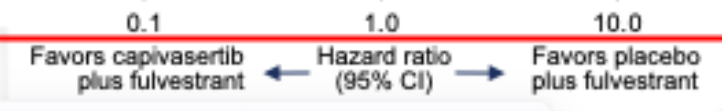


29+ by ctDNA only, 22+ by tissue only

Turner et al, SABCS 2025; Abstract RF7-05

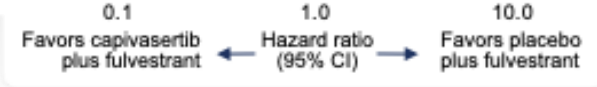
PFS by ctDNA alteration status

	n	Median PFS (months) Capivasertib + fulvestrant	Placebo + fulvestrant	HR (95% CI)
Overall CAPItello-291 population	708	7.2	3.6	0.60 (0.51–0.71)
PIK3CA/AKT1/PTEN-altered by tissue	289	7.3	3.1	0.50 (0.38–0.65)
All patients with a ctDNA result	658	7.2	3.5	0.59 (0.50–0.71)
PIK3CA/AKT1/PTEN alteration detected in ctDNA	279	5.6	2.1	0.43 (0.33–0.56)
*ESR1*m co-mutation	149	5.5	2.1	0.52 (0.36–0.76)
No *ESR1*m detected	130	7.4	2.6	0.36 (0.23–0.54)
PIK3CA/AKT1/PTEN alteration not detected in ctDNA	379	7.3	3.7	0.76 (0.60–0.95)
PIK3CA/AKT1/PTEN alteration detected in either tissue or ctDNA	359	7.2	2.8	0.49 (0.38–0.62)
PIK3CA/AKT1/PTEN alteration not detected (either both methods or with one unknown)	335	7.2	3.7	0.74 (0.58–0.95)



PFS by ctDNA alteration status: post-IL ET/CDK4/6i for ABC

	n	Median PFS (months) Capivasertib + fulvestrant	Placebo + fulvestrant	HR (95% CI)
Overall CAPItello-291 population	370	5.6	3.5	0.64 (0.51–0.81)
PIK3CA/AKT1/PTEN-altered by tissue	155	7.0	2.6	0.50 (0.35–0.71)
All patients with a ctDNA result	353	5.6	3.5	0.61 (0.48–0.77)
PIK3CA/AKT1/PTEN alteration detected in ctDNA	161	7.0	2.0	0.41 (0.29–0.58)
*ESR1*m co-mutation	94	7.0	2.0	0.45 (0.29–0.73)
No *ESR1*m detected	67	7.4	2.0	0.32 (0.18–0.57)
PIK3CA/AKT1/PTEN alteration not detected in ctDNA	192	5.5	3.7	0.83 (0.61–1.14)
PIK3CA/AKT1/PTEN alteration detected in either tissue or ctDNA	196	7.0	2.0	0.44 (0.32–0.61)
PIK3CA/AKT1/PTEN alteration not detected (either both methods or with one unknown)	172	4.9	3.7	0.83 (0.60–1.16)



Turner et al, SABCS 2025; Abstract RF7-05

Conclusions

- ctDNA testing has revolutionized testing for targetable mutations
  - Offers a non-invasive option to identify *PIK3CA*/*AKT1*/*PTEN* alterations in HR+ ABC
  - Important alternative for those without suitable tumor tissue analysis
- *PIK3CA*/*AKT1*/*PTEN* alterations were detected by ctDNA only (non-altered or unknown by tissue) in ~10% of patients, and by tissue only in ~11% of patients
  - Discordance between detection in ctDNA and tissue NGS was greatest for PTEN deletions
  - PIK3CA pathway alterations are generally conserved
    - Important to check NGS on tumor tissue AND ctDNA for optimal identification of pathway alterations
- PFS benefit from capivasertib + fulvestrant in the ctDNA-altered group was consistent with primary tissue-based analysis, irrespective of *ESR1*m

Capivasertib (C) + ribociclib (R) + fulvestrant (F) in patients (pts) with HR-positive/HER2-negative advanced breast cancer (ABC): CAPItello-292 Phase 1b

Based on the PK and overall safety profile, capivasertib 320 mg + ribociclib 600 mg + fulvestrant 500 mg was selected as the RP3D

Figure 3. Duration of patient response to capivasertib plus ribociclib and fulvestrant at the RP3D

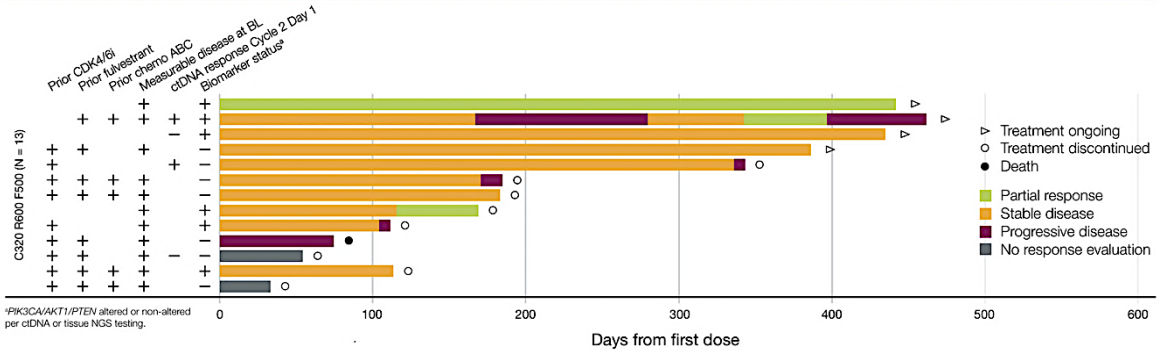
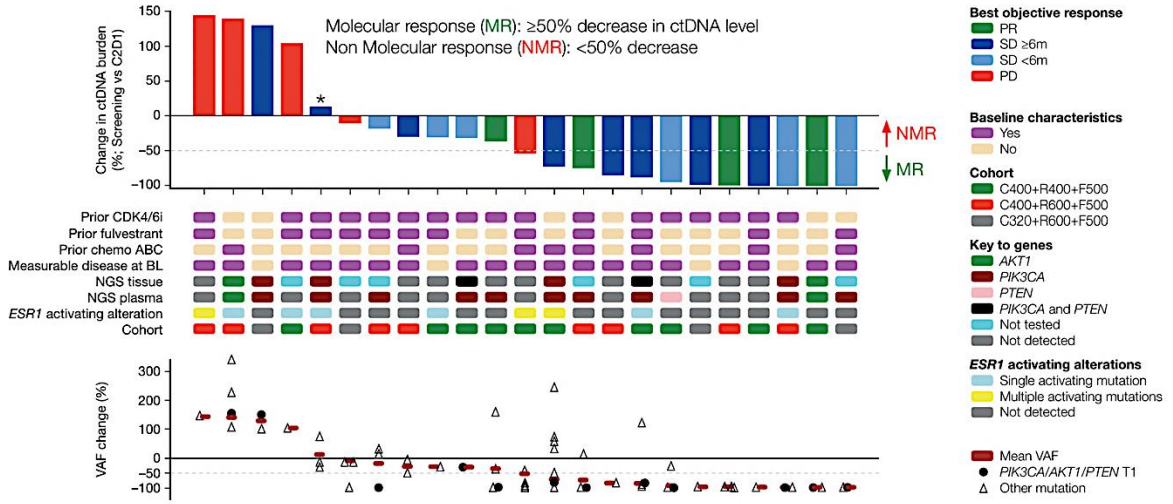
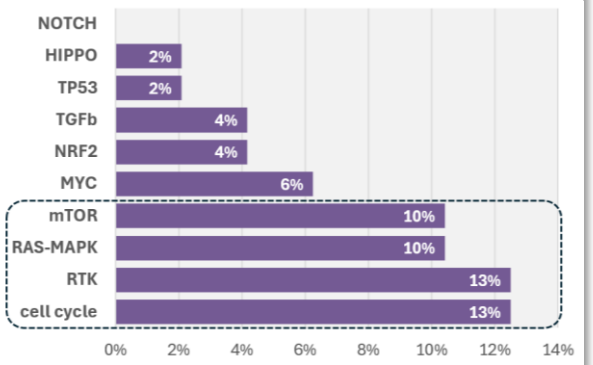


Figure 4. ctDNA molecular response across all evaluable patients



CBR: 23.1%

Prevalence of newly detected genomic alterations at EoT in key pathways[a]



- New *PIK3CA*/*PTEN* alterations were **detected at EoT in 6% of patients**, and no acquired *AKT* mutations were detected
- This suggests **robust PI3K/AKT pathway inhibition**, i.e., that acquisition of AKT and upstream alterations does not confer survival advantage in the presence of capivasertib

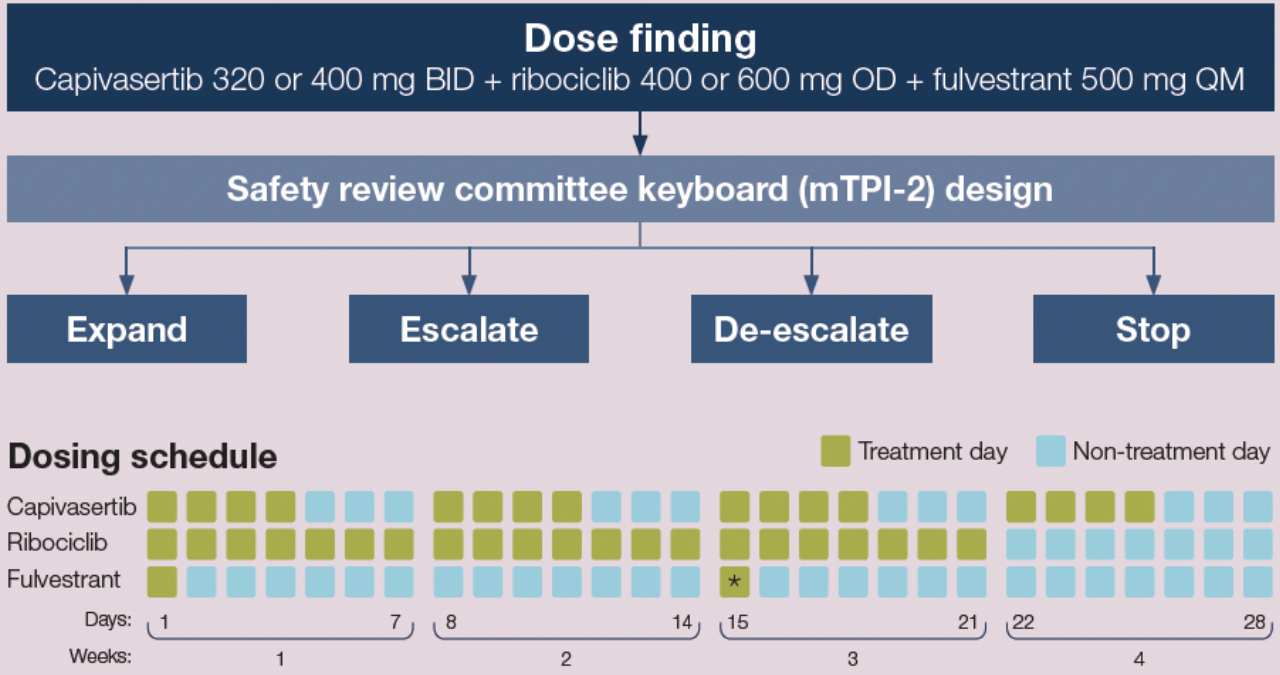
Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Neven ESMO Breast 2025;Abstract 316P & Sudhan SABCS 2025;Abstract RF4-04

CAPItello-292 Phase Ib/III Study Design

Phase 1b inclusion criteria

- Adults >18 years of age with locally advanced (inoperable) or metastatic HR+/HER2– breast cancer
- At least one prior ET in the advanced setting or disease recurrence within 12 months of completing (neo)adjuvant ET (no limit on the number of prior endocrine therapies received; SERDs were permitted)
- Up to two lines of prior chemotherapy for advanced breast cancer were permitted
- Prior CDK4/6i was permitted, provided there was a CDK4/6i treatment–free interval of at least 12 months prior to study start
- Eligible for ribociclib and fulvestrant therapy
- ECOG PS 0 or 1



Phase 1b endpoints

Primary

- Safety and tolerability (CTCAE version 5.0)
- Recommended Phase 3 dose

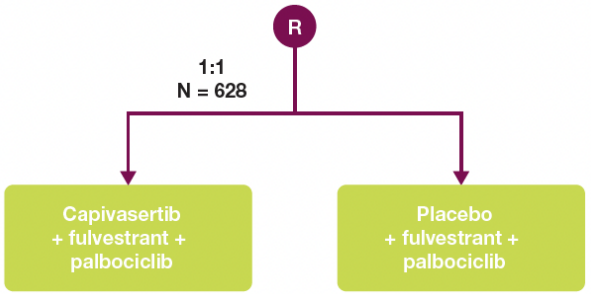
Secondary

- PK parameters for ribociclib and capivasertib
- Preliminary assessment of clinical activity (ORR, CBR24, DoR, PFS)

Exploratory

- Biomarker analysis

*Cycle 1 only, loading dose.



Phase III endpoints

Primary endpoints

- Safety/tolerability (DLTs, AEs, SAEs, vital signs, clinical chemistry/haematology/glucose metabolism, cardiac parameters)

Secondary endpoints

- PK parameters for palbociclib and capivasertib
- Preliminary signs of clinical activity (ORR, CBR24, DoR, PFS)

AEs, adverse events; BD, twice daily; CBR24, clinical benefit rate at 24 weeks; DLTs, dose-limiting toxicities; DoR, duration of response; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; OD, once daily; ORR, overall response rate; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; QM, every month; R, randomization; SAEs, serious adverse events.

Neven P et al. ESMO 2024;Abstract 316P.
Hamilton EP et al. ESMO 2021;Abstract 338TiP.

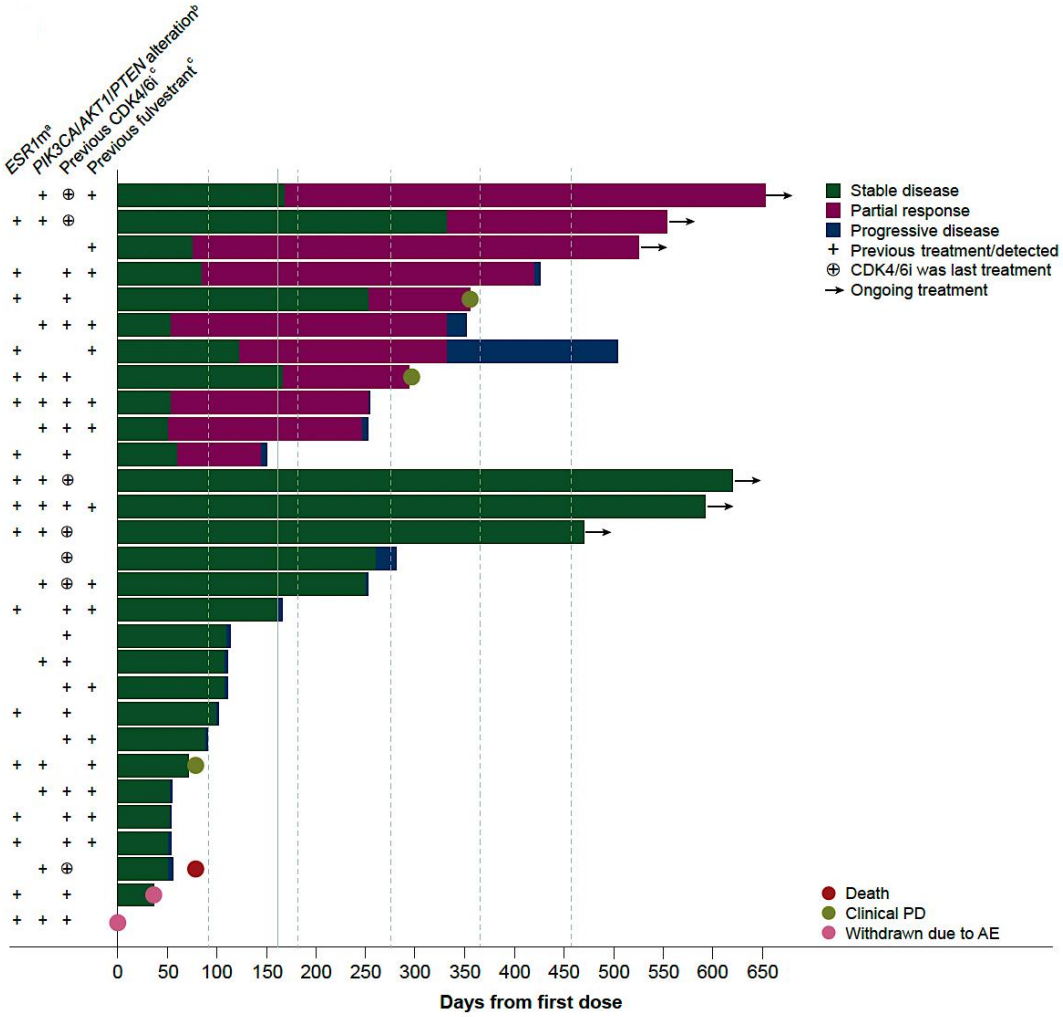
RTP RESEARCH TO PRACTICE

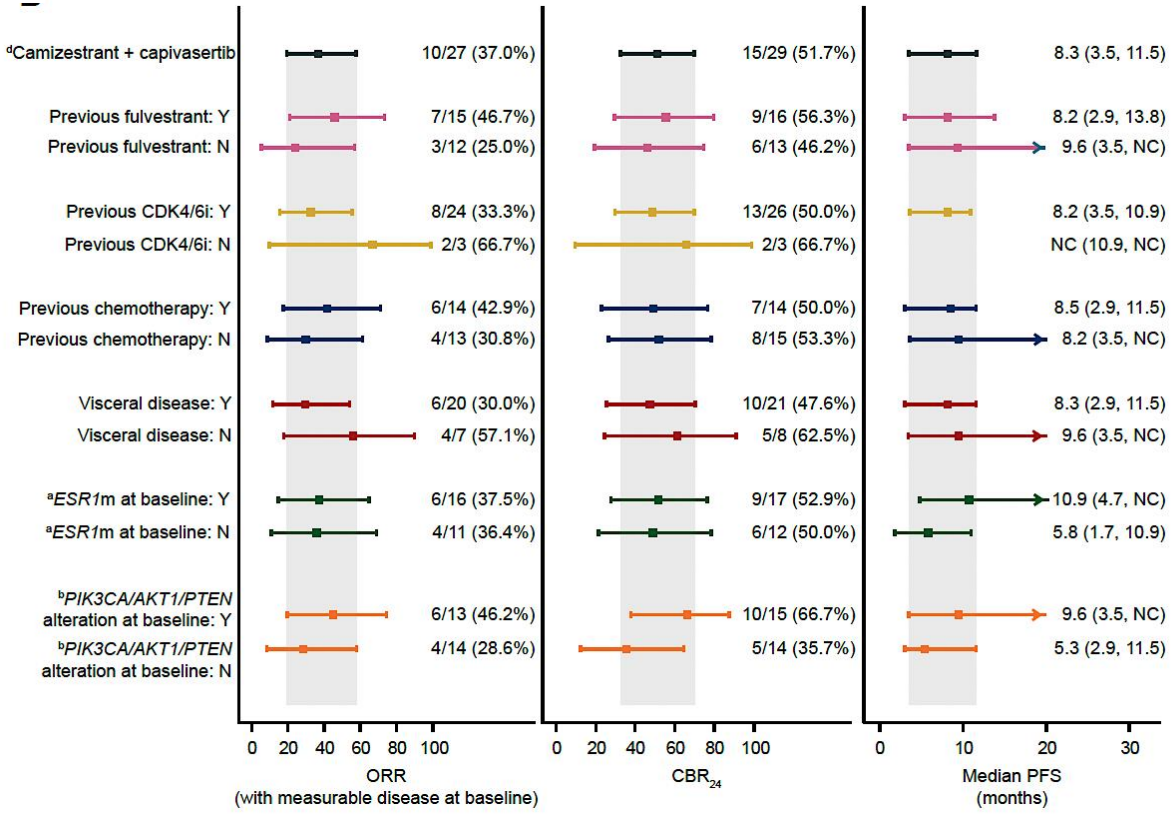
SERENA-1: Phase I Study of Camizestrant and Capivasertib

- 29 patients treated with camizestrant 75 mg/d and capivasertib 400 mg 4d on, 3d off
  - Median 2 lines prior therapy
  - 90% prior CDK4/6i, 55% prior fulvestrant,
  - 15 (52%) with PIK3CA/AKT/PTEN alterations, 17 (59%) with ESR1m
- The mean (±SD) treatment duration was 8.6 ± 6.7 months for camizestrant and 7.3 ± 6.7 months for capivasertib.
- Safety
  - Most common TEAEs (all grade): diarrhea (75.9%) and nausea (44.8%)
  - Most common grade ≥3 TEAE was diarrhea (3/10.3%); grade 3 rash (2/6.9%)
  - All grade 1: sinus bradycardia (37.9%), photopsia (20.7%), visual impairment (20.7%)

Vaklavas et al, ESMO Open 2026

Clinical Efficacy





- ≥50% reduction from baseline in summed *ESR1*m VAF seen in 92% (11/12) treated with camizestrant plus capivasertib,
- Clearance to undetectable levels seen in 67% (8/12)

Conclusions

- The oral SERD camizestrant can be safely combined with the AKT inhibitor capivasertib
- No new toxicity signals
- All oral combination is appealing but needs further study in a larger population
- The ongoing Elevate trial evaluated elacestrant and capivasertib in a phase II expansion cohort, enrollment completed

Key Datasets

- Rugo HS et al. Capivasertib (C) and fulvestrant (F) for patients (pts) with HR+/HER2- advanced breast cancer (ABC): Final overall survival (OS) results from the phase III CAPItello-291 trial. ESMO Breast Cancer 2026;Abstract 417O.
- Rugo HS et al. Capivasertib plus fulvestrant as first and second-line endocrine-based therapy in PIK3CA/AKT1/PTEN-altered hormone receptor-positive advanced breast cancer: Subgroup analysis from the phase 3 CAPItello-291 trial. ESMO 2025;Abstract 526P.
- Turner NC et al. Capivasertib plus fulvestrant in hormone receptor-positive (HR+) advanced breast cancer (ABC): Exploratory ctDNA analyses from the phase 3 CAPItello-291 trial. San Antonio Breast Cancer Symposium 2025;Abstract RF7-05.
- Neven P et al. Capivasertib (C) + ribociclib (R) + fulvestrant (F) in patients (pts) with HR-positive/HER2-negative advanced breast cancer (ABC): CAPItello-292 phase Ib. ESMO Breast Cancer 2025;Abstract 316P.
- Sudhan DR et al. Mechanisms of resistance to capivasertib in combination with CDK4/6 inhibitor (CDK4/6i) plus fulvestrant in patients with hormone receptor-positive/HER2-negative (HR+/HER2−) advanced breast cancer (ABC): Exploratory analysis from the phase 1b CAPItello-292 study. San Antonio Breast Cancer Symposium 2025;Abstract RF4-04.
- Vaklavas C et al. Camizestrant in combination with capivasertib for women with ER-positive, HER2-negative advanced breast cancer: Results from SERENA-1. *ESMO Open* 2026;11(2):106049.

Year in Review:
PI3K/AKT/mTOR Pathway in HR-Positive Metastatic Breast Cancer

INTRODUCTION: San Antonio Memories

MODULE 1: PI3K/AKT/PTEN Alterations and Therapies

MODULE 2: Capivasertib

MODULE 3: Gedatolisib

MODULE 4: Inavolisib

MODULE 5: New Agents and Ongoing Trials

RTP Year in Review 2026

Gedatolisib Combined with Palbociclib and Letrozole in Patients with No Prior Systemic Therapy for Hormone Receptor–Positive, HER2-Negative Advanced Breast Cancer

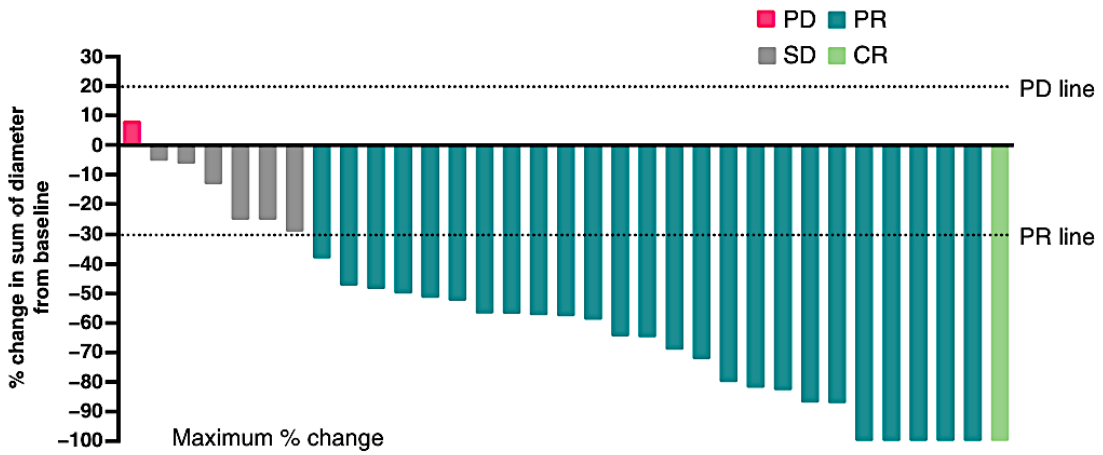
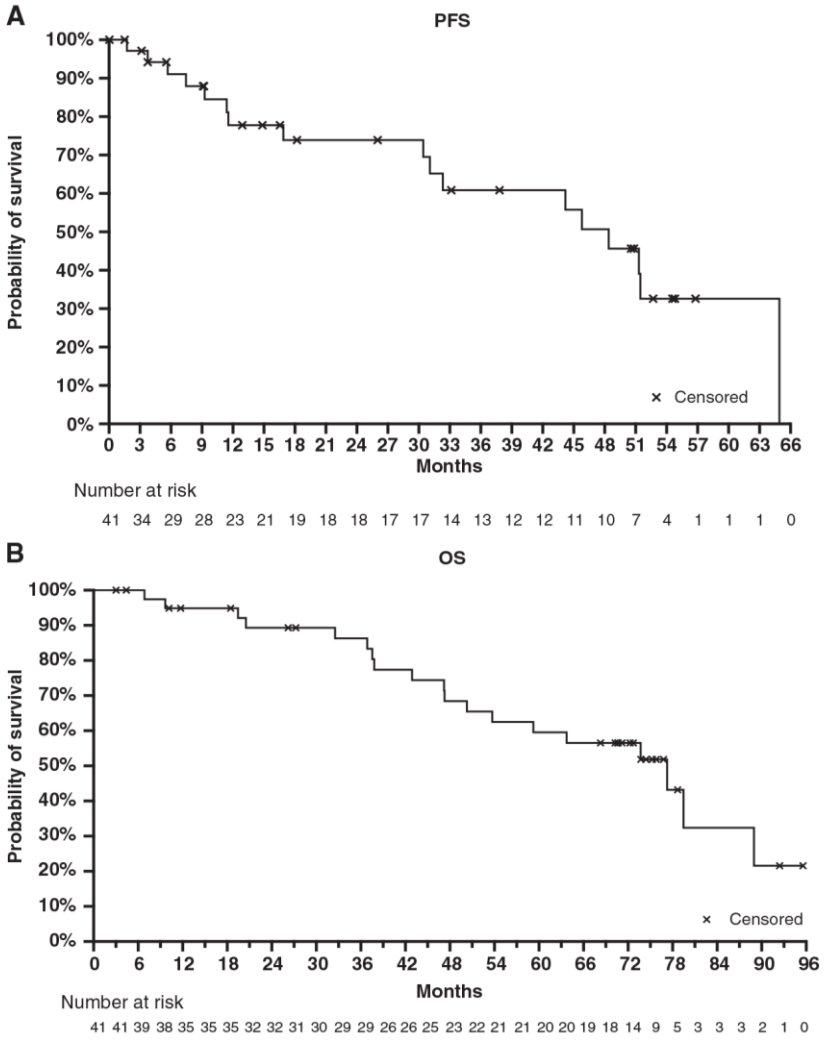


Figure 1.
Best overall response and target lesion improvement. Percentage change from baseline in the sum of the diameters of all target lesions at the time of best response. There were five subjects with 100% target lesion responses, but they were classified as PR due to nontarget lesions. Each bar represents a single patient with no prior systemic therapy for advanced breast cancer in the response evaluable set ($N = 33$).



ORR: 79%
mPFS: 48.4 months, and the mOS: 77.3 months.
The overall response rate and PFS were comparable in patients with and without PIK3CA mutations.

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Wesolowski Clin Cancer Res 2025;31(19):4040-8.

VIKTORIA-1 (Phase 3): Gedatolisib + fulvestrant ± palbociclib vs fulvestrant for HR+, HER2–, PIK3CA WT advanced breast cancer

- Gedatolisib is a multitarget PAM inhibitor of all class I P13K isoforms, mTORC1 and mTORC2
- **Aim:** Evaluate gedatolisib in patients with HR+/HER2– advanced breast cancer after progression on CDK4/6i and NSAI

Key eligibility
- HR+/HER2– ABC
- 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

STUDY 1
PIK3CA-WT

R
1:1:1

N=392

Assign

Arm A
Gedatolisib 180 mg IV QW
(3 weeks on, 1 week off)
+ palbociclib 125 mg QD
(21 days on, 7 days off)
+ fulvestrant 500 mg
(cycle 1: days 1 & 15, then Q4W)

Arm B
Gedatolisib 180 mg IV QW
(3 weeks on, 1 week off)
+ fulvestrant 500 mg
(same schedule)

Arm C
Fulvestrant 500 mg
(cycle 1: days 1 & 15, then Q4W)
Optional crossover to Arm A or Arm B at progression

STUDY 2
PIK3CA-MT

R
3:1:3

- **Gedatolisib[a] + palbociclib + fulvestrant**
- **Gedatolisib[a] + fulvestrant**
- **Alpelisib + fulvestrant**

Primary endpoint:
- PFS (BICR):
  Arm A vs Arm C;
  Arm B vs Arm C

Secondary endpoints:
- OS
- Response
- Safety
- QOL

[a]Prophylactic use of a steroid-containing "swish and spit" regimen was protocol-mandated; oral non-sedating antihistamine therapy was recommended.
Hurvitz SA, et al. JCO 2026; Pistilli et al, ESMO BC 2026;Abstract 505P

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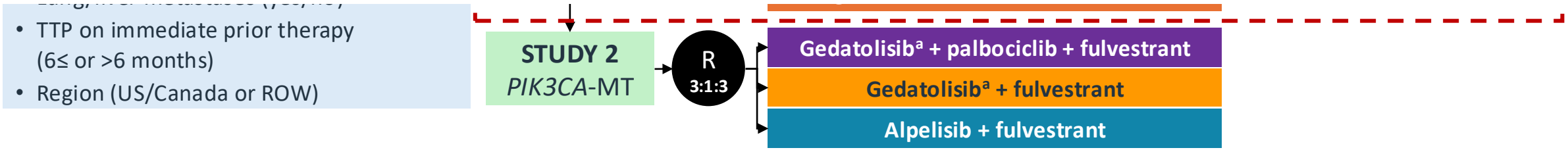
- **Aim:** Evaluate gedatolisib in patients with HR+/HER2– advanced breast cancer after progression on CDK4/6i and NSAI

Study 1 Efficacy:

- Gedatolisib + palbo + fulvestrant: mPFS 9.3 mo. (HR, 0.24; 95% CI, 0.17-0.35; P< 0.0001)
- Gedatolisib + fulvestrant: mPFS 7.4 mo. (HR, 0.33; 95% CI, 0.24-0.48; P< 0.0001)

Treatment-related AEs associated with gedatolisib:

- Mainly grade 1-2
- Hyperglycemia and diarrhea were relatively uncommon
- Grade 3 stomatitis: triplet, 19.2%; doublet, 12.3%



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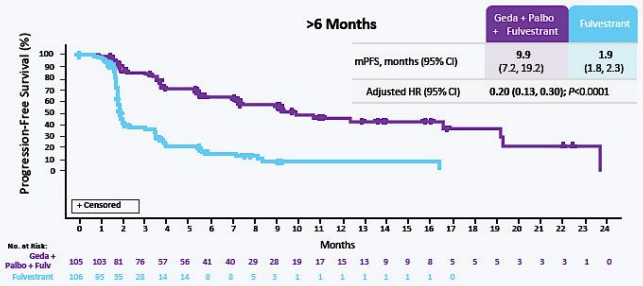
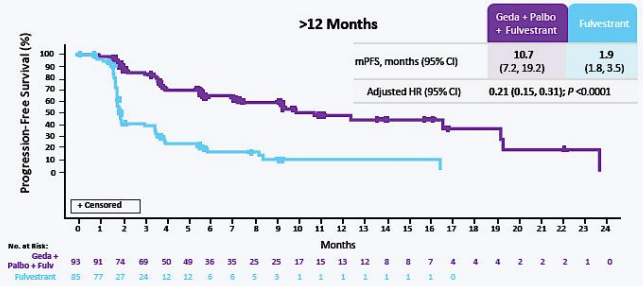
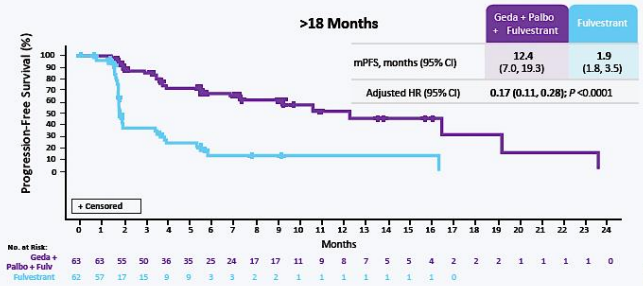
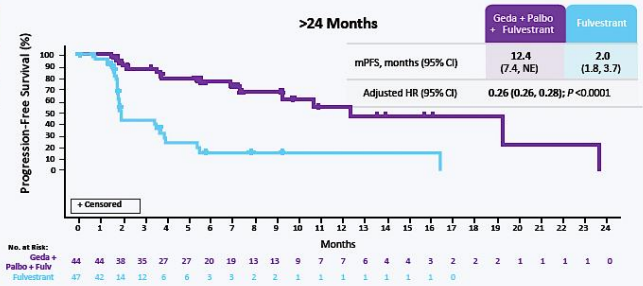
Updated Data: Study 1

PFS by TTP on Immediate Prior Therapy:
Gedatolisib Triplet vs. Fulvestrant

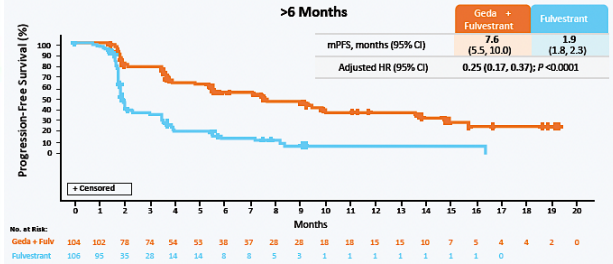


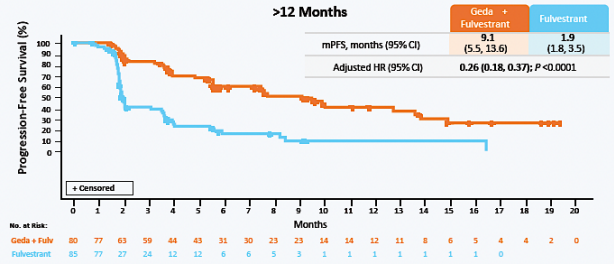


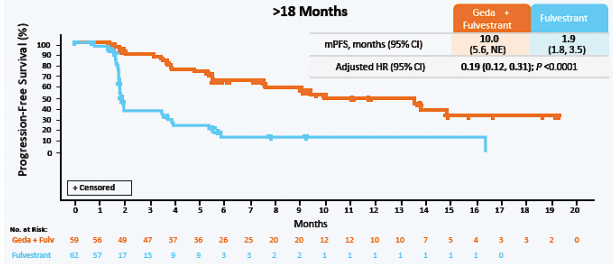


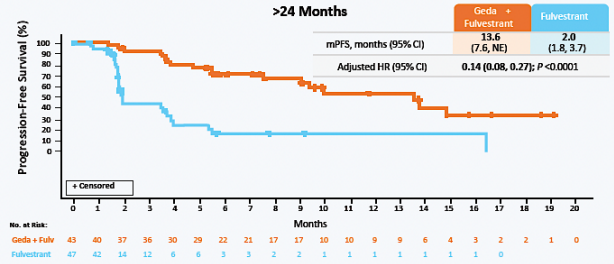


PFS by TTP on Immediate Prior Therapy:
Gedatolisib Doublet vs. Fulvestrant

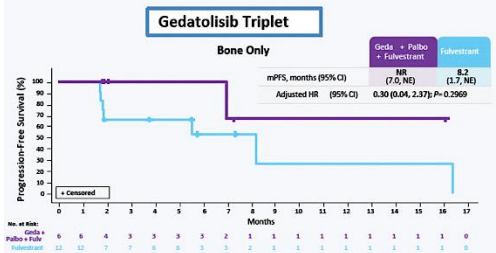


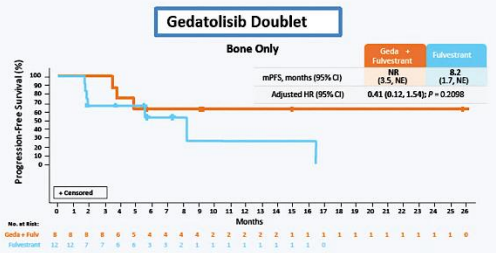


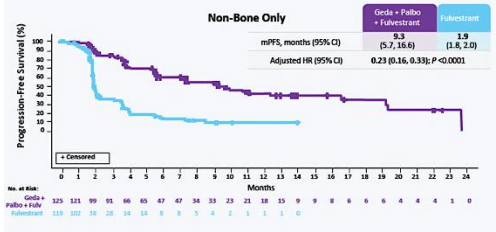


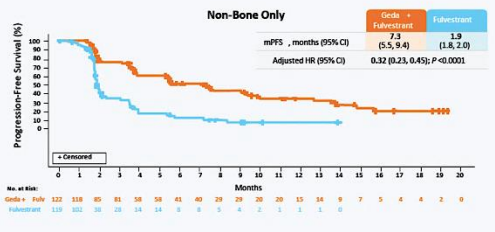


PFS by Bone Metastases Status:
Bone Only vs. Non-Bone Only









Pistilli et al, ESMO BC 2026; Abstract 505P

Stomatitis: Time to First Onset

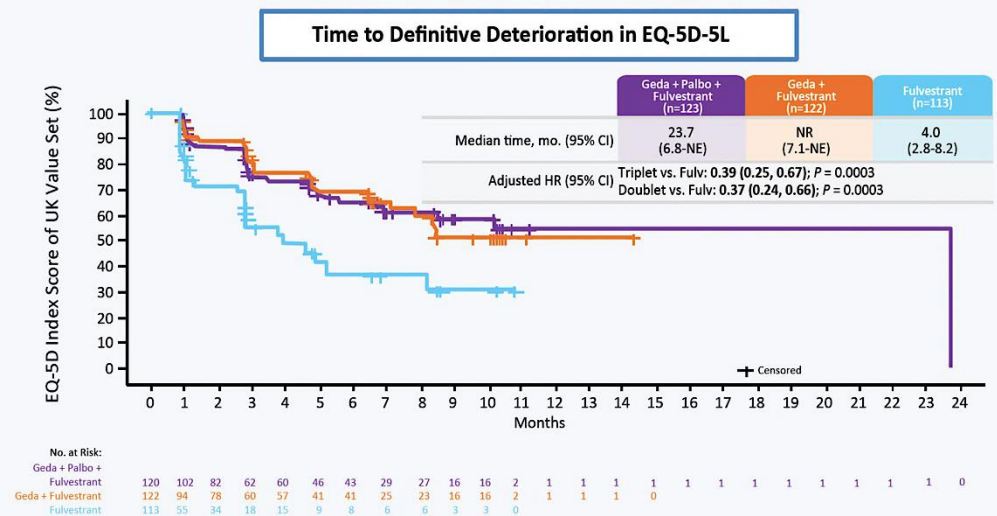
Event		Gedatolisib + Palbo + Fulvestrant (n=130)		Gedatolisib + Fulvestrant (n=130)	
Pts with treatment-related stomatitis*†, n (%)		90 (69.2%)		74 (56.9%)	
Median time to onset (first instance), days (range)		7.5 (1-259)		4.0 (1-524)	
	Grade 1	n=57	**8.0** (1-259)	n=48	**4.5** (1-524)
	Grade 2	n=24	**7.5** (1-146)	n=16	**3.5** (1-158)
	Grade 3	n=9	**4.0** (1-20)	n=10	**3.5** (2-87)

Stomatitis: Time to Improvement

Event		Gedatolisib + Palbo + Fulvestrant (n=130)		Gedatolisib + Fulvestrant (n=130)	
Pts with treatment-related stomatitis*†, n (%)		90 (69.2%)		74 (56.9%)	
Median time to improvement (from worst grade), days (range)					
	Grade 3 to lower	n=25	**12.0** (3-103)	n=16	**7.5** (2-112)
	Grade 2 to lower	n=25	**14.0** (4-229)	n=18	**9.0** (3-41)
	Grade 1 to lower	n=40	**27.5** (1-402)	n=40	**17.5** (1-317)

*Stomatitis is a combination of the following terms: aphthous ulcer; gingival pain; gingivitis; lip ulceration; oral mucosal inflammation; mouth ulceration; stomatitis.
†Dexamethasone "swish-and-spit" mouthwash, provided by the sponsor, was required prophylactic treatment for gedatolisib, starting prior to first infusion and continued daily for 8 weeks, and as clinically indicated thereafter.
Abbreviations: Palbo, palbociclib, Pts, patients

PRO: Temporal and Mean Change, EQ-5D-5L



- **Efficacy with gedatolisib was observed regardless of duration of prior treatment**
- **Stomatitis generally an early event, with resolution to a lower grade in ~2 weeks**
- **Hyperglycemia rates were low, HgbA1c levels stable over time**
- **The triplet and doublet delayed TTDD in well-being**

Pistilli et al, ESMO BC 2026; Abstract 505P

FDA Approves Gedatolisib with Fulvestrant, with or without Palbociclib, for HR-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer

Press Release: July 14, 2026

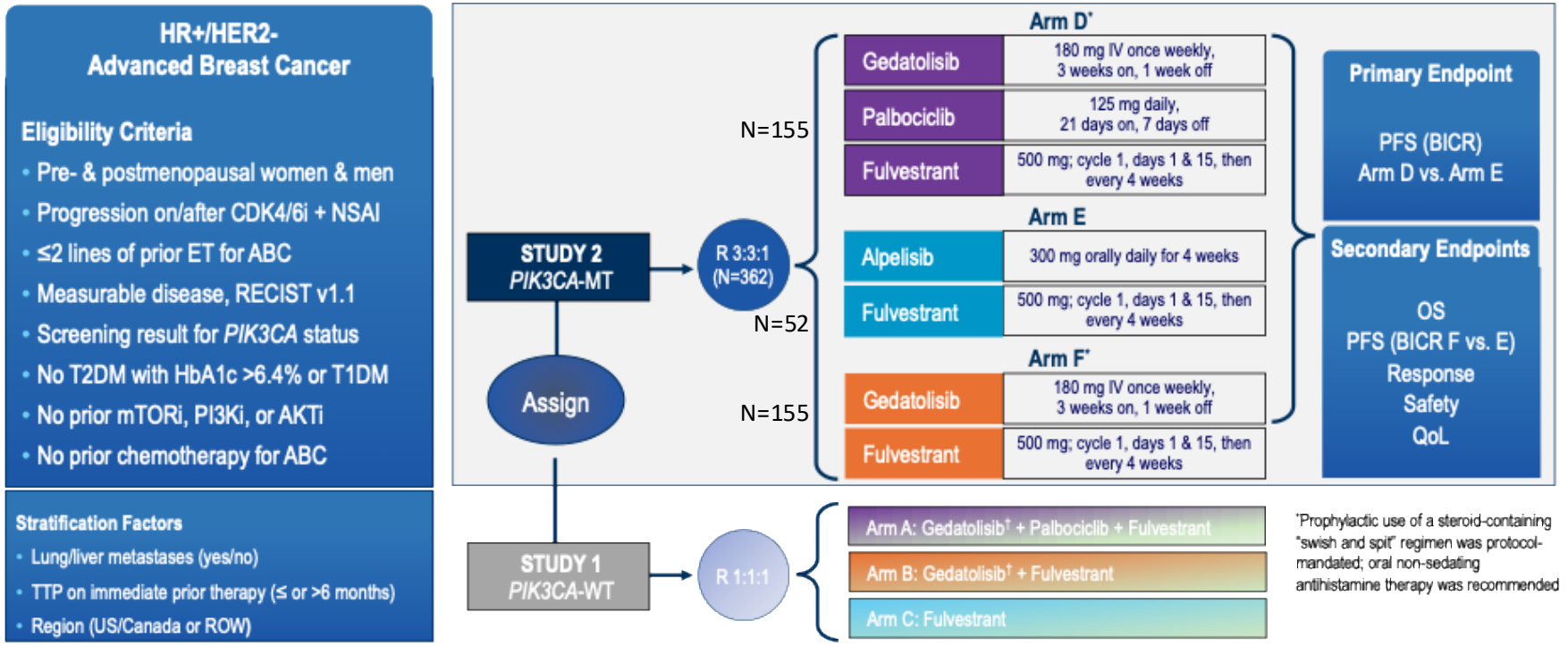
"On July 14, 2026, the Food and Drug Administration approved gedatolisib in combination with fulvestrant, with or without palbociclib, for adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer without a PIK3CA mutation detected following progression on or after treatment with at least one line of endocrine therapy in the metastatic setting.

Efficacy was evaluated in Study 1 of VIKTORIA-1 (NCT05501886), an open-label, randomized, multicenter trial that enrolled 392 adults with locally advanced (inoperable) or metastatic HR-positive, HER2-negative breast cancer. Patients were randomized (1:1:1) to receive either gedatolisib in combination with fulvestrant and palbociclib (Arm A), gedatolisib in combination with fulvestrant (Arm B), or fulvestrant alone (Arm C). Patients received treatment until disease progression or unacceptable toxicity.

There was a statistically significant improvement in PFS for Arm A vs Arm C, with a median PFS of 9.3 months (95% CI: 7.2, 16.6) in Arm A and 2.0 months (95% CI: 1.8, 2.3) in Arm C (hazard ratio [HR] 0.24 [95% CI: 0.17, 0.35]; *p*-value <0.0001). There was also a statistically significant improvement in PFS for Arm B vs Arm C with a median PFS of 7.4 months (95% CI: 5.5, 9.9) in Arm B and 2.0 months (95% CI: 1.8, 2.3) in Arm C (HR 0.33 [95% CI: 0.24, 0.48]; *p*-value <0.0001). At the time of the PFS analysis, OS data were not mature with 25% deaths in the overall population."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-gedatolisib-fulvestrant-or-without-palbociclib-hr-positive-her2-negative-locally

VIKTORIA-1: Study 2

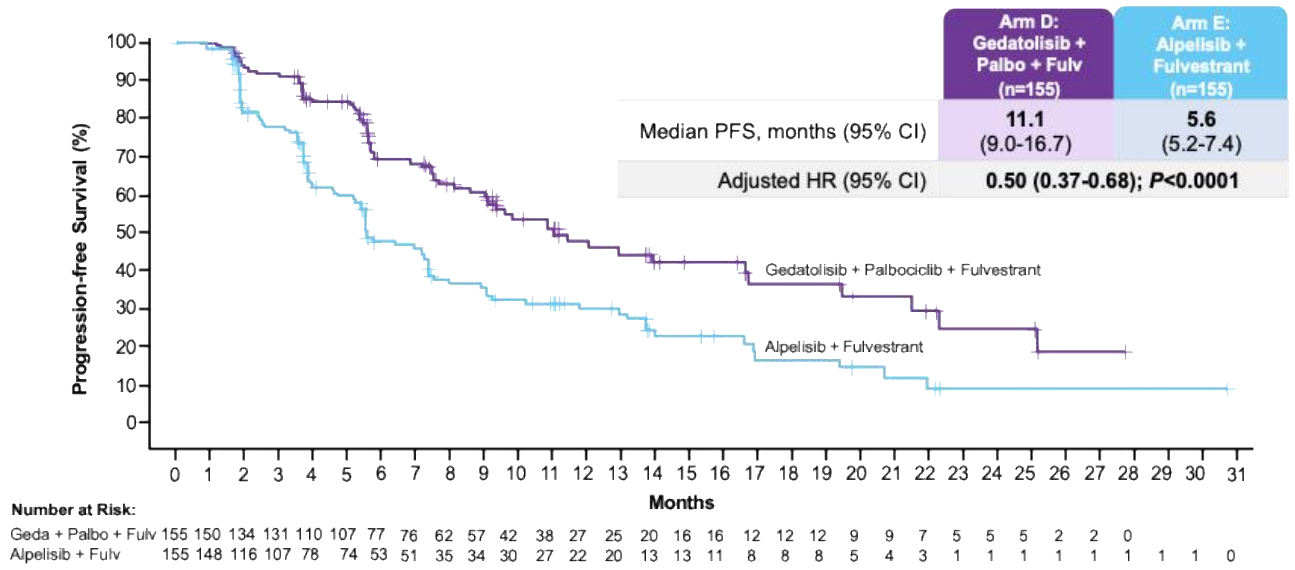


- Demographics
  - 85-90% had 1 line of prior therapy
    - Median duration of prior CDK4/6i 17.5 – 22.1 mo
  - 14-17% progressed <6 mo on last therapy
  - ~44% de novo mBC; 75% visceral mets

Hurvitz SA, et al. ASCO 2026;LBA1008

Primary Endpoint: Progression-Free Survival (BICR)

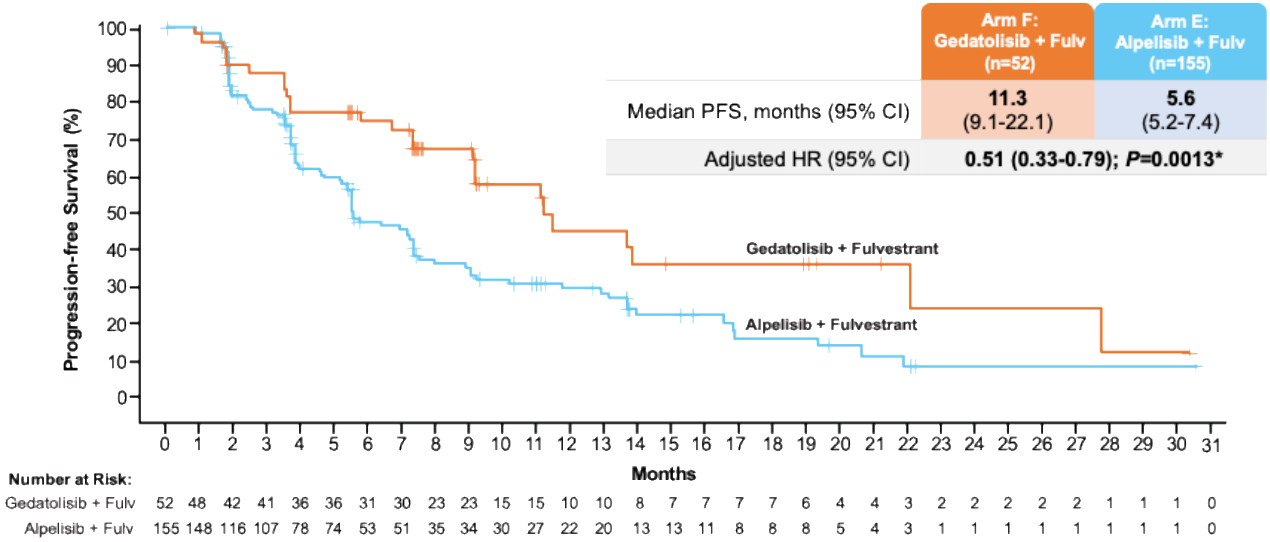
Gedatolisib Triplet vs. Alpelisib + Fulvestrant in VIKTORIA-1 Study 2



	Arm D: Gedatolisib + Palbo + Fulv (n=155)	Arm E: Alpelisib + Fulvestrant (n=155)
Median PFS, months (95% CI)	11.1 (9.0-16.7)	5.6 (5.2-7.4)
Adjusted HR (95% CI)	0.50 (0.37-0.68); *P*<0.0001	

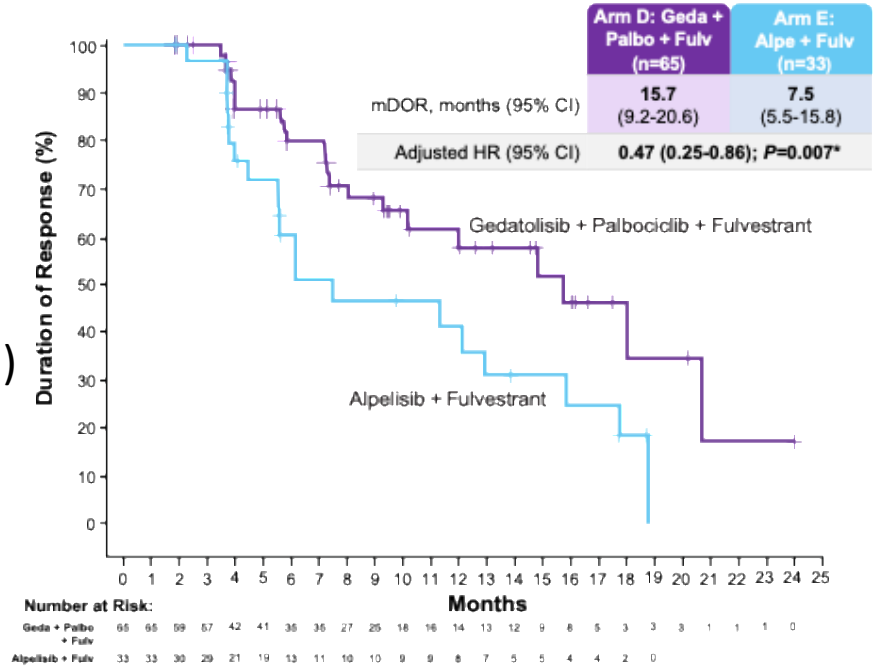
Secondary Endpoint: Progression-Free Survival (BICR)

Gedatolisib Doublet vs. Alpelisib + Fulvestrant in VIKTORIA-1 Study 2

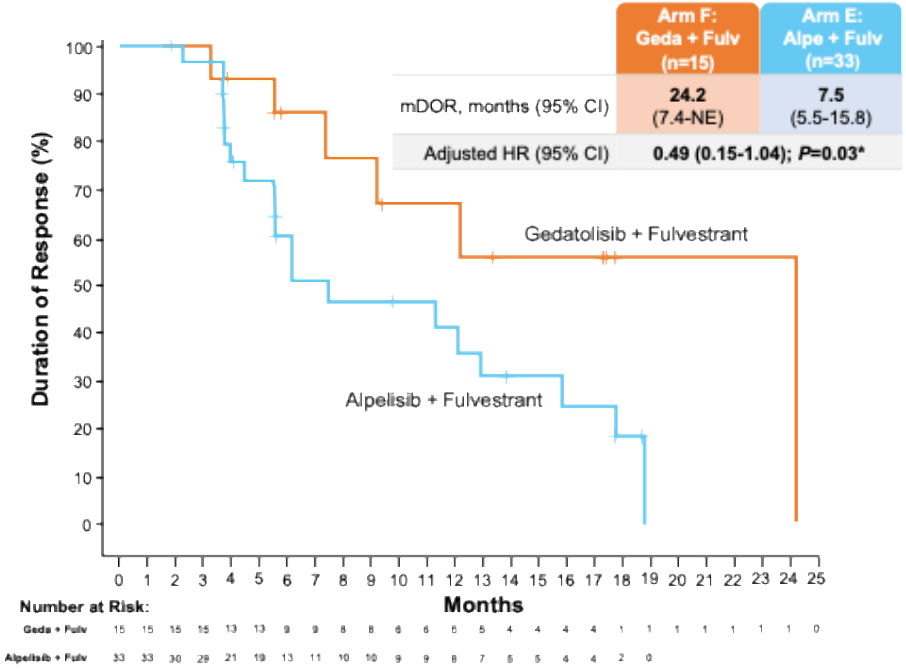


	Arm F: Gedatolisib + Fulv (n=52)	Arm E: Alpelisib + Fulv (n=155)
Median PFS, months (95% CI)	11.3 (9.1-22.1)	5.6 (5.2-7.4)
Adjusted HR (95% CI)	0.51 (0.33-0.79); *P*=0.0013*	

ORR:
49%, 36% and 26% (control)



	Arm D: Geda + Palbo + Fulv (n=65)	Arm E: Alpe + Fulv (n=33)
mDOR, months (95% CI)	15.7 (9.2-20.6)	7.5 (5.5-15.8)
Adjusted HR (95% CI)	0.47 (0.25-0.86); *P*=0.007*	



	Arm F: Geda + Fulv (n=15)	Arm E: Alpe + Fulv (n=33)
mDOR, months (95% CI)	24.2 (7.4-NE)	7.5 (5.5-15.8)
Adjusted HR (95% CI)	0.49 (0.15-1.04); *P*=0.03*	

Hurvitz SA, et al.
ASCO 2026;LBA1008

Safety and Tolerability

Safety Population in VIKTORIA-1 Study 2

Exposure	Arm D: Gedatolisib + Palbociclib + Fulvestrant (n=153)			Arm F: Gedatolisib + Fulvestrant (n=52)			Arm E: Alpelisib + Fulvestrant (n=152)		
Median RDI, Geda (IQR)	93.3 (80.6-100)			100 (97.8-100)			--		
Median RDI, Alpe (IQR)	--			--			81.7 (64.8-96.2)		
TRAE and TR-SAE, n (%)									
Pts with ≥1 TRAE	150 (98.0)			50 (96.2)			147 (96.7)		
Study tx D/C for TRAE	4 (2.6)			2 (3.8)			11 (7.1)		
Pts with ≥1 TR-SAE	16 (10.5)			2 (3.8)			20 (13.2)		
Deaths due to TR-SAE*	1 (0.7)			0			2 (1.3)		
TRAE, n (%)†	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Neutropenia‡	97 (63.4)	73 (47.7)	17 (11.1)	1 (1.9)	0	0	2 (1.3)	0	1 (0.7)
Stomatitis‡	94 (61.4)	25 (16.3)	0	32 (61.5)	3 (5.8)	0	52 (34.2)	8 (5.3)	0
Nausea	70 (45.8)	5 (3.3)	0	21 (40.4)	1 (1.9)	0	50 (32.9)	2 (1.3)	0
Rash‡	40 (26.1)	10 (6.5)	0	17 (32.7)	3 (5.8)	0	56 (36.8)	23 (15.1)	0
Vomiting	39 (25.5)	0	0	10 (19.2)	0	0	23 (15.1)	1 (0.7)	0
Fatigue	33 (21.6)	5 (3.3)	0	11 (21.2)	1 (1.9)	0	32 (21.1)	4 (2.6)	0
Diarrhea§	23 (15.0)	2 (1.3)	0	5 (9.6)	0	0	61 (40.1)	9 (5.9)	1 (0.7)
Hyperglycemia‡,§	23 (15.0)	4 (2.6)	0	6 (11.5)	0	0	88 (57.9)	21 (13.8)	1 (0.7)

*Grade 5 events include fatal cerebral hemorrhage (gedatolisib triplet), urosepsis (alpelisib + fulvestrant group), and general physical health decline (alpelisib + fulvestrant group)
†Shown are treatment-related adverse events of any grade that occurred in at least 20% of the patients in any trial group unless otherwise noted
‡For stomatitis, neutropenia, rash, and hyperglycemia, combined preferred terms are used in the table; if a patient experienced multiple terms, it was counted once for the highest grade.
§ Additional events of clinical importance
Abbreviations: Alpe, alpelisib; D/C, discontinued; Geda, gedatolisib; IQR, interquartile range; Pts, patients; RDI, relative dose intensity; TRAE, treatment-related adverse event; TR-SAE, treatment-related serious adverse events; tx, treatment

Hurvitz SA, et al. ASCO 2026;LBA1008

VIKTORIA-2 Study Schema

Eligibility Criteria:

- Pre- & postmenopausal women and men
- No prior therapy for advanced disease
- Measurable disease, RECIST v1.1
- No prior mTORi, PI3Ki, or AKTi

Endocrine Status:

- **Endocrine resistant (ER):** Progressed on or recurred within 12 months of completing adjuvant endocrine therapy (ET)
- **Endocrine sensitive (ES):** Recurred >12 months after completing adjuvant ET or have de novo metastatic disease

Patients manually assigned to Study 1 (ER) vs. Study 2 (ES) based on endocrine status

Study 1
Endocrine Resistant
N = 440

R
1:1

Arm A
Gedatolisib: 180 mg IV once weekly; 3 weeks on, 1 week off
Palbociclib: 125 mg daily; 21 days on, 7 days off
Fulvestrant: 500 mg; cycle 1: Days 1 & 15, then every 4 weeks

Arm B
Ribociclib: 600 mg daily; 21 days on, 7 days off
Fulvestrant: 500 mg; cycle 1: Days 1 & 15, then every 4 weeks

Primary Endpoint:
- PFS (BICR): Arm A vs. Arm B

Secondary Endpoints:
- OS
- Response
- Safety
- QoL

Study 2
Endocrine Sensitive
N = 740

R
1:1

Arm C
Gedatolisib: 180 mg IV once weekly; 3 weeks on, 1 week off
Palbociclib: 125 mg daily; 21 days on, 7 days off
Letrozole: 2.5 mg daily

Arm D
Ribociclib: 600 mg daily; 21 days on, 7 days off
Letrozole: 2.5 mg daily

Primary Endpoint:
- PFS (BICR): Arm C vs. Arm D

Secondary Endpoints:
- OS
- Response
- Safety
- QoL

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

NCT06757634

Conclusions

- Dual inhibition of PI3K and mTOR ('PAM' pathway) in combination with fulvestrant, with or without palbociclib:
  - Markedly improves PFS and response compared to standard therapy in patients with progressive disease in an AI plus CDK4/6 inhibitor
    - In PI3K wild-type compared to fulvestrant
      - Independent of TTP on prior therapy or bone vs non bone-only disease
    - In PI3K mutant disease compared to fulvestrant plus alpelisib
      - Similar benefit seen with triplet and doublet, although doublet underpowered
  - Less rash, hyperglycemia, diarrhea compared to other inhibitors of the PAM pathway
    - Primary toxicity grade 3 stomatitis despite steroid mouthwash (was this used by all upfront?)
    - Primary limitation IV dosing – 3 weeks out of each month
      - Subcutaneous dosing formulation under development
  - First-line VIKTORIA-2 trial (NCT06757634) in the ET-resistance and ET-sensitive populations

Key Datasets

- Wesolowski R et al. Gedatolisib combined with palbociclib and letrozole in patients with no prior systemic therapy for hormone receptor-positive, HER2-negative advanced breast cancer. *Clin Cancer Res* 2025;31(19):4040-8.
- Pistilli B et al. Gedatolisib (Geda), a multitarget PI3K/AKT/mTOR (PAM) inhibitor, plus fulvestrant (Fulv) ± palbociclib (Palbo) for second-line (2L) treatment of patients (Pts) with HR+/HER2-/PIK3CA-wild type (WT) advanced breast cancer (ABC): Updated results from VIKTORIA-1. ESMO Breast Cancer 2026;Abstract 505P.
- Hurvitz S et al. A randomized, open-label, phase 3 study of gedatolisib + fulvestrant ± palbociclib vs standard of care in HR+/HER2−/PIK3CA-mutant (MT) advanced breast cancer (VIKTORIA-1 Study 2). ASCO 2026;Abstract LBA1008.
- VIKTORIA-2: A randomized, open-label, phase 3 study evaluating efficacy and safety of gedatolisib with endocrine therapy and palbociclib vs endocrine therapy and ribociclib as first-line treatment in patients with HR-positive and HER2-negative advanced breast cancer. NCT06757634.

Year in Review:
PI3K/AKT/mTOR Pathway in
HR-Positive Metastatic Breast Cancer

INTRODUCTION: San Antonio Memories

MODULE 1: PI3K/AKT/PTEN Alterations and Therapies

MODULE 2: Capivasertib

MODULE 3: Gedatolisib

MODULE 4: Inavolisib

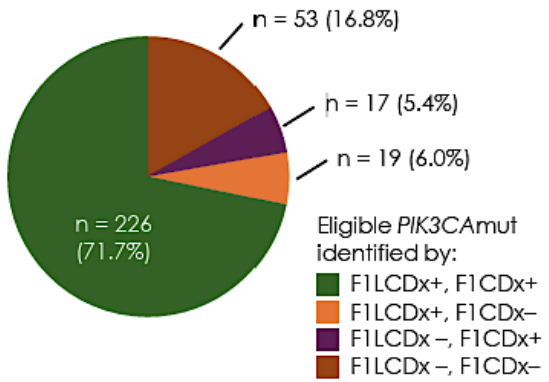
MODULE 5: New Agents and Ongoing Trials

RTP Year in Review 2026

Comparative analysis of blood- and tissue-based PIK3CA mutation detection methods in the pivotal Phase 3 INAVO120 trial of palbociclib + fulvestrant ± inavolisib in hormone receptor-positive, HER2-negative advanced breast cancer

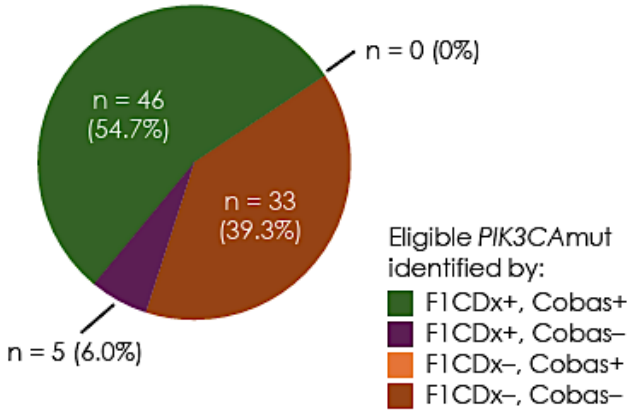
SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research

(A) F1LCDx vs F1CDx* *PIK3CA*mut detection



89% concordance between tissue and liquid

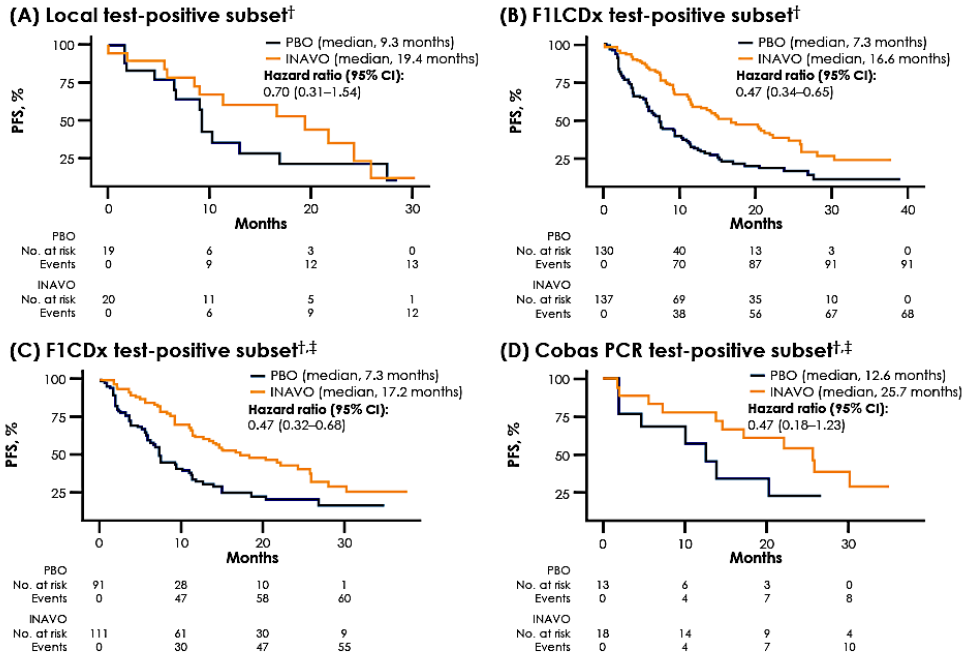
(A) F1CDx NGS and Cobas PCR



94% concordance between NGS and PCR with NGS more sensitive

Figure 8: Progression-free survival for the inavolisib arm vs the placebo arm for participants with *PIK3CA*-mutated advanced breast cancer by test type

- PFS benefit, regardless of test type, was generally consistent* with that observed in the intention-to-treat population (hazard ratio 0.43) at the time of the INAVO120 primary analysis.[5]



* The increased hazard ratio for patients that had *PIK3CA*mut-positive samples based on a local test result is likely due to the small pt numbers in this subgroup. † All analyses unstratified.
‡ Pt subgroups already selected for eligibility based on F1LCDx or local test.
CI, confidence interval; Cobas PCR, Cobas® PIK3CA Mutation Test; F1CDx, FoundationOne®CDx; F1LCDx, FoundationOne®Liquid CDx; INAVO, inavolisib; PBO, placebo; PFS, progression-free survival; *PIK3CA*mut, *PIK3CA* mutation; pt, participant.

Efficacy of Inavolisib regardless of assay used

Kalinsky SABCS 2025;Abstract PS1-10-26.

INAVO120: A Phase III, randomized, double-blind, placebo-controlled study[1,2]

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– aBC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **No prior therapy for aBC**
- **Fasting glucose <126 mg/dL and HbA_{1c} <6.0%**

Enrollment period: January 2020 to September 2023

N = 325

R 1:1

- **Inavolisib (9 mg PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)†**
- **Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)†**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral disease (yes vs. no)
- Endocrine resistance (primary vs. secondary)‡
- Region (North America/Western Europe vs. Asia vs. Other)

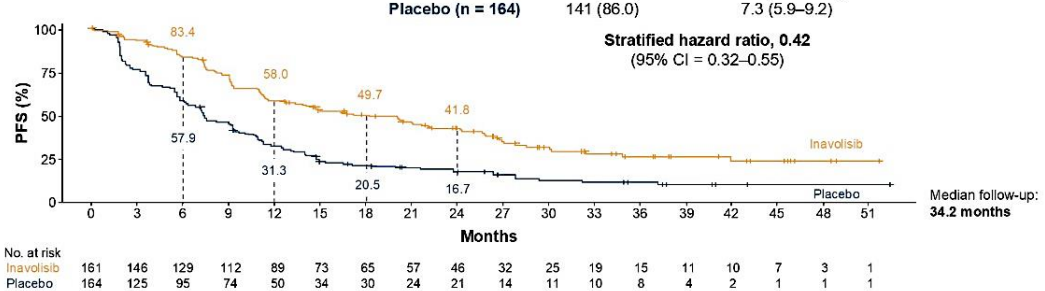
- Primary endpoint: Investigator-assessed PFS
- Secondary endpoints included: OS; investigator-assessed ORR, BOR, CBR, and DoR; PROs

ClinicalTrials.gov number, NCT04191499.
Adapted from Jhaveri KJ, *et al.* SABCS 2023 (Abstract GS03-13). * Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine, Inc.). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu); † Pre-menopausal women received ovarian suppression; ‡ Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[3]
Primary: Relapse while on the first 2 years of adjuvant ET; secondary: Relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.
aBC, advanced breast cancer; BOR, best overall response; C, cycle; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; D, day; DoR, duration of response; ET, endocrine therapy; HbA_{1c}, glycated hemoglobin; HER2–, HER2-negative; HR+, hormone receptor-positive; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, by mouth; PRO, patient-reported outcome; Q4W, every 4 weeks; QD, daily; R, randomization.
1. Turner NC, *et al. N Engl J Med* 2024; **391**:1584–1596; 2. Jhaveri KJ, *et al.* SABCS 2023 (Abstract GS03-13); 3. Cardoso F, *et al. Ann Oncol* 2018; **29**:1634–1657.

INAVO120 updated PFS

	Events, n (%)	Median, months (95% CI)
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, 0.42
(95% CI = 0.32–0.55)



Median follow-up: **34.2 months**

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

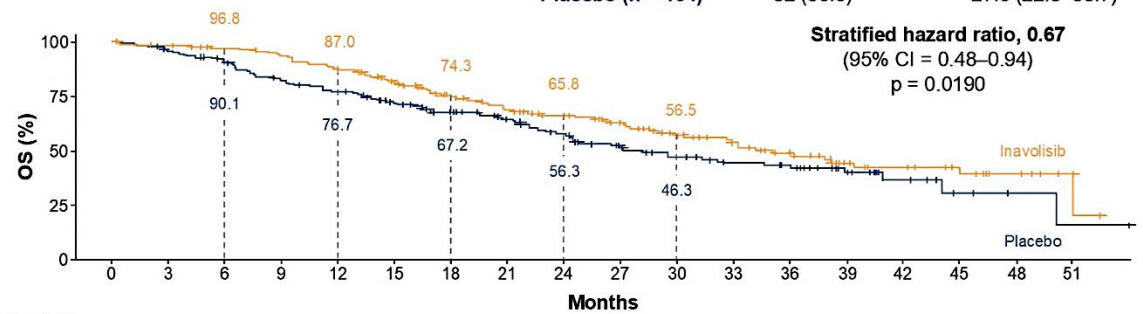
The improvement in PFS was maintained during longer follow-up

Data cutoff: November 15, 2024.
CI, confidence interval; PFS, progression-free survival. © Copyright 2025.

INAVO120 key secondary endpoint: OS

	Deaths, n (%)	Median, months (95% CI)
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, 0.67
(95% CI = 0.48–0.94)
p = 0.0190



Median follow-up: **34.2 months**

No. at risk

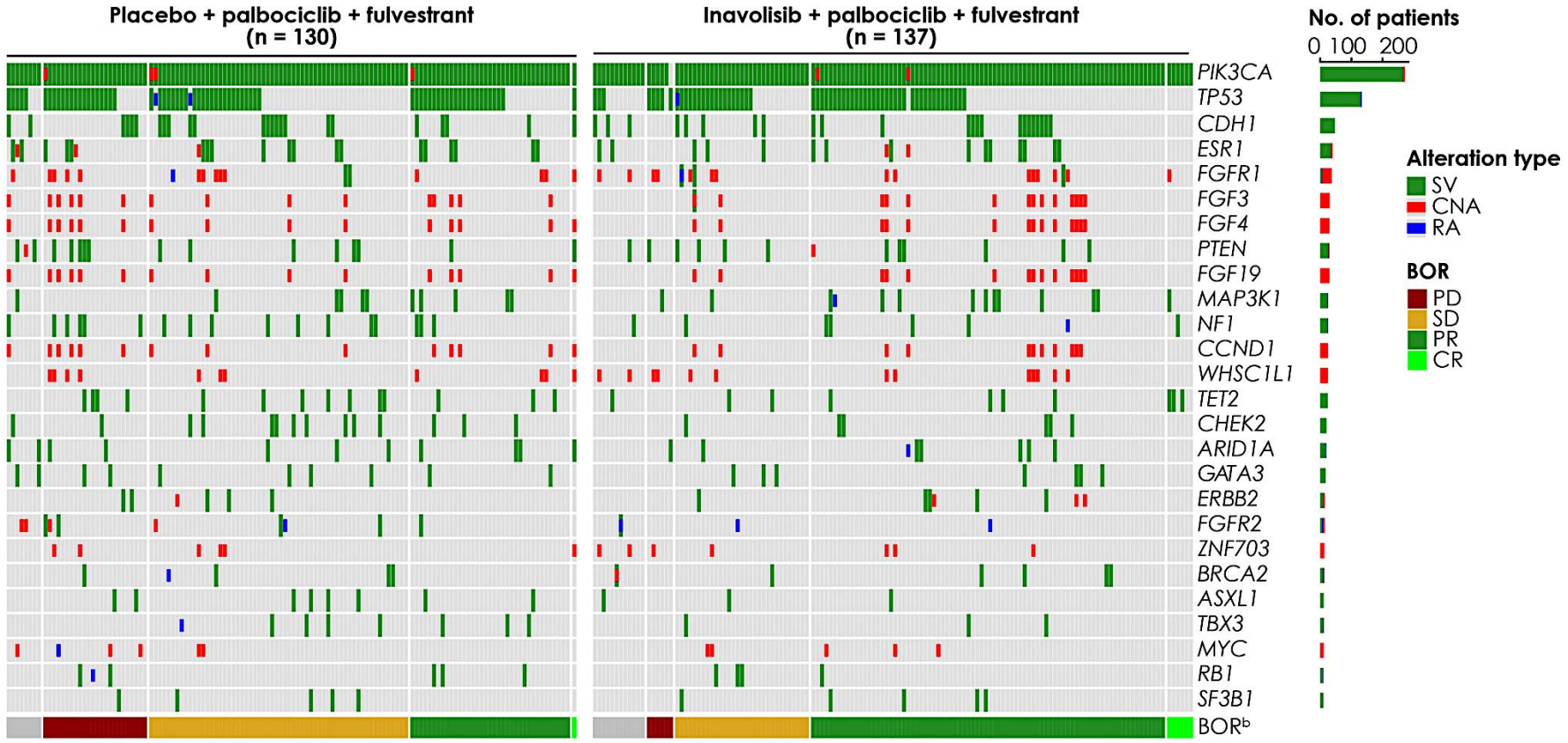
Inavolisib	161	155	149	142	131	114	99	88	78	67	54	43	34	22	19	13	7	1
Placebo	164	155	142	127	119	104	90	77	63	48	42	36	32	18	10	4	2	1

Improvement in median OS: 7 months. The prespecified boundary for statistical significance (p < 0.0469) was crossed

Data cutoff: November 15, 2024.
CI, confidence interval; OS, overall survival. © Copyright 2025.

Turner ASCO 2025; Abstract 1003 & Jhaveri N Engl J Med 2025

Molecular features of response to palbociclib + fulvestrant ± inavolisib in hormone receptor-positive, HER2-negative, *PIK3CA*-mutated advanced breast cancer as assessed from baseline circulating tumor DNA in the pivotal Phase 3 INAVO120 trial



Of the 277 enrolled patients with F1LCDx-profiled plasma DNA, 267 had *detectable* ctDNA.

The most commonly-altered genes were:

- **PIK3CA** (99.6%; 266 / 267)[c]
- ***TP53*** (49.4%; 132 / 267)
- ***CDH1*** (17.6%; 47 / 267)
- ***ESR1*** (14.5%; 39 / 267)

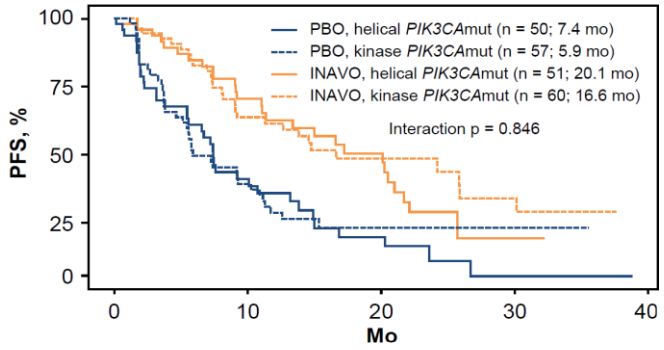
[a] Occurring in ≥ 10 samples. [b] BOR not available for n = 20 patients (dark gray boxes in BOR annotation). [c] A small number of patients were enrolled based on a *PIK3CA*-mutation-positive result from a locally-conducted molecular test; F1LCDx did not detect a *PIK3CA* mutation in one of these patients' ctDNA samples.

BOR, best overall response; CNA, copy number alteration; CR, complete response; mut, mutation; PD, progressive disease; PR, partial response; RA, rearrangement alteration; SD, stable disease; SV, short variant

Turner SABCS 2025;Abstract PD5-09

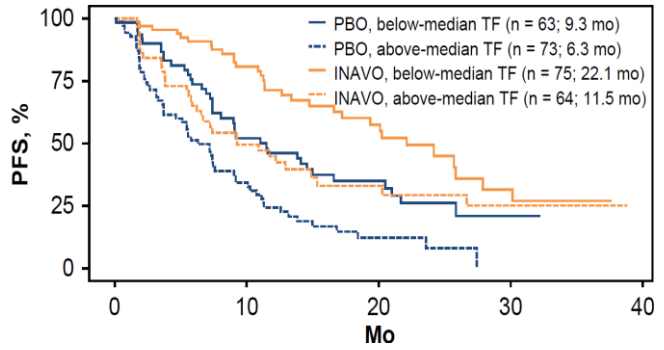
The efficacy of INAVO + PALBO + FULV was consistent across a variety of genomic subgroups and the ITT population[a]

PIK3CA helical vs kinase domain mutations



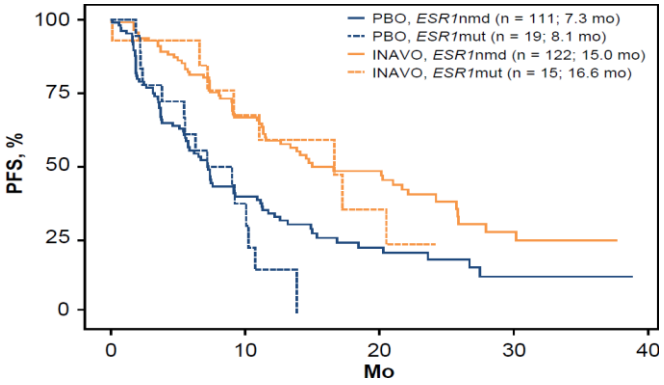
	Helical (n = 101)	Kinase (n = 117)
PFS HR (95% CI)	0.5 (0.3–0.8)	0.5 (0.3–0.8)
p-value	0.003**	0.003**

Above- vs below-median ctDNA tumor fraction



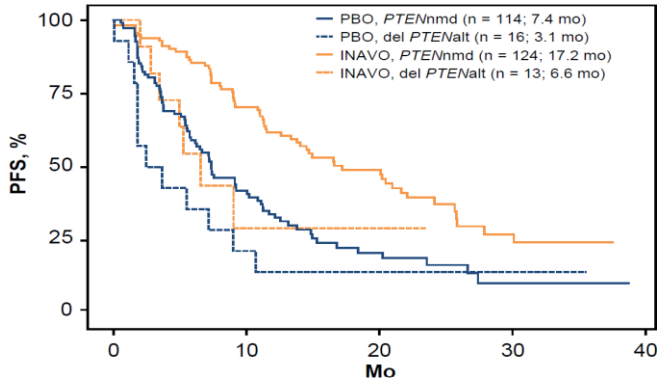
	Below-median TF (n = 138)	Above-median TF (n = 137)
PFS HR (95% CI)	0.5 (0.3–0.8)	0.5 (0.3–0.8)
p-value	0.007**	0.001***

ESR1 mutation vs no mutation detected



	*ESR1*nmd (n = 233)	*ESR1*mut (n = 34)
PFS HR (95% CI)	0.5 (0.4–0.7)	0.2 (0.1–0.7)
p-value	4.705×10^{-5}***	0.005**

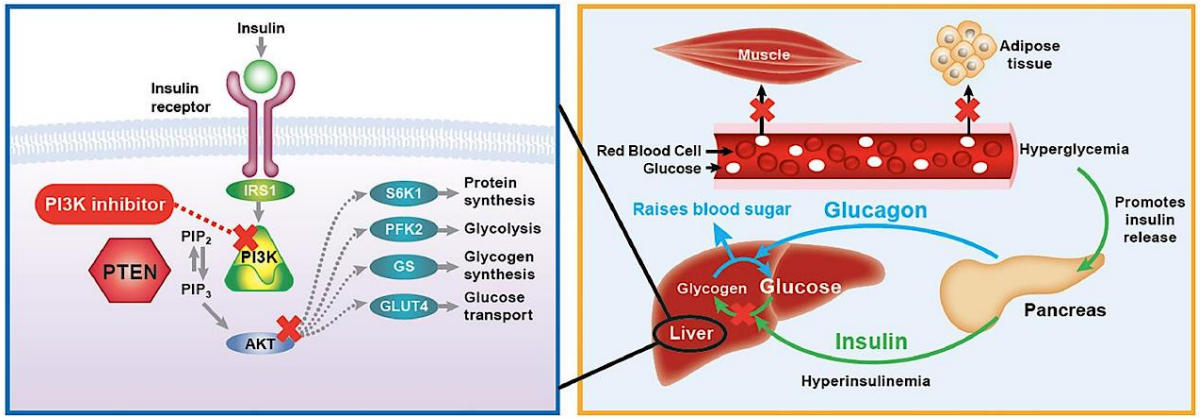
Deleterious *PTEN* detected vs not detected



	*PTEN*nmd (n = 238)	Del *PTEN*alt (n = 29)
PFS HR (95% CI)	0.5 (0.3–0.6)	0.6 (0.2–1.4)
p-value	7.120×10^{-6}***	0.215

HRs for INAVO vs PBO are shown herein. Mo are medians. [a] INAVO120 ITT population HR 0.43 (95% CI 0.32–0.59); p < 0.001 (Turner NC, *et al. N Engl J Med* 2024; **391:**1584–1596). p-values from likelihood ratio test (significant p-values are indicated by asterisks). *ESR1*mut is defined here as any known / likely short variant alteration in *ESR1*; *PTEN*alt is any known / likely oncogenic alt in the *PTEN* gene. Median ctDNA TF for enrolled subset was 3.8%. alt, alteration; CI, confidence interval; ctDNA, circulating tumor DNA; del, deleterious; FULV, fulvestrant; HR, hazard ratio; INAVO, inavolisib; ITT, intent-to-treat population; mo, months; mut, mutation; nmd, no mutation detected; PALBO, palbociclib; PBO, placebo; PFS, progression-free survival; TF, ctDNA tumor fraction.

Efficacy of inavolisib (INAVO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with PIK3CA-mutated, hormone receptor-positive, HER2-negative (HER2-), endocrine-resistant advanced breast cancer (aBC) with and without hyperglycaemia (HG) in the phase III INAVO120 trial



Following a meal, insulin decreases blood glucose by activating the PI3K pathway. Insulin responses are mediated by class I PI3Ks like p110α in muscle, liver, and adipose tissue, and p110β in liver tissue, which suppress hepatic glucose production and stimulate glucose uptake in muscle and adipose tissue.

Moore HN, Clinical Breast Cancer 2025.

On target Hyperglycemia is associated with improved efficacy of inavolisib

Analysis Arm	Median PFS (mo)	Hazard Ratio (95% CI)	ORR (%)
INAVO Triplet: with HG	21.0	**0.38 (0.27–0.52)**	64.7%
INAVO Triplet: without HG	12.8	**0.51 (0.35–0.74)**	59.3%
Placebo Control (All)	7.3	Reference	28.0%

HG: Hyperglycaemia is on-target PI3K inhibition effect.
Survival benefit consistently maintained regardless of HG status.

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Loibl ESMO Breast 2026;Abstract 420RO

INAVO123: Phase 3 study of first-line inavolisib / placebo + a cyclin-dependent kinase 4/6 inhibitor + letrozole in participants with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative, endocrine-sensitive advanced breast cancer

Reva K. Basho[1], Komal L. Jhaveri[2], Judy King[3], Sherko Kümmel[4], Yeon Hee Park[5], Victor K. Khor[6], Xiaoyan Liu[6], Patience Gyamfi[6], Venkatesh Krishnan[6], Aruna Mani[6], Javier Cortés[7]

Figure 1: Study design

* *De novo* or relapsed after at least 2 years of standard neoadjuvant / adjuvant endocrine therapy. † Palbociclib was the only option under version 1 of the protocol. ‡ Pre- and perimenopausal women, and men will receive a luteinizing hormone-releasing hormone agonist for the duration of the study treatment.
aBC, advanced breast cancer; D, day; HER2–, HER2-negative; HR+, hormone receptor-positive; INAVO, inavolisib; LET, letrozole; mut, mutated; PBO, placebo; PO, orally; QD, daily; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Table 1: Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Pts with locally advanced (unresectable) or metastatic, HR+, endocrine-sensitive,* BC that is not HER2-positive per ASCO / CAP guidelines	• Any prior systemic therapy for locally advanced (unresectable) or metastatic BC
• Qualifying *PIK3CA* mutation (determined by central ctDNA or pre-existing local tissue or ctDNA test)	• Pts with aBC who progressed while on / within 12 months of ending adjuvant therapy
• HR+, HER2– aBC that is *de novo*, or alternatively, relapsed aBC after at least 2 years neo / adjuvant endocrine therapy	• Pregnant or breastfeeding, or intention of becoming pregnant during the study or within the timeframe in which contraception is required
• Measurable disease (RECIST v1.1)	• History of or active inflammatory bowel disease
• ECOG PS 0–1	• Any history of leptomeningeal disease or carcinomatous meningitis
• Fasting blood glucose < 126 mg/dl and HbA_{1c} < 6.5%	• Symptomatic active lung disease
• Adequate hematologic and organ function within 14 days prior to initiation of study treatment	• Known and untreated, or active CNS metastases

Basho SABCS 2025; Abstract PS5-07-27.

Key Datasets

- Kalinsky K et al. Comparative analysis of blood- and tissue-based PIK3CA mutation detection methods in the pivotal phase 3 INAVO120 trial of palbociclib + fulvestrant ± inavolisib in hormone receptor-positive, HER2-negative advanced breast cancer. San Antonio Breast Cancer Symposium 2025;Abstract PS1-10-26.
- Jhaveri KL et al. Overall survival with inavolisib in PIK3CA-mutated advanced breast cancer. *N Engl J Med* 2025;393(2):151-61.
- Turner N et al. Molecular features of response to palbociclib + fulvestrant ± inavolisib in hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer as assessed from baseline circulating tumor DNA in the pivotal phase 3 INAVO120 trial. San Antonio Breast Cancer Symposium 2025;Abstract PD5-09.
- Loibl S et al. Efficacy of inavolisib (INAVO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with PIK3CA-mutated, hormone receptor-positive, HER2-negative (HER2-), endocrine-resistant advanced breast cancer (aBC) with and without hyperglycaemia (HG) in the phase III INAVO120 trial. ESMO Breast Cancer 2026;Abstract 420RO.
- Basho R et al. INAVO123: Phase 3 study of first-line inavolisib / placebo + a cyclin-dependent kinase 4/6 inhibitor + letrozole in participants with PIK3CA-mutated, hormone receptor-positive, HER2-negative, endocrine-sensitive advanced breast cancer. San Antonio Breast Cancer Symposium 2025;Abstract PS5-07-27.

Year in Review:
PI3K/AKT/mTOR Pathway in HR-Positive Metastatic Breast Cancer

INTRODUCTION: San Antonio Memories

MODULE 1: PI3K/AKT/PTEN Alterations and Therapies

MODULE 2: Capivasertib

MODULE 3: Gedatolisib

MODULE 4: Inavolisib

MODULE 5: New Agents and Ongoing Trials

RTP Year in Review 2026

A Phase 1/2 trial of LY4064809 (STX-478, Tersolisib), a Pan-Mutant-Selective PI3Kα Inhibitor in HR+, HER2- MBC: Updated Results from PIKALO-1

HR+, HER2- *PIK3CA*-mutant[a] ABC

- FBG <140 mg/dL, HbA1c <8%, controlled T2DM permitted
- Prior PI3K/AKT/mTOR inhibitor permitted if stopped due to intolerance
- Measurable / evaluable disease per RECIST v1.1

LY4064809[b] Monotherapy N=50
- **Prior standard therapy required**

LY4064809[c] + Fulvestrant N=41
- **1-2 prior therapies**
  - ≥1 CDK4/6i + ET
  - ≤1 prior chemotherapy

LY4064809[c] + ET[d] + CDK4/6i[e] N=63
- **≤2 prior therapies**
  - CDK4/6i-naïve/ongoing[f]/pretreated
  - ≤1 prior chemotherapy

Objectives
- Safety
- Pharmacokinetics
- Dose determination
- ORR and DCR per RECIST v1.1

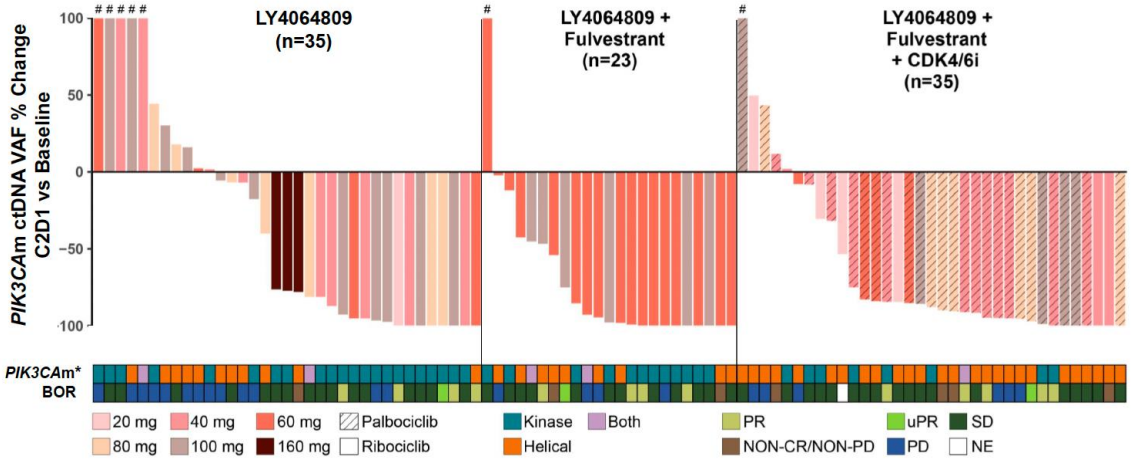
- Biomarker analysis: Serial plasma samples were collected for ctDNA analysis (InVisionSeq or Foundation One Liquid assay was used)
- Data cutoff date was 7 Oct 2025

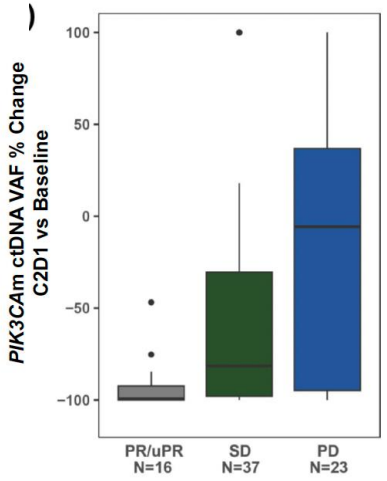
Demographics, N=154
- 17-18% pre-diabetic
- 52% prior oral SERDs
- Prior PI3Ki: 18% monotherapy arm
- Prior chemo/ADC: 62%/24% monotherapy arm;
- Palbociclib (49/63; 78%); Ribociclib (13/63; 21%); Abemaciclib (1/63; 2%).

Safety
- Most common LY4064809 related AEs (TRAEs) were fatigue (27%), nausea (23%), hyperglycemia (23%; 33%/12% in pts with/without pre-DM/DM), and diarrhea (21%)
- Grade ≥3 TRAEs occurred in 20% of patients, most commonly ALT/AST increased (7%), fatigue (4%), and neutropenia (4%)
- 1 patient discontinued due to a TRAE (AST increased in 100 mg LY4064809 + fulvestrant)
- Minimal impact on glucose metabolism

Jhaveri et al, SABCS 2025;Abstract PS1-08-24

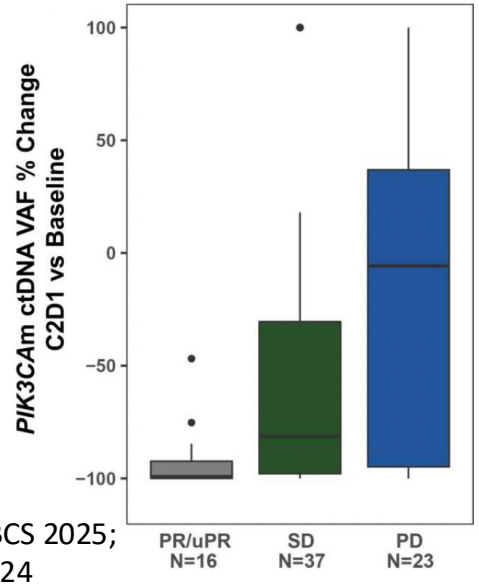
PIK3CAm ctDNA VAF Dynamics





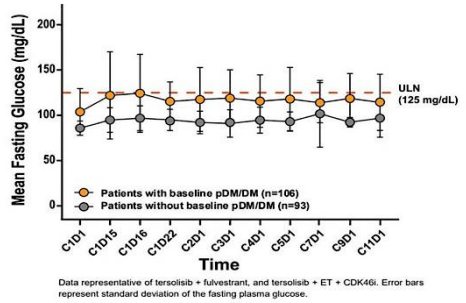
(A, B) Breast cancer patients with *InVisionSeq- or Foundation Medicine One Liquid-detected baseline enrollment-eligible *PIK3CA* mutations (*PIK3CA*m) with variant allele frequency (VAF) ≥0.4%. Percent changes calculated using only enrollment-eligible *PIK3CA*m. **(B)** Objective response limited to patients with measurable disease. #Patients with >100% *PIK3CA*m VAF % change from baseline

- Consistent with LY4064809 target engagement, kinase and helical domain *PIK3CA*m VAF decreases at C2D1 were observed
- Greater declines in *PIK3CA*m VAF correlated positively with objective responses



Jhaveri et al, SABCS 2025; Abstract PS1-08-24

Impact on Glucose Metabolism by Glycemic Status

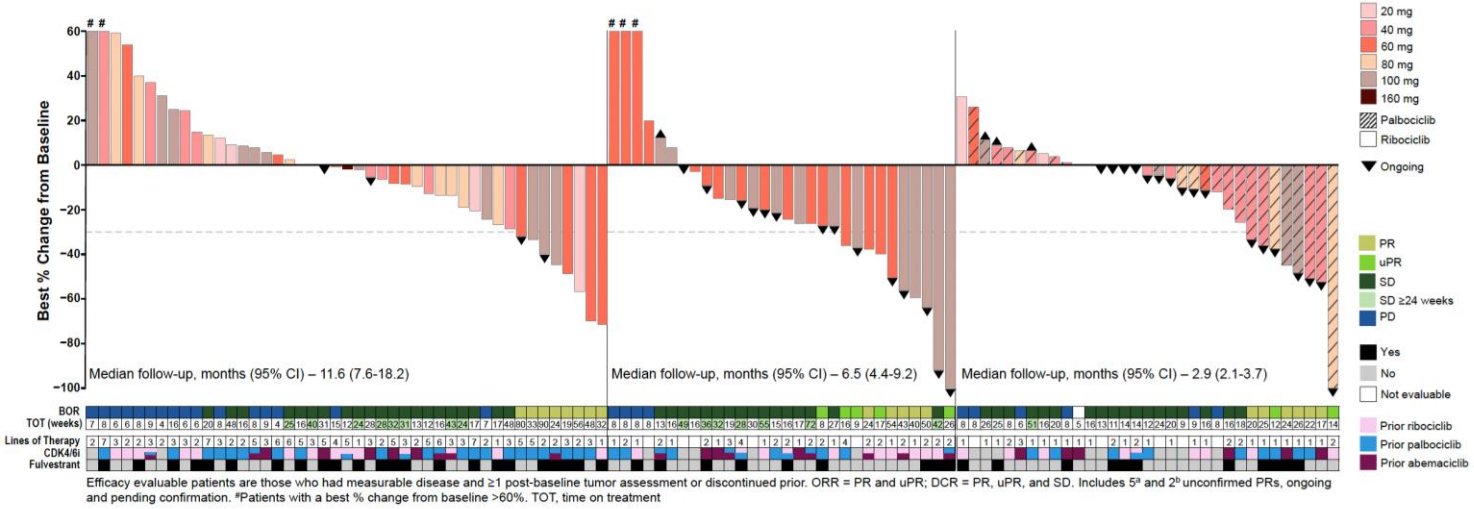


Data representative of tersolisib + fulvestrant, and tersolisib + ET + CDK46i. Error bars represent standard deviation of the fasting plasma glucose.

- Overall minimal impact on glucose metabolism with a marginal impact in patients with pDM/DM.
- Across doublet and triplet cohorts (n=199), hyperglycemia as a TEAE was observed in 51 (26%) patients, predominantly low-grade and effectively managed with supportive care, including adjustments to antihyperglycemic medications.

Tumor Response in ABC Patients with Measurable Disease

	LY4064809 (n=45)	LY4064809 + fulvestrant (n=30)	LY4064809 + fulvestrant + CDK4/6i (n=33)
ORR, n (%)	8 (18)	10 (33)[a]	8 (24)[b]
DCR, n (%)	29 (64)	26 (87)[a]	26 (79)[b]



Efficacy evaluable patients are those who had measurable disease and ≥1 post-baseline tumor assessment or discontinued prior. ORR = PR and uPR; DCR = PR, uPR, and SD. Includes 5[a] and 2[b] unconfirmed PRs, ongoing and pending confirmation. #Patients with a best % change from baseline >60%. TOT, time on treatment

Majority of patients in the combination cohorts are ongoing

PIKALO-2 Phase 3 Study Design NCT07174336

1L *PIK3CA*-mutant[a] HR+, HER2- aBC

- Men & pre/post-menopausal women
- HbA1c <8.0% & T2DM not requiring insulin allowed
- **Prior therapy: 0 for aBC**

  Patients may be:

  i. Newly diagnosed (de novo) aBC

  ii. Relapsed >12 months from completion of (neo)adjuvant ET ± CDK4/6i

  iii. Relapsed on or within 12 months from completion of (neo)adjuvant ET ± CDK4/6i[b]

R 1:1
N ~800

Tersolisib

LY4064809
+ CDK4/6i[d]
+ ET[e]

Placebo
+ CDK4/6i[d]
+ ET[e]

All Endpoints Independently Assessed in each population:
1. **Endocrine Sensitive**
2. **Endocrine Resistant**

Primary endpoint:
Investigator-assessed PFS

Key Secondary endpoints:
- OS (key), BIRC-PFS, ORR, PK & PRO
- Safety in the ITT population

Populations according to Endocrine sensitivity[c]
1. Endocrine Sensitive (n=550)
2. Endocrine Resistant (n=200)

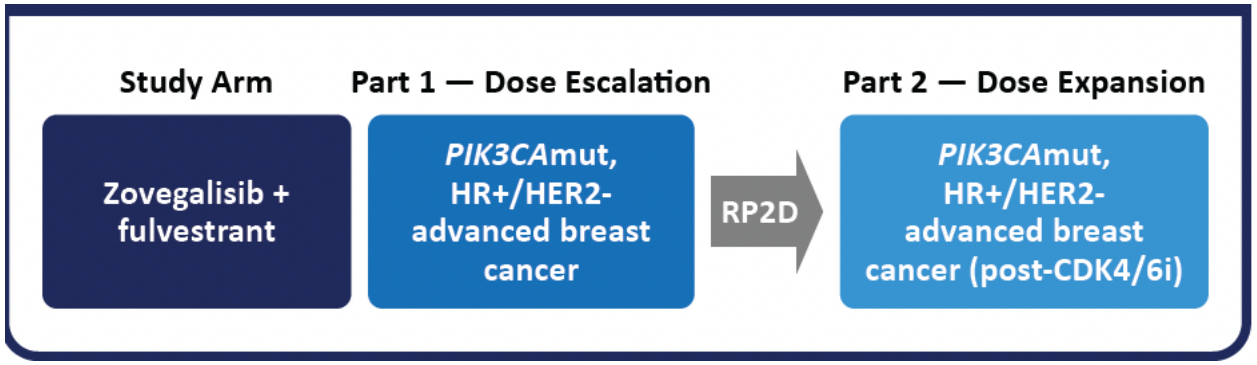
Randomization within each Population Stratified by:
1. Physician's choice of CDK4/6i[d] (abemaciclib/ribociclib/palbociclib)
2. Prior CDK4/6i (Y vs N)
3. Visceral metastases (Y vs N)

[a] PIK3CA testing by central ctDNA (FoundationOne® Liquid/ XXX assay in China) OR local tissue/ctDNA test; [b] Relapse must be >12 months of CDK4/6i portion of adjuvant therapy
[c] Sensitive defined as newly diagnosed aBC or relapse >12 months after completion of Adjuvant ET ± CDK4/6I. Resistant defined as relapse on or within 12 months of Adjuvant ET ± CDK4/6i
[d] Physician's choice CDK4/6i (abemaciclib/ribociclib/palbociclib); [e] ET for Endocrine sensitive = AI, ET for Endocrine resistant = fulvestrant

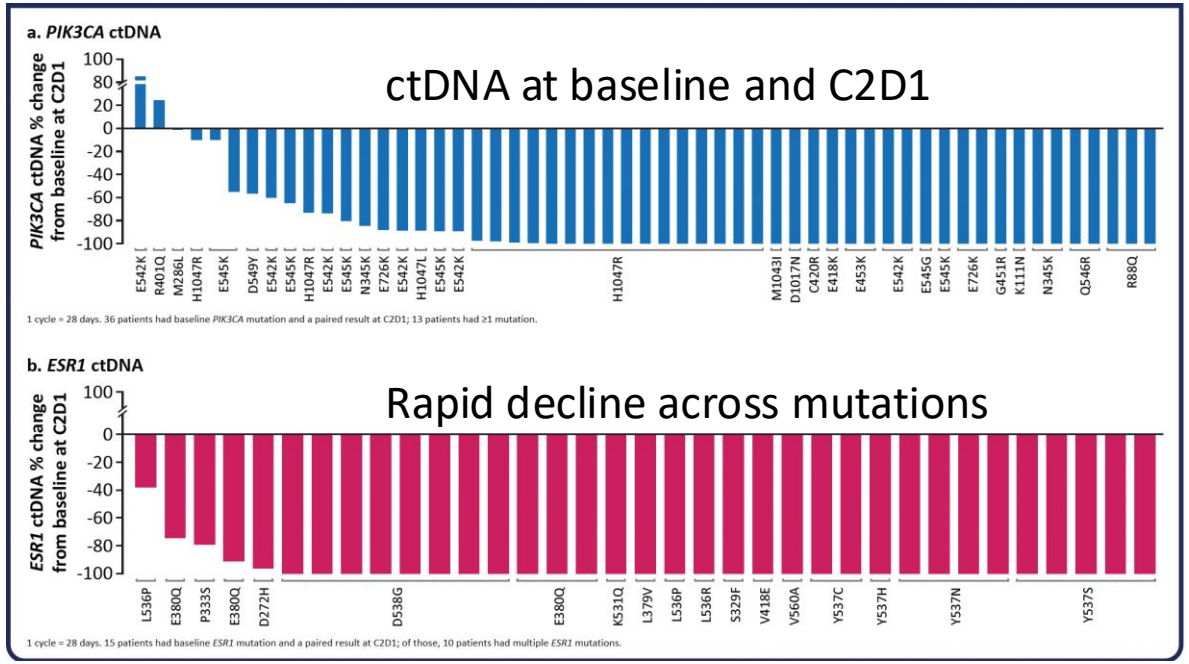
Conclusions

- Tersolisib (LY4064809) alone or in combination with fulvestrant or fulvestrant/CDK4/6i was well-tolerated
  - Low incidence of PI3K inhibitor (PI3Ki)-class toxicities
- Promising antitumor activity observed in heavily pre-treated patients with *PIK3CA*m HR+, HER2- ABC
  - Follow-up is short as many remain on therapy
- PIKALO-2, a phase 3 global registrational trial investigating tersolisib in combination with ET and CDK4/6i is actively enrolling a dose optimization lead-in with phase III to open mid 2026 (NCT07174336)

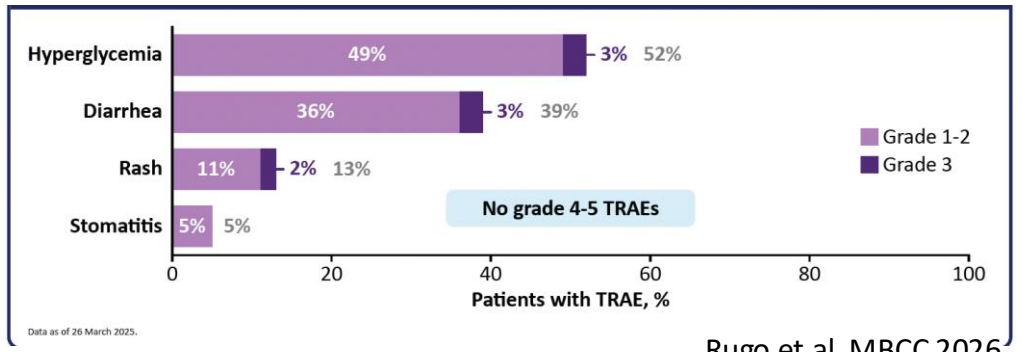
ReDiscover Trial: Zovegalisib (RLY-2608), a mutant-selective PI3Kα inhibitor, plus fulvestrant in patient subsets, including pts with *PIK3CA*-mutant HR+/ HER2- MBC



- 64 pts treated, all with mPIK3CA
  - Zovegalisib 600 mg BID
- Demographics
  - 34% BMI ≥30 or HgbA1c >5.7%
  - 55% one line, 44% 2+ lines Rx
  - 52% prior fulvestrant
  - 27% prior ADC/chemo
  - 29% ESR1m

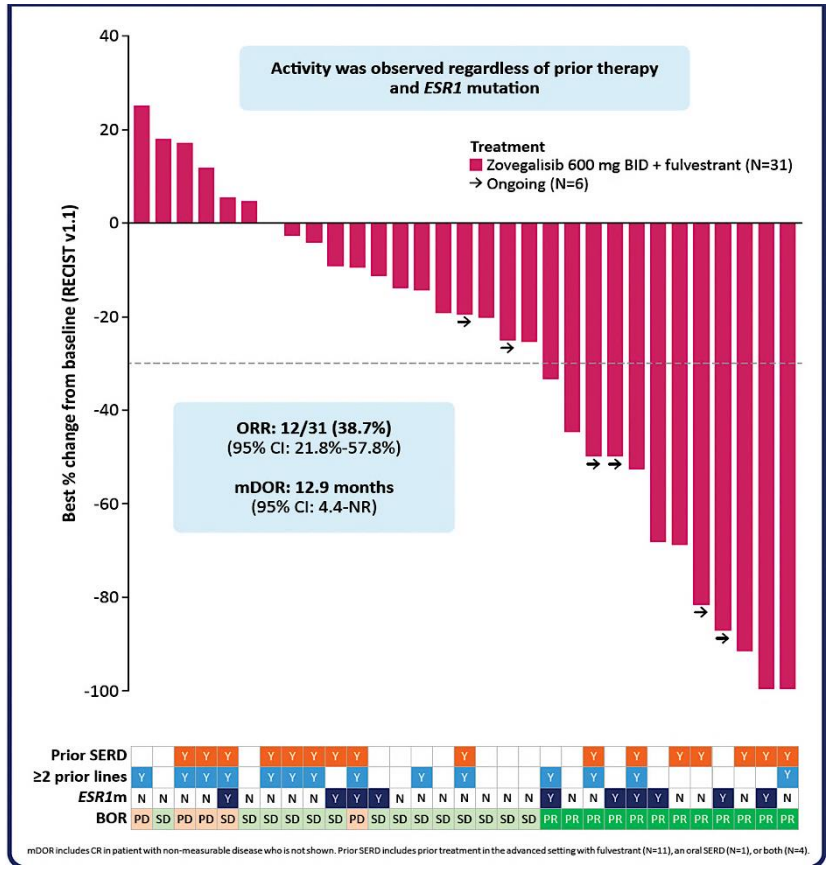


Only 2 pts discontinued Rx due to AEs



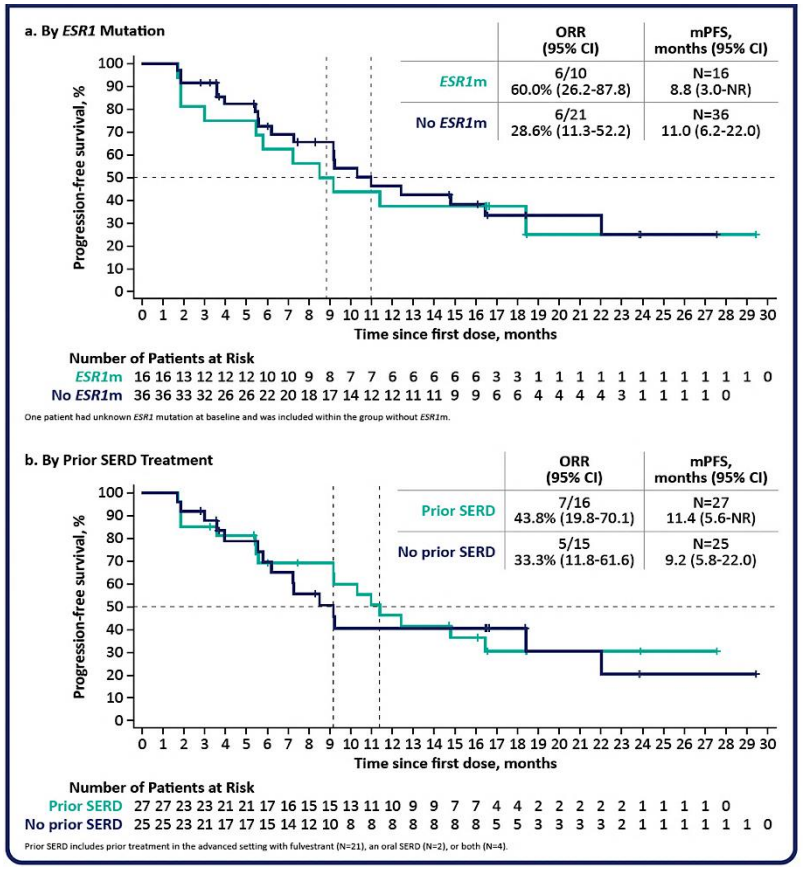
Saura et al, SABCS 2025:Abstract PD10-07

Rugo et al, MBCC 2026

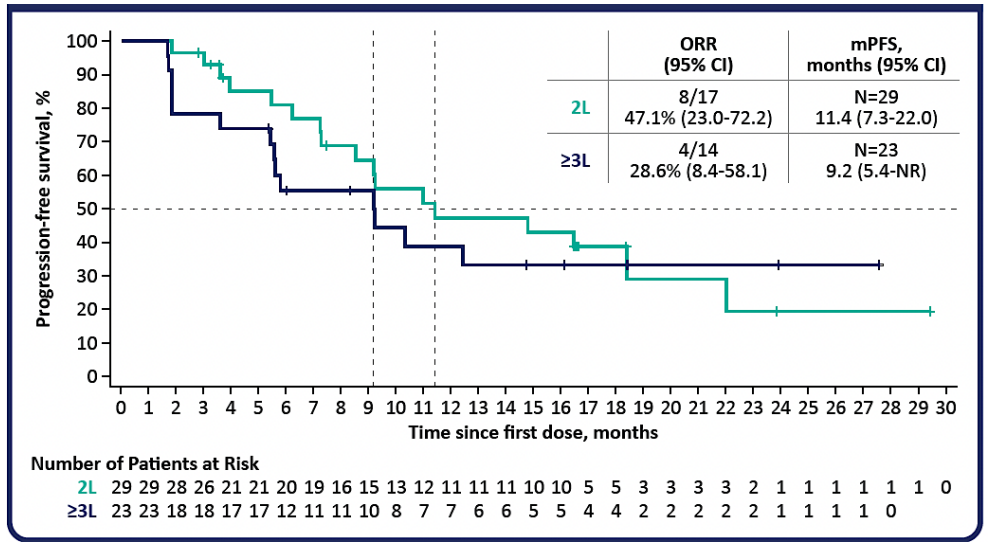


ORR per RECIST v1.1 (N=31)

PFS by ESR1m and Prior SERD (N=52)



Progression-Free Survival by Line of Therapy (N=52)



Saura et al, SABCS 2025:Abstract Abstract PD10-07

Conclusions

- Zovegalisib in combination with fulvestrant showed promising efficacy in patients with PIK3CA mutated HR+/HER2 negative MBC with disease progression on CDK4/6i
  - Including those with co-mutations in ESR1
  - Including those with prior exposure to SERDs
- Discontinuation due to AEs is rare despite a high risk population
- Encouraging PFS regardless of line of therapy
- These findings support the ongoing ReDiscover 2 phase III global registration trial

Key Datasets

- Jhaveri K et al. A phase 1/2 trial of tersolisib (LY4064809/STX-478), a pan-mutant-selective PI3Kα inhibitor (PI3Kαi), in PIK3CA-mutant advanced solid tumors: Updated results from PIKALO-1. ASCO 2026;Abstract 1072.
- A phase 3, randomized, double-blind, placebo-controlled study of LY4064809 combined with a CDK4/6 inhibitor and endocrine therapy in adults with HR+, HER2-advanced breast cancer with a PIK3CA mutation who received no prior treatment for advanced breast cancer (PIKALO-2). NCT07174336.
- Saura C et al. Efficacy of mutant-selective PI3Kα inhibitor RLY-2608 in combination with fulvestrant in patient (pt) subset populations, including pts with PIK3CA-mutant HR+/HER2- advanced breast cancer (BC) pre-treated with fulvestrant or other SERD. San Antonio Breast Cancer Symposium 2025;Abstract PD10-07.
- Rugo H et al. ReDiscover-2, a phase 3 study of zovegalisib (zovega, RLY-2608) + fulvestrant (fulv) versus capivasertib (capi) + fulv as treatment for locally advanced or metastatic PIK3CA-mutant HR+/ HER2- breast cancer following recurrence or progression on or after treatment with a CDK4/6 inhibitor. ASCO 2026;Abstract TPS1148.

The Implications of Recent Datasets for the Current and Future Management of Genitourinary Cancers — An ASCO 2026 Review

A CME/MOC-Accredited Live Webinar

Thursday, July 16, 2026
5:00 PM – 6:30 PM ET

Faculty

Rahul Aggarwal, MD
Matthew D Galsky, MD
Tian Zhang, MD, MHS, FASCO

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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RTP Year in Review 2026