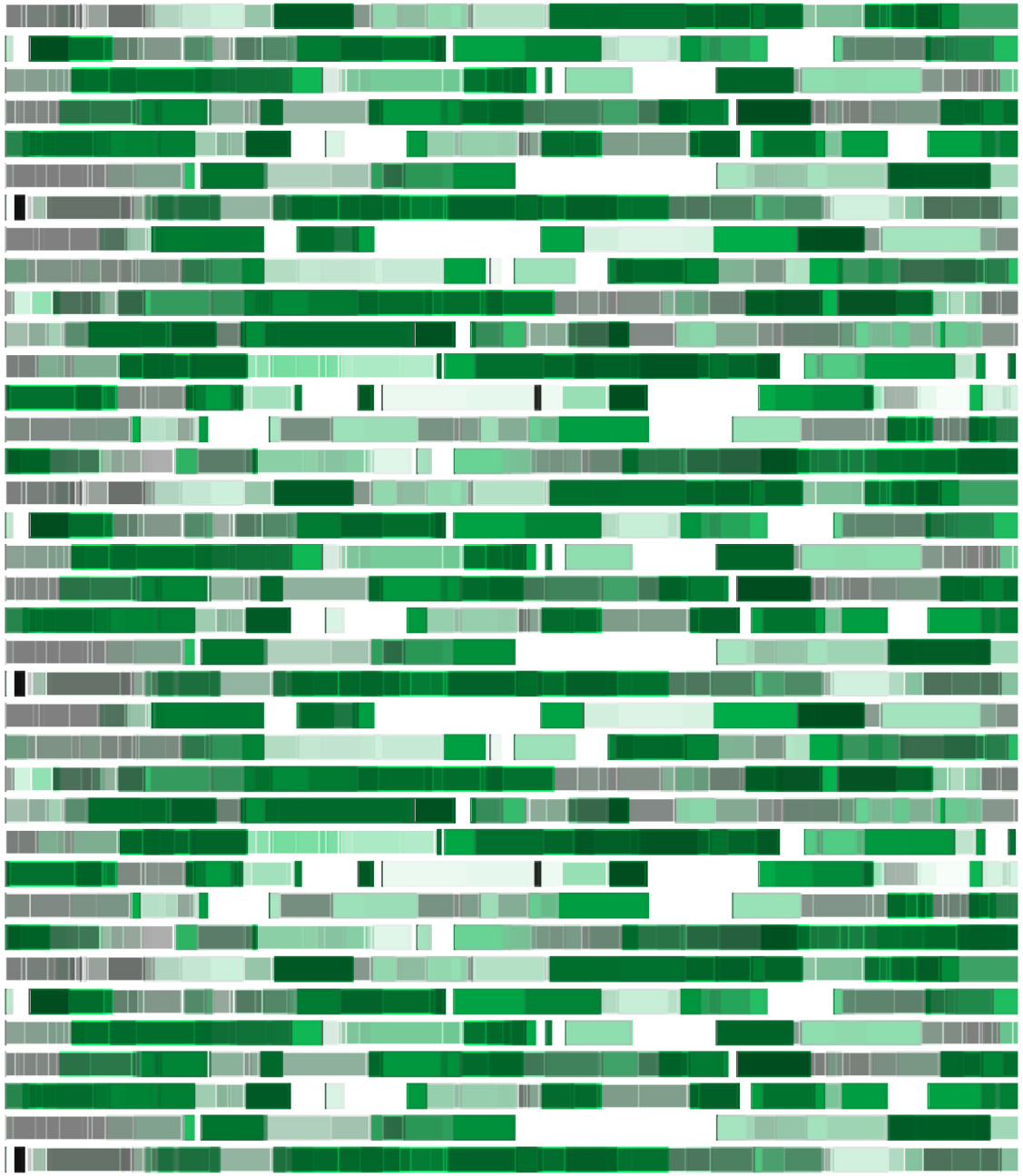
III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

VIA PAM: Nuevas estrategias en cáncer de mama

Begoña Bermejo de las Heras
HCU Valencia

Organizador por:
HENDERE HEALTHCARE



COIS DISCLOSURE

-Employment: Hospital Clinico Universitario Valencia ,INCLIVA. Universidad de medicina de Valencia , Universidad de medicina Cardenal Herrera CEU San Pablo

-Consultant or Advisory Role: Novartis, Pfize,, Astra-Zeneca, Daichii-Sankyo,MSD , Gilead, and Lilly

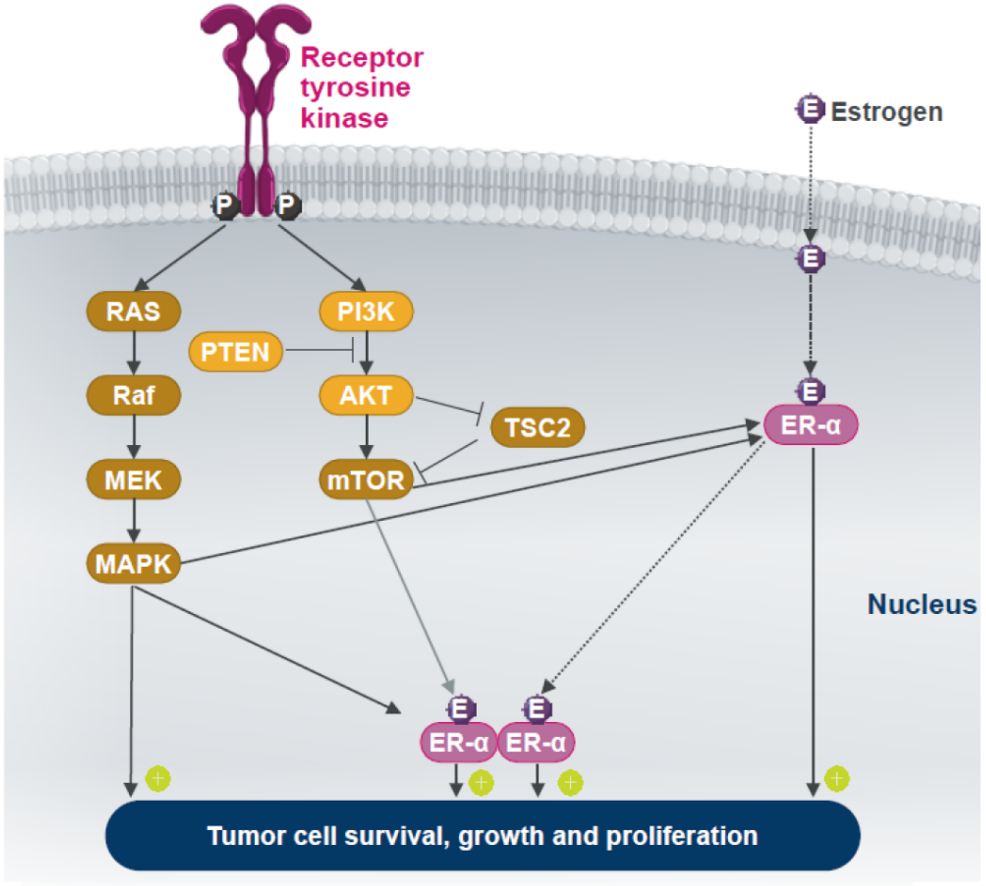
-Research Funding (clinical trial participation as PI: Novartis, Genentech, MSD ,Daiichi-Sankyo, Gilead

-Speaking: Novartis, Astra Zeneca, Daichii Sankyo , Lilly , Pfizer, Gilead.

VIA PAM: NEW STRATEGIES IN BREAST CANCER

- **UPDATING THE "CLASSIC". AVAILABLE STRATEGIES**
- NEW INDICATIONS FOR APPROVED DRUGS
- NEW DRUGS
- MECHANISM OF RESISTAN

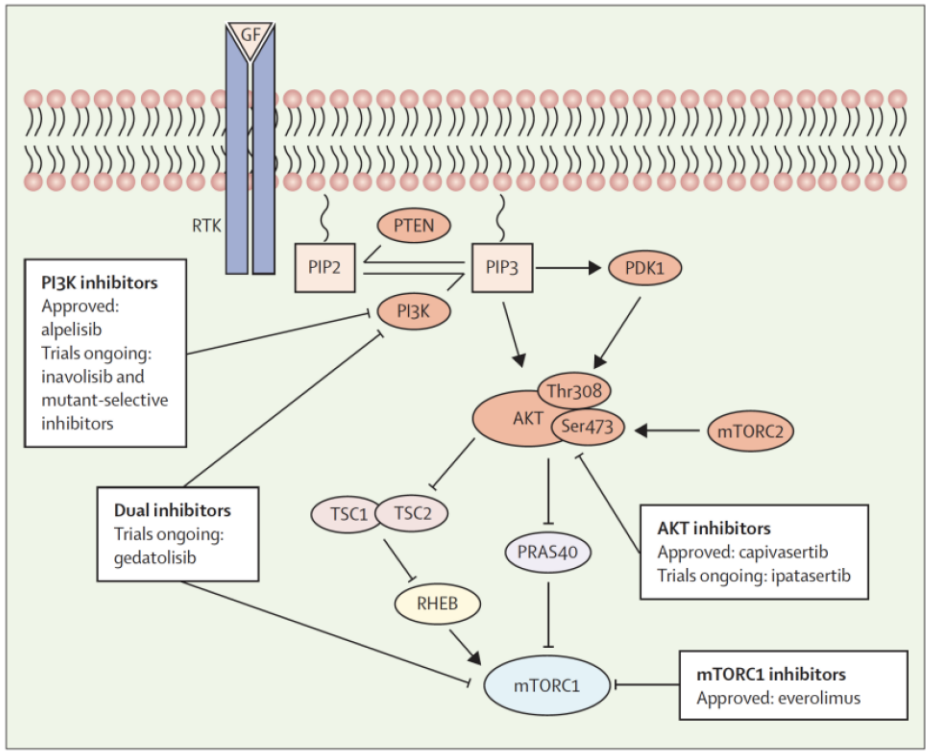
PI3K PATHWAY OFTEN ABERRANTLY ACTIVATED IN BREAST CANCER



Breast Cancer	*PIK3CA/AKT/PTEN* alterations
HR+/HER2-	~50%
HER2+	~35-40%
TNBC	~25-30%

THE PI3K/AKT PATHWAY

	HR+/HER2-	HER2+	TNBC
PIK3CA mut	30-50%	30-35%	7-10%
PTEN dysreg	6%	~20%	~15%
AKT1 mut	5%	~2%	~1%



Physiological functions:

- Cell growth and proliferation
- Cell survival and apoptosis inhibition
- Metabolism Regulation: glucose and lipid metabolism
- Neural development and function
- Angiogenesis
- Muscle growth and maintenance
- Immune system regulation

Narrow therapeutic index

Browne IM et al. Lancet Oncol. 2024 Apr:25(4): e139-e151 | TCGA Nature 490:61-70. 2012: Ciriello G. Cell 163:506-19. 2015: Nik-Zainal S. Nature 534:47-54. 2016: Pereira B. Nat Commun 7:11479. 2016

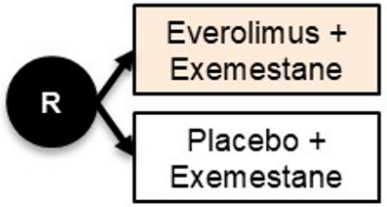
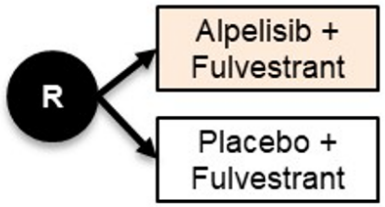
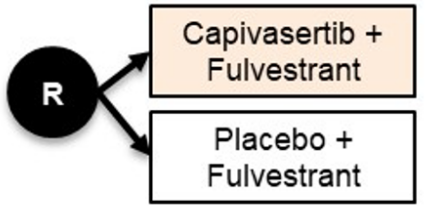
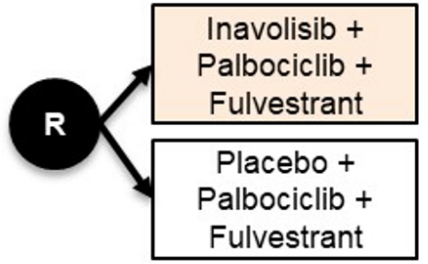
ACTIONABLE MUTATIONS IN MBC

Mutation	Site of testing	Targeted therapy	Trial	FDA approved
BRCA1/2 (PALB2)	Germline / tumor / plasma	Olaparib	OlympiaD	Yes
		Talazoparib	EMBRACA	Yes
PIK3CA	Tumor / plasma	Alpelisib + Fulvestrant	SOLAR-1, BYLIEVE	Yes
	Tumor / plasma	Inavolisib + Palbociclib + Fulvestrant	INAVO-120	Yes
	Tumor	Capivasertib + Fulvestrant	Capitello-291	Yes
	Plasma	Ipatasertib + Fulvestrant	FINER	No
AKT1	Tumor	Capivasertib + Fulvestrant	Capitello-291	Yes
PTEN	Tumor	Capivasertib + Fulvestrant	Capitello-291	Yes
ESR1	Plasma	Elacestrant	EMERALD	Yes
		Imlunestrant	EMBER-3	Yes
		Vepdegestrant	VERITAC	No
		Camizestrant	SERENA-6	No

APPROVED DRUGS TARGETING PI3K/AKT PATHWAY

	Everolimus	Alpelisib	Capivasertib	Inavolisib
Mechanism of action	mTORC1 inhibitor	PI3Kα-specific, non mutant selective inhibitor	ATP-competitive pan-AKT inhibitor	PI3Kα-specific, mutant-selective inhibitor
Indication	After an AI	*PIK3CA*-mut, HR+/HER2- ABC, after ET	At least one *PIK3CA*, *AKT1* or *PTEN* alteration, after ≥1 ET in HR+/HER2- ABC	*PIK3CA*-mut HR+/HER2- ABC, progressing on or <12 months after end of adjuvant ET

PIVOTAL TRIALS ENROLLED DIFFERENT PATIENTS POPULATIONS

	BOLERO-2 N=724	SOLAR-1 N=341 (*PIK3CA*mut)	Capitello-291 N=289 (AKT-alt)	INAVO-120 N=325
Drug	Everolimus	Alpelisib	Capivasertib	Inavolisib
Arms				
Setting	2L	2L	1-2L	1L
Liver metastasis	33%	29%	45%	48%
Prior Therapies				
CDK4/6 inhibitor	0	5.3%†	73%	2%*
Chemotherapy	26%	0	19%	0

† In BYLIEVE, 100% of patients received prior CDK4/6 inhibitors
*In the adjuvant setting

Baselga J et al, NEJM 2012 | André F et al, NEJM 2019 | Turner NC et al, NEJM 2023l Turner NC et al, NEJM 2024

SUMMARY OF THE EFFICACY RESULTS

	Everolimus	Alpelisib	Capivasertib	Inavolisib
PFS, median (months)	HR=0.36 6.9 vs 2.8	HR=0.65 11.0 vs 5.0	HR=0.50 7.3 vs 3.1	HR=0.43 15.0 vs 7.3
OS, median (months)	No difference	No difference	Pending	HR=0.67 34.0 vs 27.0

AEs: adverse events; HR: hazard ratio; OS: overall survival; PFS: progression-free survival

December 11, 2025 1:00-2:0 PM CST
RF7-04: EPIK-B5: Alpelisib plus fulvestrant for *PIK3CA*-mut, HR+/HER2- MBC after a CDK4/6 inhibitor
De Laurentiis M et al.

December 11, 2025 1:00-2:00 PM CST
RF7-05: Exploratory ctDNA analyses from the Phase 3 CAPItello-291 trial
Turner N et al

December 11, 2025 7:00-0:30 AM CST
PD5-09: Molecular features of response to inavolisib from INAVO-120
Turner N et al

Baselga J et al, NEJM 2012 . André F et al, NEJM 2019. Turner NC et al, NEJM 2023 .Turner NC et al, NEJM 2024 . Jhaveri. K et al, NEJM 2025

TOLERABILITY OF THE APPROVED AGENTS

	Everolimus	Alpelisib	Capivasertib	Inavolisib
Drug discontinuation	26%	25%	13%	7%
Dose reduction	38%	64%	20%	Inavo 14% Palbo 38%
G3-5 AEs	42%	76%	38%	92%*
Common AEs	Mucositis, metabolic dysregulation, altered AST/ALT, pneumonitis	Hyperglycemia, rash, nausea, vomiting, diarrhea, asthenia	Neutropenia, hyperglycemia, stomatitis, diarrhea, thrombocytopenia	Diarrhea, rash, nausea, fatigue, vomiting, neutropenia (palbo)
Hyperglycemia	13%	64%	16%	59%
Diarrhea	30%	58%	72%	48%
Stomatitis	56%	25%	15%	51%
Rash	36%	36%	38%	25%

*Mainly neutropenia related with palbociclib

Baselga J et al, NEJM 2012 | André F et al, NEJM 2019 | Turner NC et al, NEJM 2024 | Turner NC et al, NEJM 2023

CHANGES IN DIAGNOSIS

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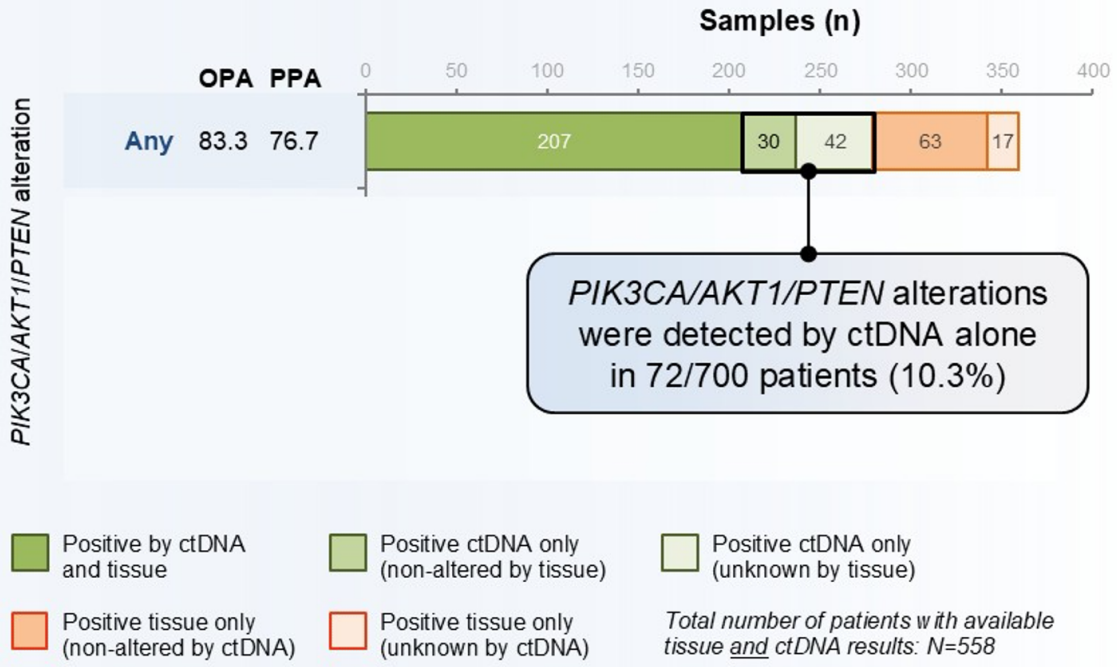
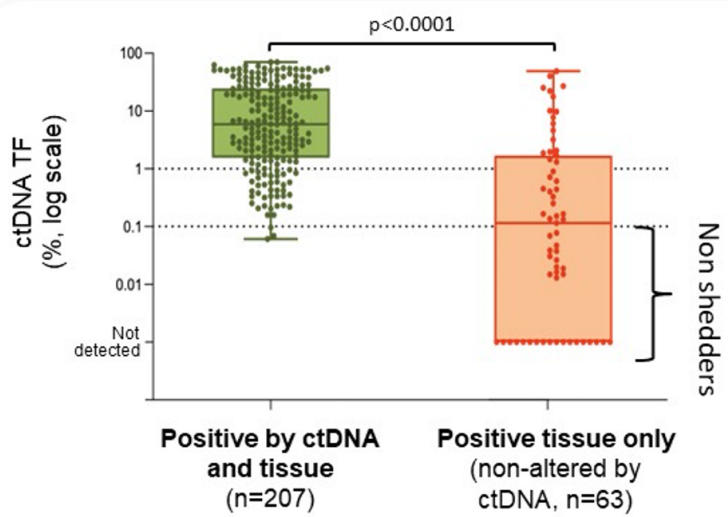
EXPLORATORY CTDNA ANALYSES FROM THE PHASE 3 CAPITELLO-291 TRIAL

PIK3CA/AKT1/PTEN ALTERATION CONCORDANCE BETWEEN CTDNA AND TISSUE

Comparison of tissue and ctDNA detected



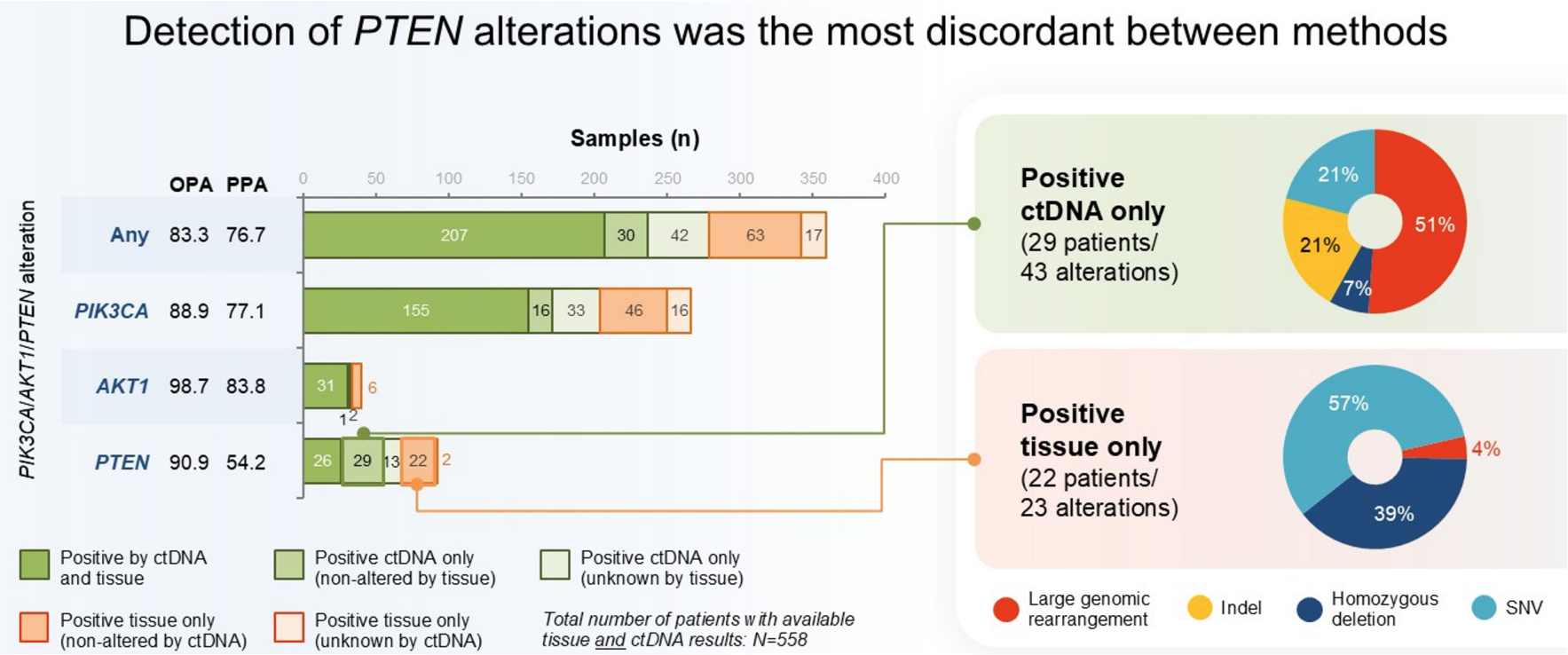
ctDNA methylation tumor fraction



Number of patients by TF %, n (%)						
	N	0	>0–0.1	>0.1–1	>1–10	>10
ctDNA+/Tissue+	207	0 (0)	3 (1)	38 (18)	81 (39)	85 (41)
ctDNA-/Tissue+	63	18 (29)	13 (21)	14 (22)	11 (17)	7 (11)

Concordance calculated using tissue results as the reference, excluding unknown; OPA and PPA calculated based on total number of patients with available tissue and/or ctDNA results (N=700). *AKT1*, AKT serine/threonine kinase; ctDNA, circulating tumor DNA; OPA, overall percentage agreement; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PPA, percentage positive agreement; *PTEN*, phosphatase and tensin homolog; TF, tumor fraction.

PIK3CA/AKT1/PTEN ALTERATION CONCORDANCE BETWEEN CTDNA AND TISSUE



- PIK3CA/AKT1/PTEN alt were detected by ctDNA only (non-altered or unknown by tissue) in ~10% of pts and by tissue only in ~11% of pts
- En comparación con la evaluación tisular de PTEN, se detectaron reordenamientos genómicos más amplios, pero menos deleciones homocigóticas mediante ctADN.
- **La evaluación de la fracción tumoral mediante metilación** puede mejorar la capacidad de identificar pacientes con baja liberación de ctADN, donde la prueba de ctADN por sí sola puede pasar por alto alteraciones.

PIVOTAL TRIALS ENROLLED DIFFERENT PATIENTS POPULATIONS

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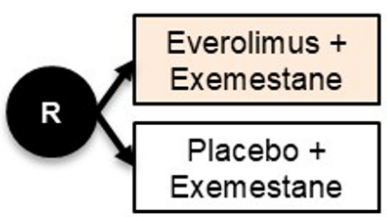
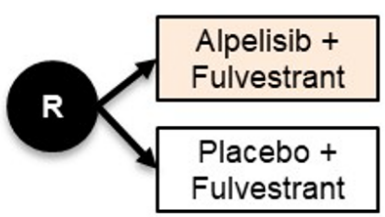
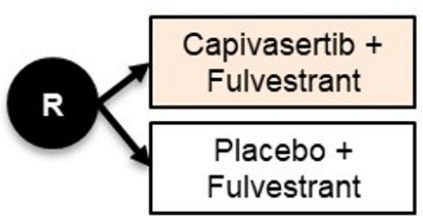
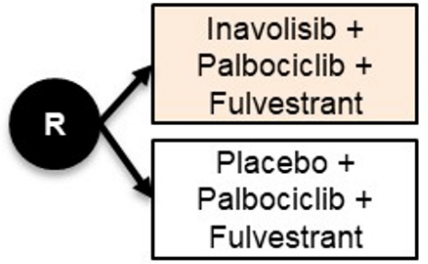
Arms				
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Liver metastasis	33%	29%	45%	48%
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CDK4/6 inhibitor	0	5.3%†	73%	2%*
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*In the adjuvant setting

Baselga J et al, NEJM 2012 | André F et al, NEJM 2019 | Turner NC et al, NEJM 2023l Turner NC et al, NEJM 2024

ALPELISIB PLUS FULVESTRANT FOR PIK3CA-MUT HR-POSITIVE, HER2- NEGATIVE ABC AFTER A CDK4/6 INHIBITOR (EPIK-B5): PHASE III

- Phase 3; 66 centers in 17 countries

Inclusion:

- Adult postmenopausal women and men with HR+, HER2- ABC with *PIK3CA* mutation who progressed or relapsed on or after CDK4/6i and AI
- ≥1 measurable lesion per RECIST v1.1, as assessed by investigator
- ≤1 line of prior chemotherapy treatment (except neoadjuvant/ adjuvant chemotherapy)
- Adequate tumour tissue for PIK3CA mutation status by central laboratory

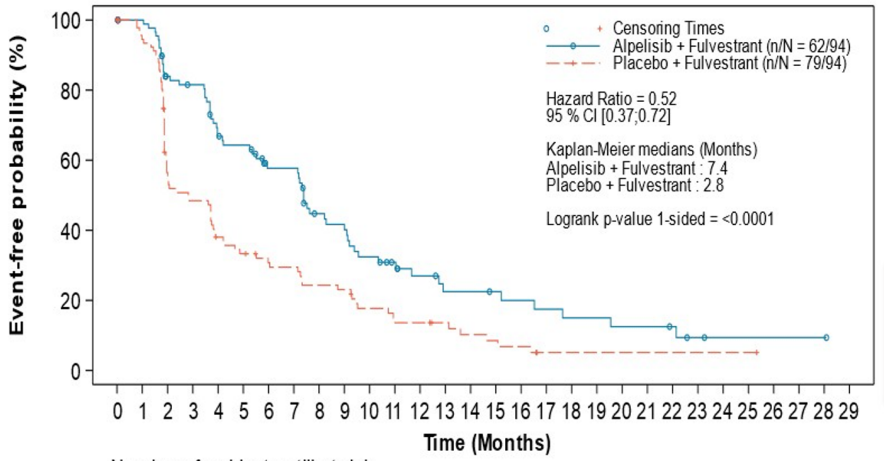
Randomization 1:1
N = 188 (until data cutoff on 15 Oct 2024)

- Alpelisib 300 mg + fulvestrant 500 mg n=94
- Placebo + fulvestrant 500 mg n=94

Stratification factors:
Presence of lung and/or liver metastases (yes vs no)
Setting at last prior CDK4/6 inhibitor therapy (adjuvant vs metastatic)

Cross-over from the placebo arm to the alpelisib arm was permitted at time of PD as assessed per RECIST v1.1 by BIRC

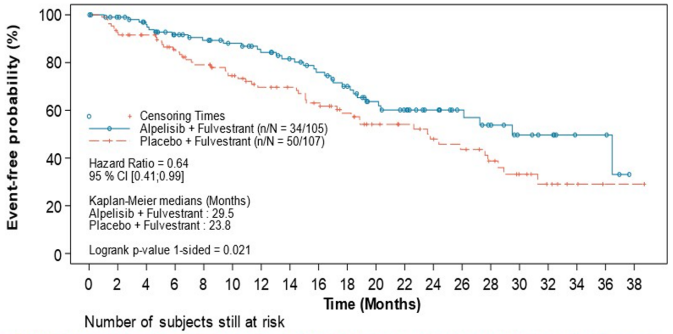
Progression-free survival by BIRC per RECIST1.1



Data cut-off: Oct 15, 2024	Alpelisib + fulvestrant (N=94)	Placebo + fulvestrant (N=94)
Number of PFS events, n (%)	62 (66.0%)	79 (84.0%)
Progression	56 (59.6%)	70 (74.5%)
Death	6 (6.4%)	9 (9.6%)
Censored	32 (34.0%)	15 (16.0%)
Median PFS (95% CI)	7.4 (5.52-9.10)	2.8 (1.94-3.84)
HR (95% CI)	0.52 (0.37-0.72)	
p-value	<0.0001	

The **ORR (95% CI) as per BIRC** assessment was **23.4%** (15.3, 33.3) for the alpelisib arm and **4.3%** (1.2%, 10.5%) for the placebo arm.

Updated Overall survival (ITT analysis*)



Data cut-off: May 26, 2025	Alpelisib + fulvestrant (N=105)	Placebo + fulvestrant (N=107)
Death	34 (32.4)	50 (46.7)
Censored	71 (67.6)	57 (53.3)
Median OS (95% CI)	29.5	23.8
HR (95% CI)	0.64 (0.41-0.99)	
Nominal p-value	0.021	

The ORR (95% CI) per BIRC assessment was 23.4% (15.3, 33.3) for the alpelisib arm and 4.3% (1.2%,10.5%) for the placebo arm.

*Data from data cutoff 26 May 2025. This includes data from 43 (40.2%) patients from the placebo arm who crossed over to the alpelisib arm upon disease progression confirmed by BIRC.

PIVOTAL TRIALS ENROLLED DIFFERENT PATIENTS POPULATIONS

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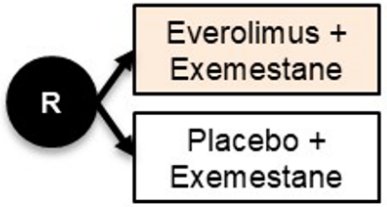
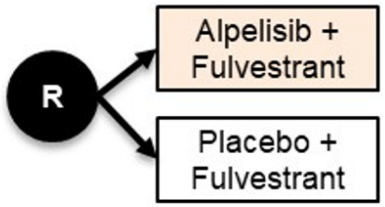
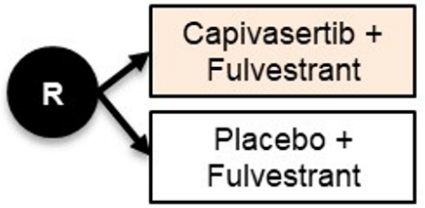
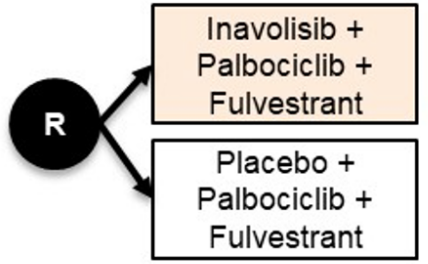
Drug	Everolimus	Alpelisib	Capivasertib	Inavolisib
Arms				
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INAVO120: 1L TRIAL OF PIK3CA MUTANT HR+/HER2- MBC

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– LA/mBC** by central ctDNA or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1c <6.0% (< 42 mmol/mol)**

N = 325

R 1:1

Inavolisib (9 mg QD PO) + 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)

Efficacy endpoints

- PFS by investigator
- OS
- ORR, BOR, CBR, DOR

Patient population:

Primary endocrine resistance: **34%**

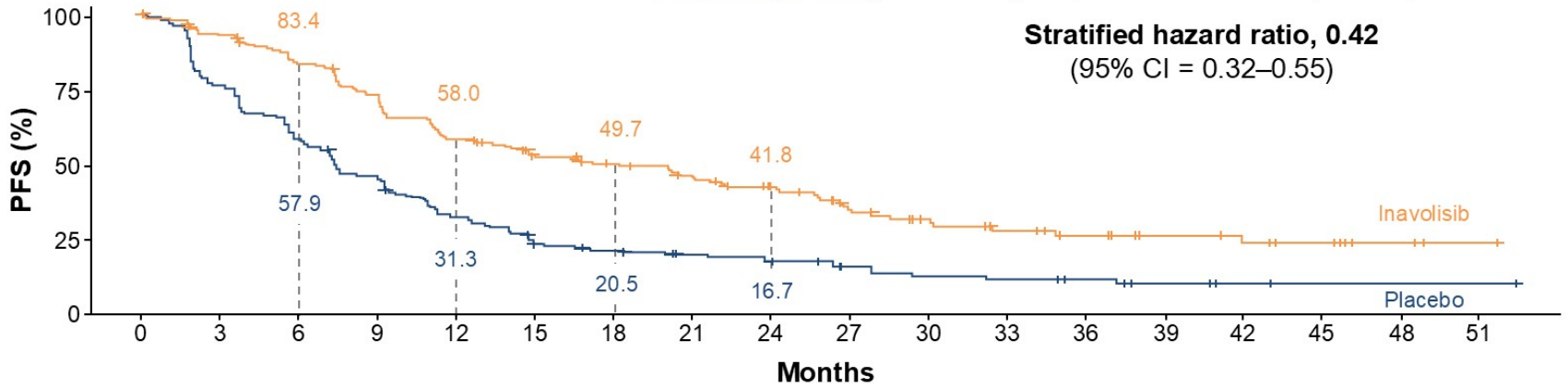
Prior (neo)adjuvant chemo: **82.8%**

Prior (neo)adjuvant ET: **99.8%**

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

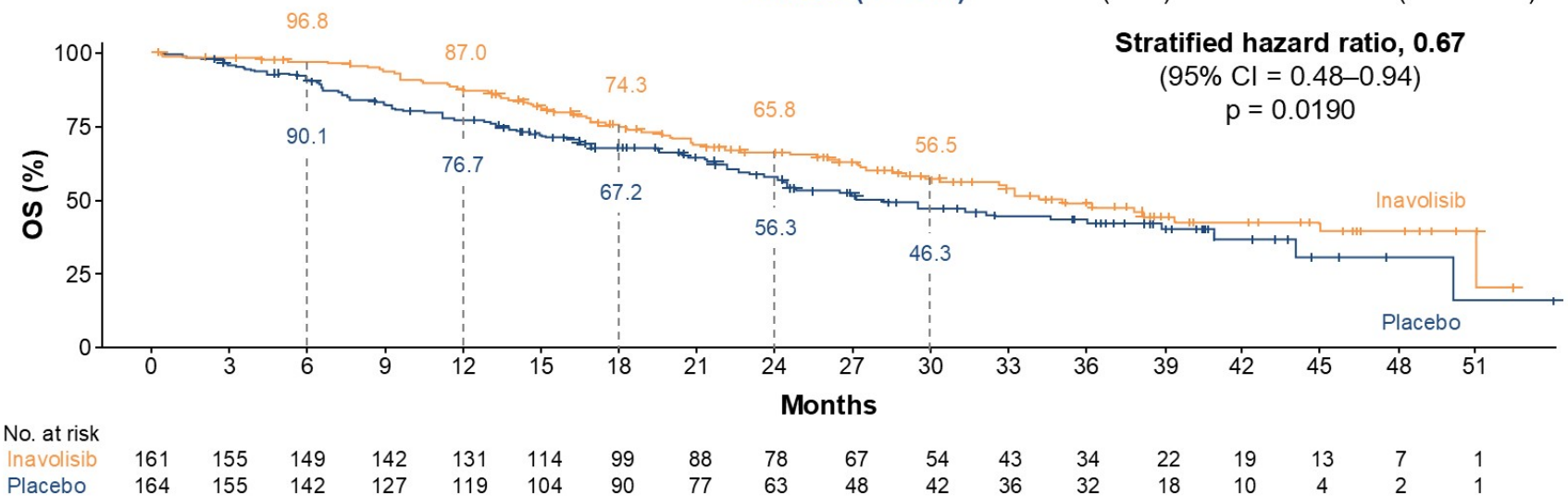
No. at risk																		
Inavolisib	161	146	129	112	89	73	65	57	46	32	25	19	15	11	10	7	3	1
Placebo	164	125	95	74	50	34	30	24	21	14	11	10	8	4	2	1	1	1

The improvement in PFS was maintained during longer follow-up

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

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)



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

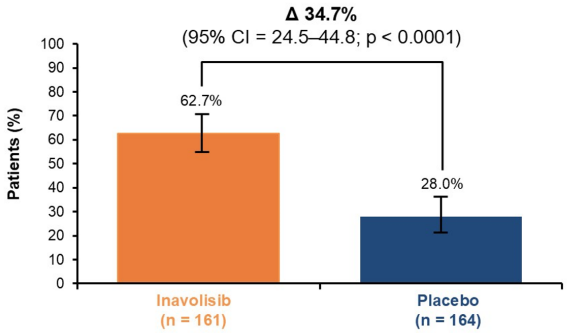
Improvement in median OS: 7 months. The prespecified boundary for statistical significance (p < 0.0469) was crossed

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

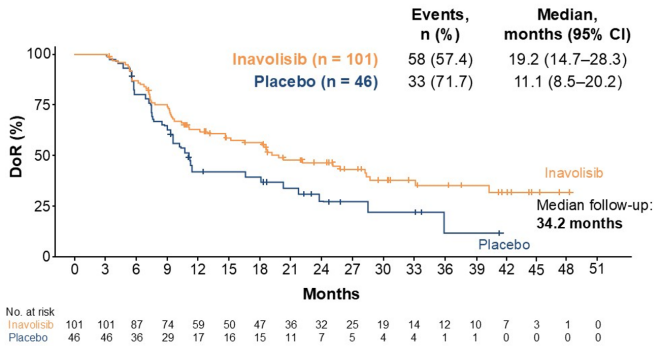
PRESENTED BY: Nicholas Turner, MD, PhD

INAVO120 other key secondary endpoints

ORR*



DoR

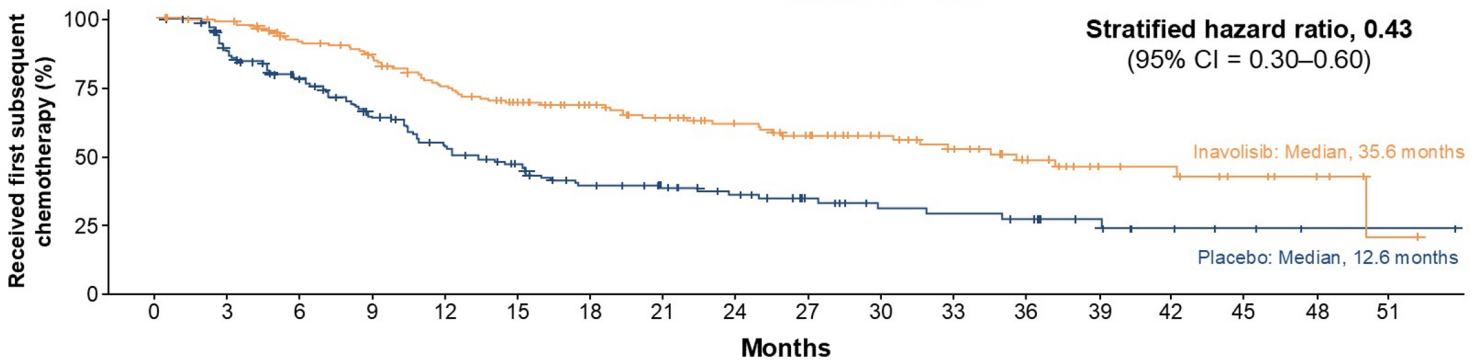


SUBSTANTIALLY HIGHER RATES OF OBJECTIVE RESPONSE WITH AN 8 MONTH MEDIAN IMPROVEMENT IN DURATION OF RESPONSE

INAVO120 time to first subsequent chemotherapy

	Events n, (%)	Median, months (95% CI)
Inavolisib (n = 161)	64 (39.8)	35.6 (25.4–NR)
Placebo (n = 164)	94 (57.3)	12.6 (10.4–16.1)

Stratified hazard ratio, 0.43
(95% CI = 0.30–0.60)



Median follow-up: **34.2 months**

Median time to first subsequent chemotherapy was substantially delayed by almost 2 years (23 months)

CAPITELLO-291:PH3 CAPIVASERTIB + FULVESTRANT IN HR+/HER2- MBC

Patients with HR+/HER2*– 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 CDK4/6 inhibitors 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 tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

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

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

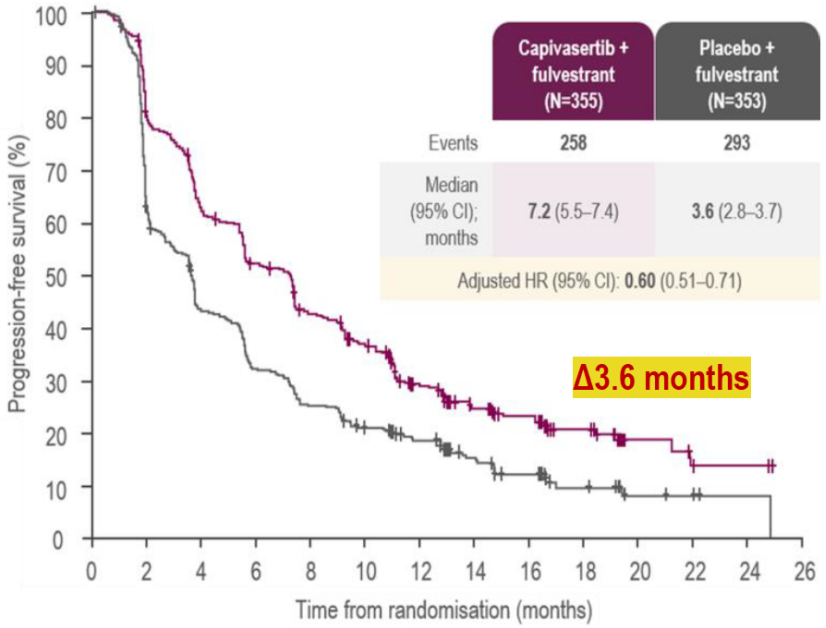
Dual primary endpoints

PFS by investigator assessment
- Overall population
- AKT pathway-altered tumours (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

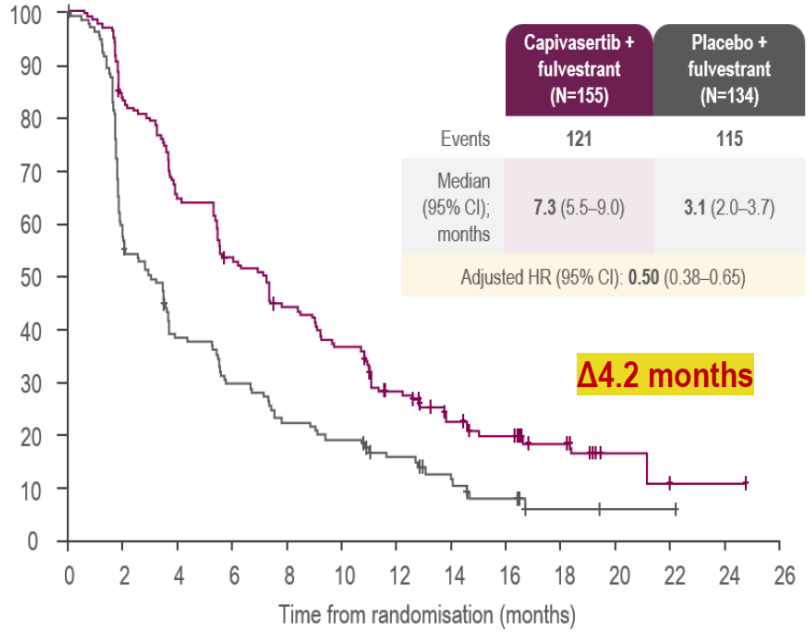
Demographics:
Primary endocrine resistance: **37%**
Prior CDK4/6i for MBC: **69.1%**
AKT pathway mutations: **40.8%**

CAPITELLO-291: PFS IN OVERALL & AKT ALTERED

Primary EP: PFS in overall population



Primary EP: PFS in AKT pathway-altered population

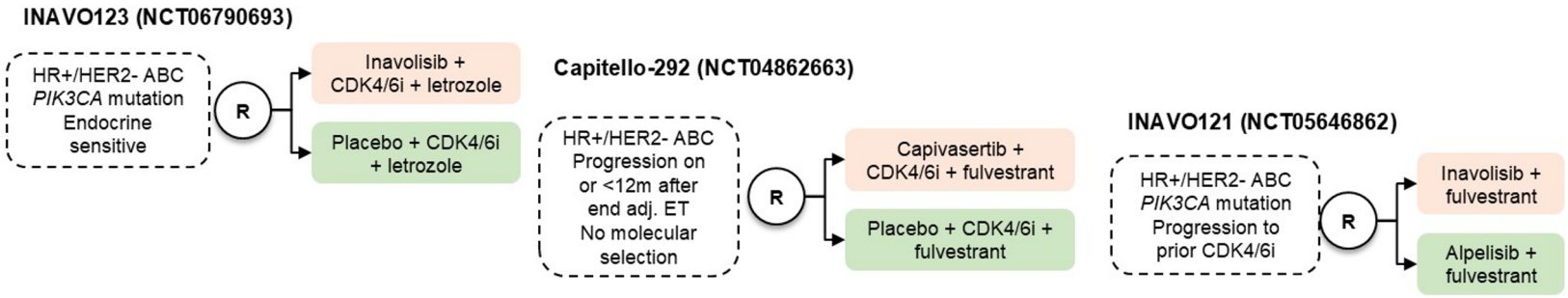


Difference in PFS with capi vs. fulvestrant alone in pts without AKT pathway alterations in tumor was 1.6 months

Capivasertib+ fulvestrant received FDA approval for *PI3K/AKT/PTEN* altered HR+/HER2- MBC after progression on ET in Nov 2023

WHAT IS NEXT IN PI3K/AKT PATHWAY INHIBITION?

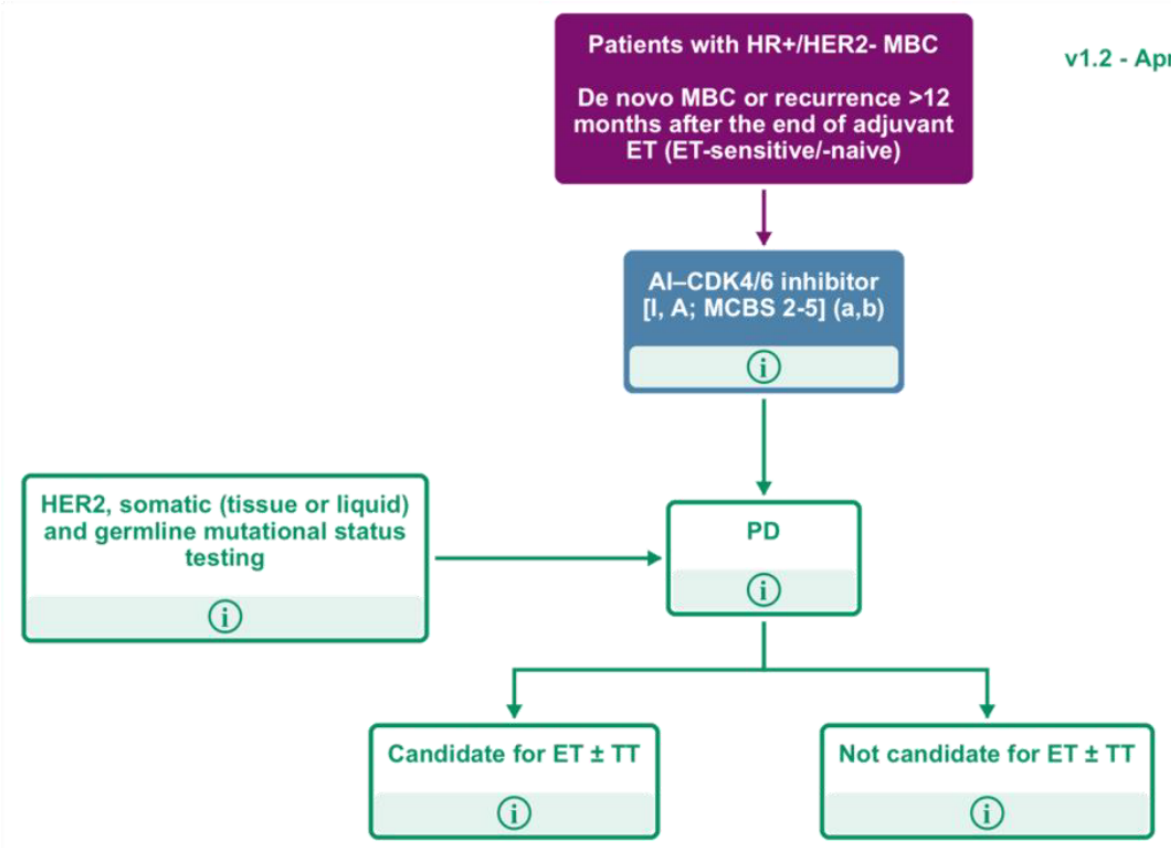
➢ NEW INDICATIONS FOR APPROVED DRUGS



➢ NEW DRUGS

➢ MECHANISM OF RESISTAN

ET-sensitive / -naïve



No current recommendation for PI3K/AKT pathway inhibitor in the ET-sensitive setting

INAVO123 (NCT06790693)

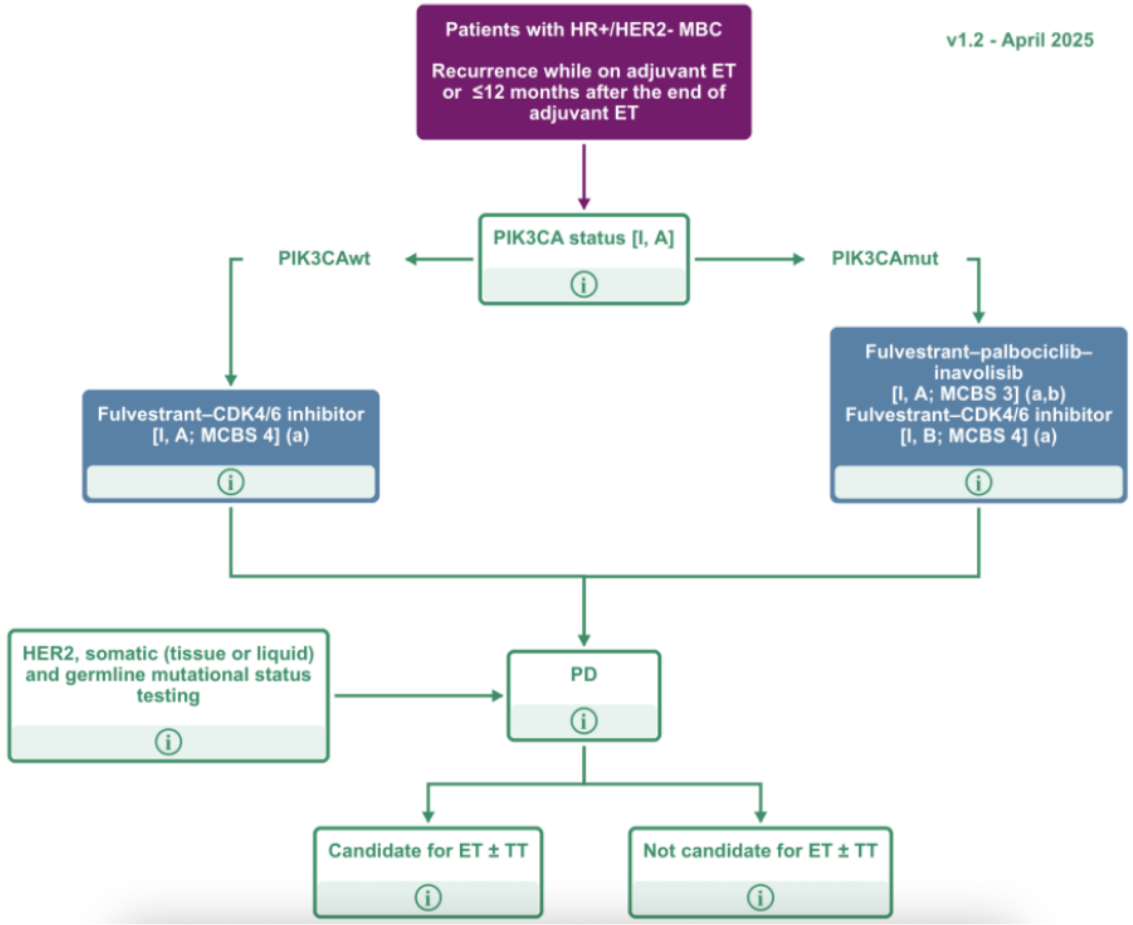
HR+/HER2- ABC
PIK3CA mutation
De novo or relapse >12m after end of adj. ET

R

- Inavolisib + CDK4/6 inhibitor + Letrozole
- Placebo + CDK4/6 inhibitor + Letrozole

ESMO Metastatic Breast Cancer Living Guidelines, v.1.2 - April 2025

Primary or secondary ET-resistance: Progressing on or <12m after end of adj. ET



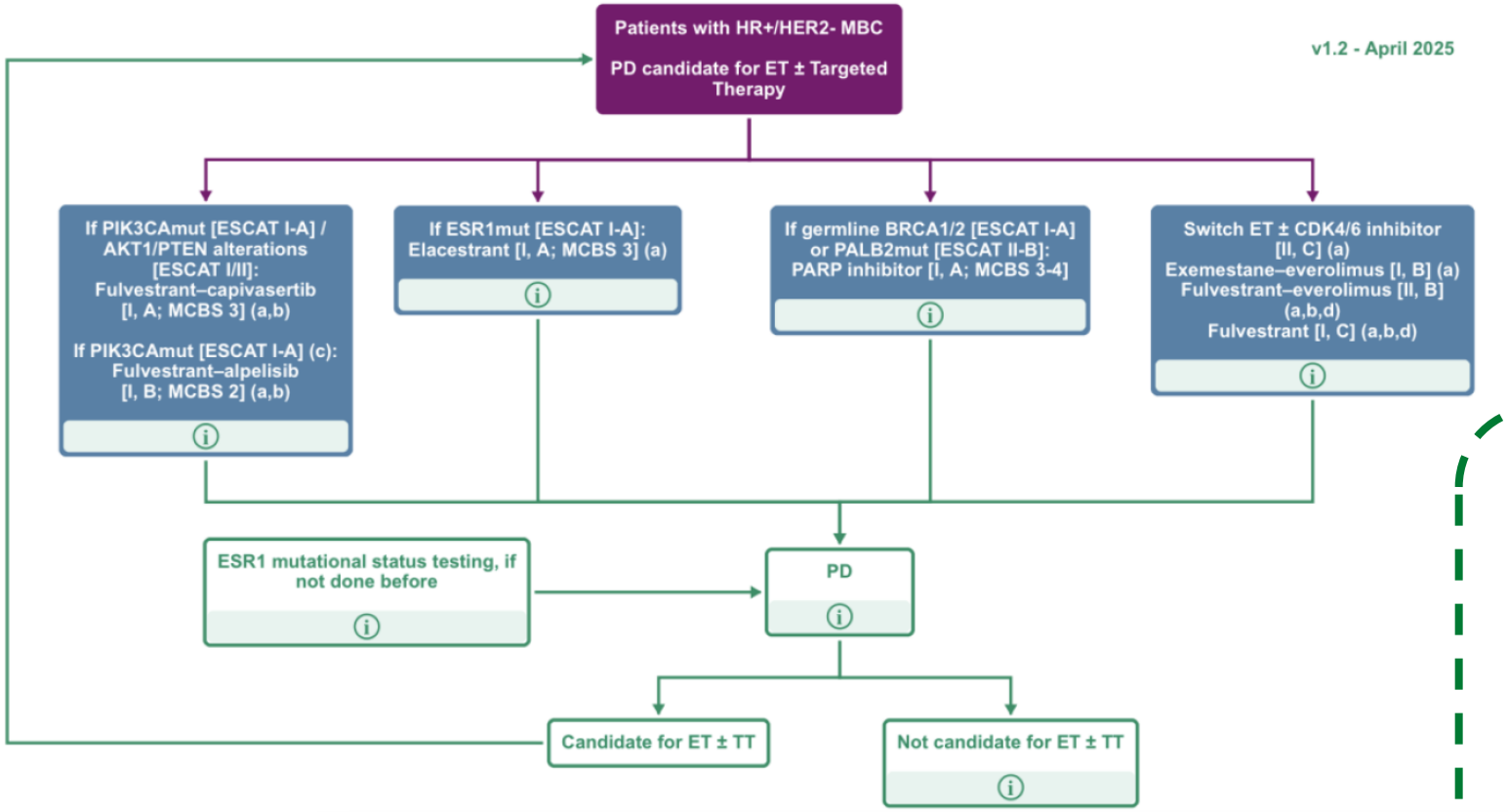
Capitello-292 (NCT04862663)

HR+/HER2- ABC
Progression on or <12m after end adj. ET
No molecular selection

R

- Capivasertib + CDK4/6i + Fulvestrant
- Placebo + CDK4/6i + Fulvestrant

Primary or secondary ET-resistance: PD and candidates to further ET



ESMO Metastatic Breast Cancer Living Guidelines, v.1.2 - April 2025

INAVO121 (NCT05646862)

HR+/HER2- ABC
PIK3CA mutation
Progression to prior CDK4/6i

R

- Inavolisib + Fulvestrant
- Alpelisib + Fulvestrant

LIMITATION WITH THE CURRENTPI3K/AKT INHIBITORS

- ✓ Not mutant-specific inhibitors

- ✓ Considerable tolerability and toxicity issues

Diarrhea (G≥3 =25% w/ Alpelisib)

Hyperglycemia (G≥3 =36% w/ Alpelisib)

Rash (G≥3 =12% w/ Capivasertib)

Stomatitis (G≥3 =5.6% w/ Inavolisib)

- ✓ Modest improvements in PFS

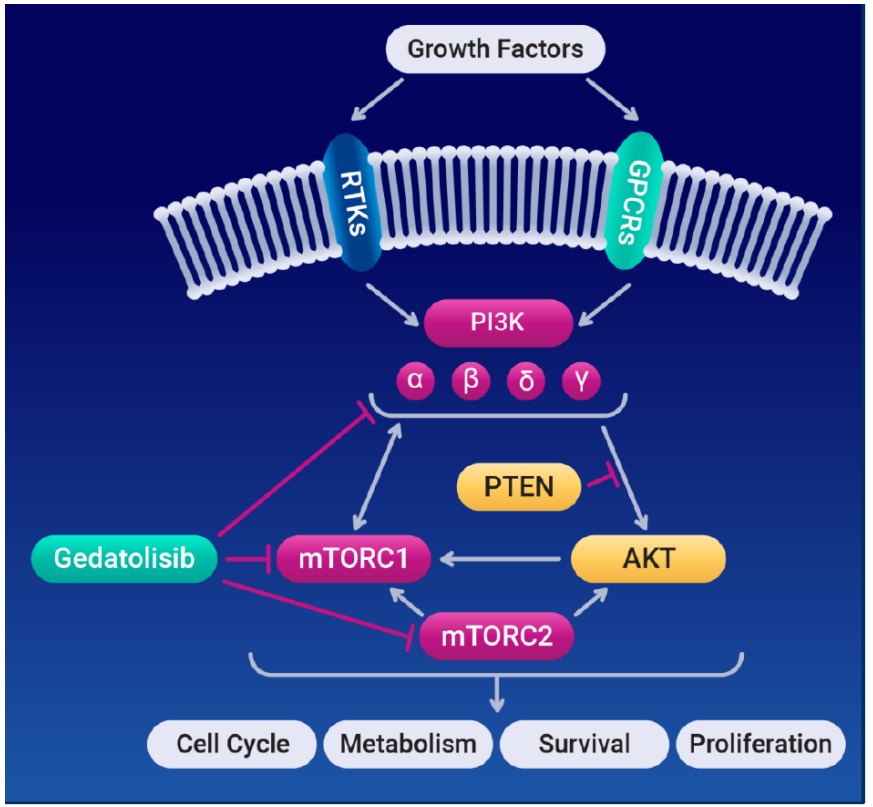
VIA PAM: NEW STRATEGIES IN BREAST CANCER

- UPDATING THE “CLASSIC”. AVAILABLE STRATEGIES
- NEW INDICATIONS FOR APPROVED DRUGS
- **NEW DRUGS**
- MECHANISM OF RESISTAN

GEDATOLISIB

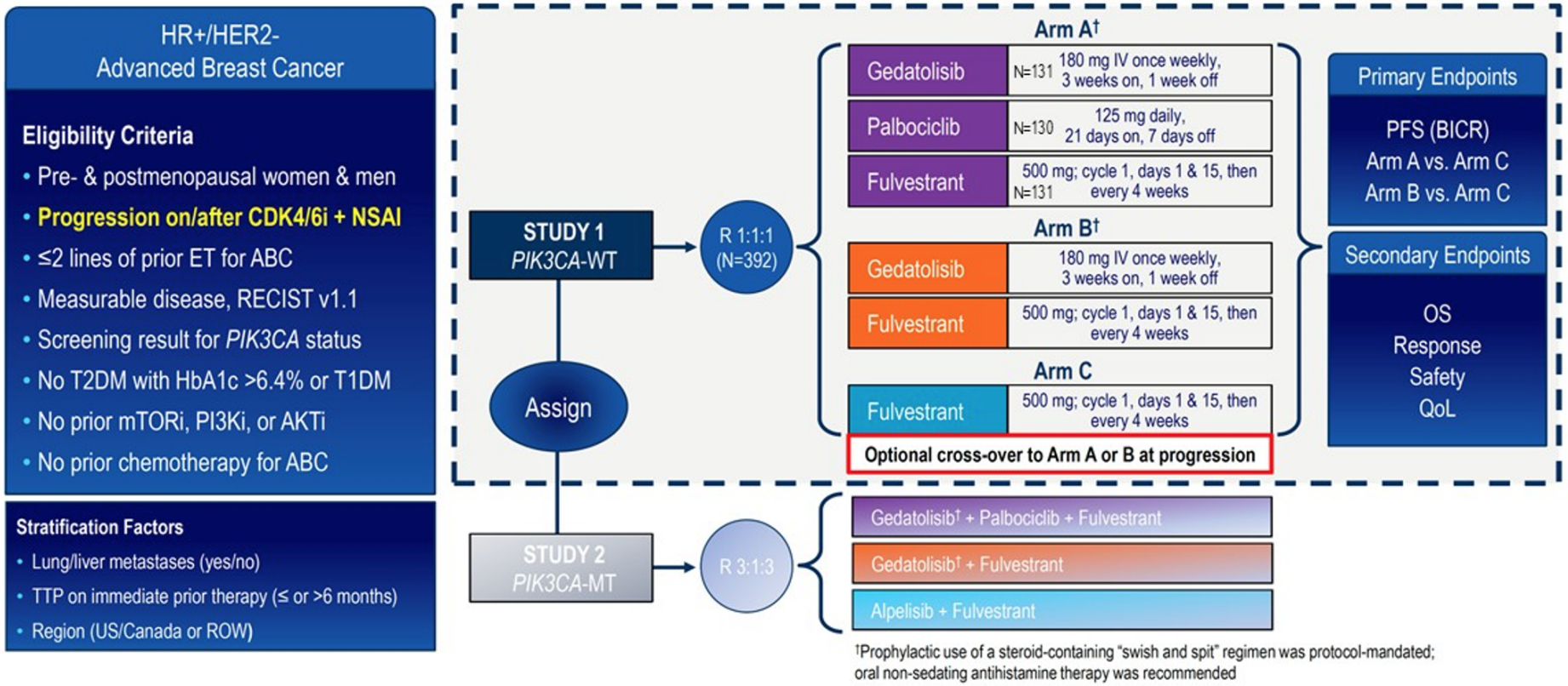
-The PI3K/AKT/mTOR (PAM) pathway drives BC growth and contributes to endocrine and CDK4/6i resistance
- Most available therapies are indicated only for patients with PI3K-pathway activation.

Gedatolisib, a highly potent multitarget PAM inhibitor of all class I PI3K isoforms, mTORC1, and mTORC2.



VIKTORIA-1: GEDATOLISIB, A PAN-PI3K+MTOR INHIBITOR, IN PIK3CA-WT HR+/HER2- ABC

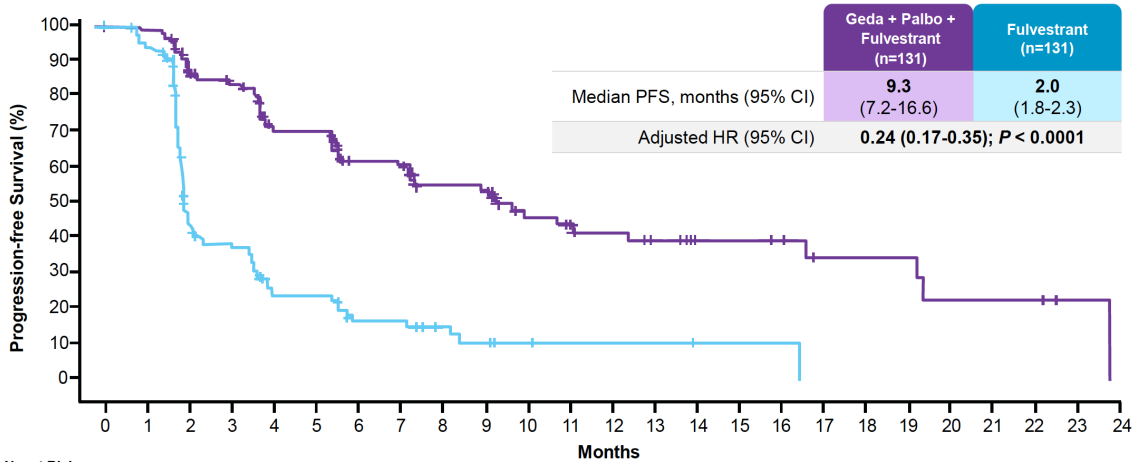
- Visceral met 80%
- TTP prior ET>6m 84%
- Adjuvant CDK4/6i 3%
- Prior CDK4/6i for ABC:
  - Palbociclib 52%
  - Ribociclib 49%
  - Abemaciclib 17%
  - Median duration ~20m



Hurwitz S et al. ESMO 2025

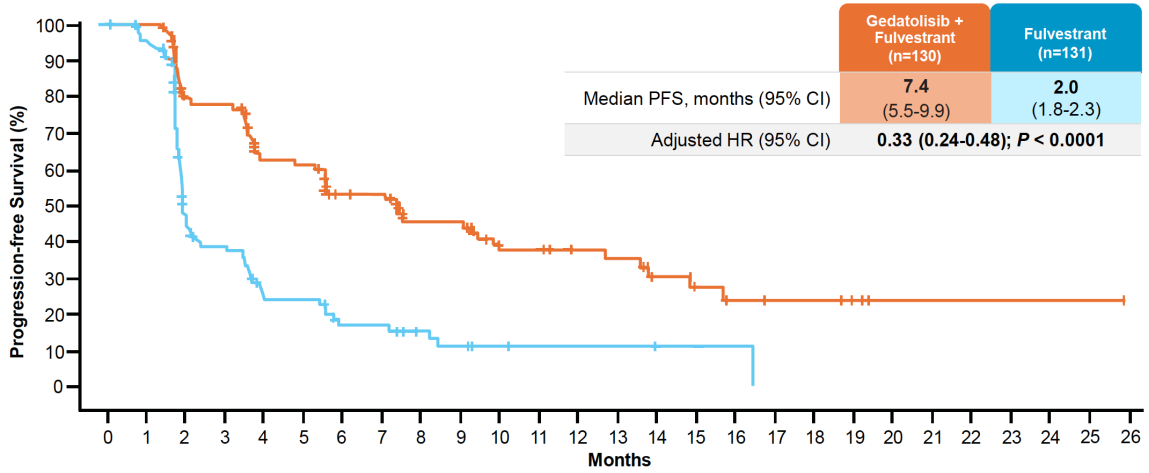
VIKTORIA-1 EFFICACY RESULTS

1st Co-Primary Endpoint: Progression-Free Survival
Gedatolisib Triplet vs. Fulvestrant, BICR Assessment



	Geda + Palbo + Fulvestrant (n=131)	Fulvestrant (n=131)
Median PFS, months (95% CI)	**9.3** (7.2-16.6)	**2.0** (1.8-2.3)
Adjusted HR (95% CI)	**0.24 (0.17-0.35); *P* < 0.0001**	

2nd Co-Primary Endpoint: Progression-Free Survival
Gedatolisib Doublet vs. Fulvestrant, BICR Assessment



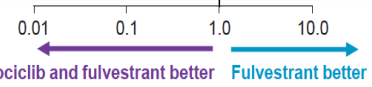
	Gedatolisib + Fulvestrant (n=130)	Fulvestrant (n=131)
Median PFS, months (95% CI)	**7.4** (5.5-9.9)	**2.0** (1.8-2.3)
Adjusted HR (95% CI)	**0.33 (0.24-0.48); *P* < 0.0001**	

These results validate the PAM pathway as a molecular driver in *PIK3CA*-WT disease

VIKTORIA-1 EFFICACY RESULTS

PFS in Key Subgroups: Gedatolisib Triplet vs. Fulvestrant

	Gedatolisib + Palbociclib + Fulvestrant		Fulvestrant		
Subgroup	**n/N**	**mPFS, mo.**	**n/N**	**mPFS, mo.**	**Hazard Ratio (90% CI)**
Age					
<65 years	39/93	9.3	74/108	1.9	0.23 (0.17-0.35)
≥65 years	20/38	9.7	15/23	2.1	0.28 (0.16-0.55)
Menopause status					
Pre/perimenopause	9/28	11.1	26/36	1.8	0.13 (0.07-0.29)
Postmenopause	50/101	8.9	62/92	2.0	0.27 (0.19-0.38)
Geographic area					
US/Canada	6/21	19.3	14/22	2.0	0.13 (0.05-0.36)
Europe	29/57	9.3	32/48	2.0	0.17 (0.12-0.31)
Latin America	16/35	5.6	20/35	3.7	0.53 (0.29-0.90)
Asia Pacific	8/18	16.6	23/26	1.8	0.18 (0.09-0.37)
Presence of visceral metastasis					
Yes	44/102	10.7	71/100	1.8	0.21 (0.16-0.30)
No	15/29	8.9	18/31	5.6	0.35 (0.20-0.71)
Liver metastasis					
Yes	37/74	9.2	60/72	1.8	0.21 (0.14-0.30)
No	22/57	9.9	29/59	5.4	0.31 (0.19-0.53)
Lines of prior tx for ABC					
<2	52/115	9.7	82/118	2.0	0.23 (0.17-0.33)
≥2	7/16	5.4	7/13	1.8	0.31 (0.09-0.99)
TTP on immediate prior tx					
≤6 months	13/26	7.4	13/25	2.1	0.47 (0.24-0.93)
>6 months	46/105	9.9	76/106	1.9	0.20 (0.14-0.28)
Prior CDK4/6i for ABC					
Ribociclib	29/59	8.9	48/70	1.9	0.22 (0.14-0.34)
Palbociclib	21/56	16.6	37/52	1.9	0.21 (0.13-0.35)
Abemaciclib	13/23	5.4	10/16	3.1	0.31 (0.23-0.97)

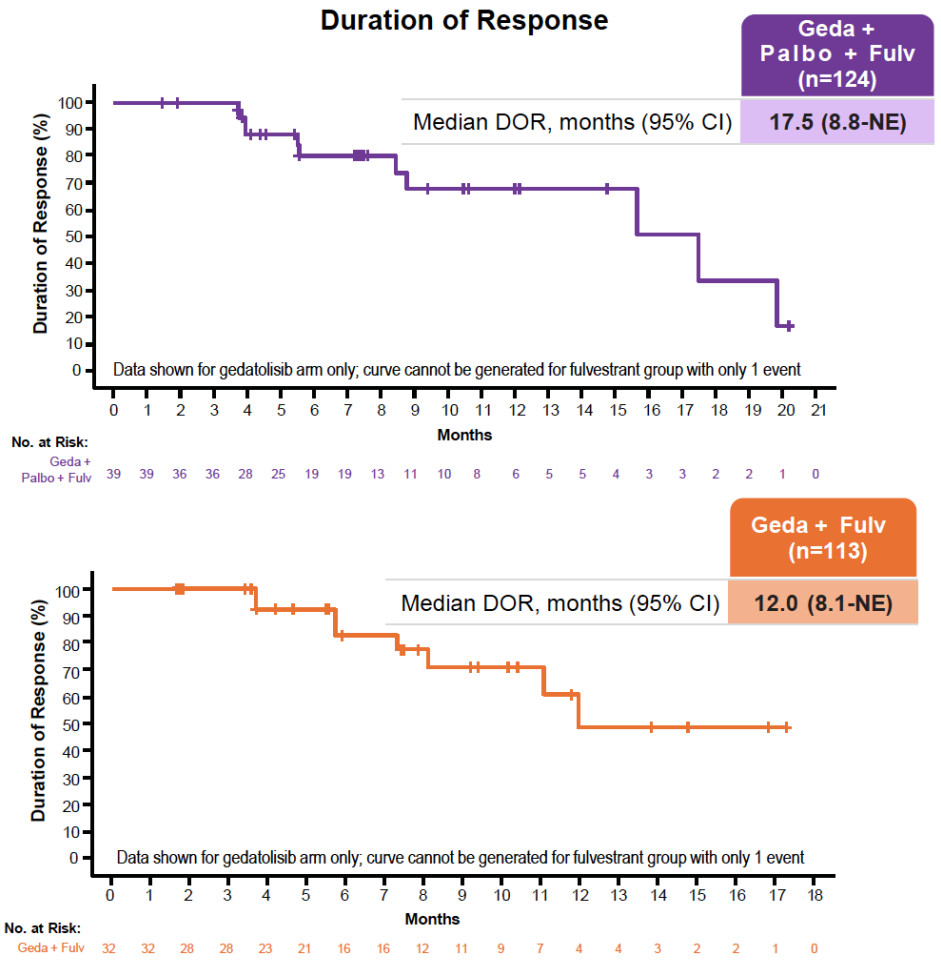


PFS assessed by blinded independent central review

VIKTORIA-1 EFFICACY RESULTS

Endpoint, n (%)	Geda + Palbo + Fulvestrant (n=124)	Gedatolisib + Fulvestrant (n=113)	Fulvestrant (n=105)
Best Overall Response			
Complete response	1 (0.8)	0	0
Partial response	38 (30.6)	32 (28.3)	1 (1.0)
Stable disease	67 (54.0)	55 (48.7)	40 (38.1)
Progressive disease	17 (13.7)	26 (23.0)	62 (59.0)
Not evaluable	1 (0.8)	0	2 (1.9)
Objective Response Rate*	39 (31.5)	32 (28.3)	1 (1.0)
Clinical Benefit Rate†	62 (50.0)	55 (48.7)	12 (11.4)
Disease Control Rate‡	106 (85.5)	87 (77.0)	41 (39.0)
Median DOR, months [95% CI]	17.5 [8.8-NE]	12.0 [8.1-NE]	NR [NE]

*Defined as CR+PR
†Defined as CR+PR+SD >24 weeks as assessed by BICR
‡Defined as CR+PR+SD
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; Fulv, fulvestrant; Geda, gedatolisib; NE, not estimable; no., number; NR, not reached; Palbo, palbociclib; PR, partial response; SD, stable disease.



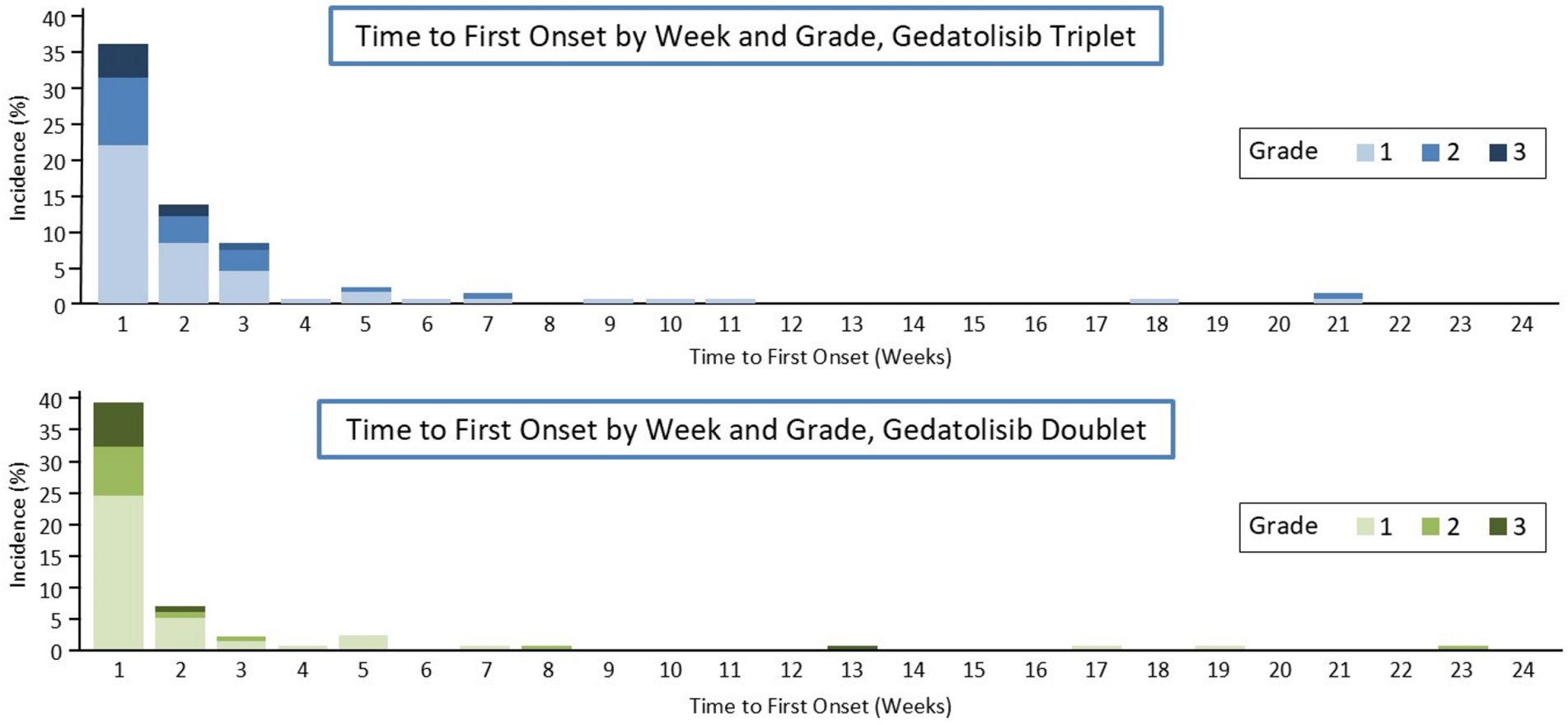
VIKTORIA-1 SAFETY RESULTS

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**

Abbreviations: D/C, discontinued; Pts, patients; SAE, serious adverse event; TRAE, treatment-related adverse event (per investigator)
*Shown are adverse events of any grade that occurred in at least 20% of the patients in any trial group unless otherwise noted
†Grade 5 events include one considered related to palbociclib (pneumonia) and one due to hepatic failure in a patient with multiple liver metastasis considered related to all three drugs (and likely associated with disease)
‡For stomatitis, neutropenia, rash, and hyperglycemia, combined preferred terms shown; if a patient experienced multiple terms, it was counted once for the highest grade.
§Additional events of clinical importance

Presenter: Sara A. Hurvitz, MD, FACP

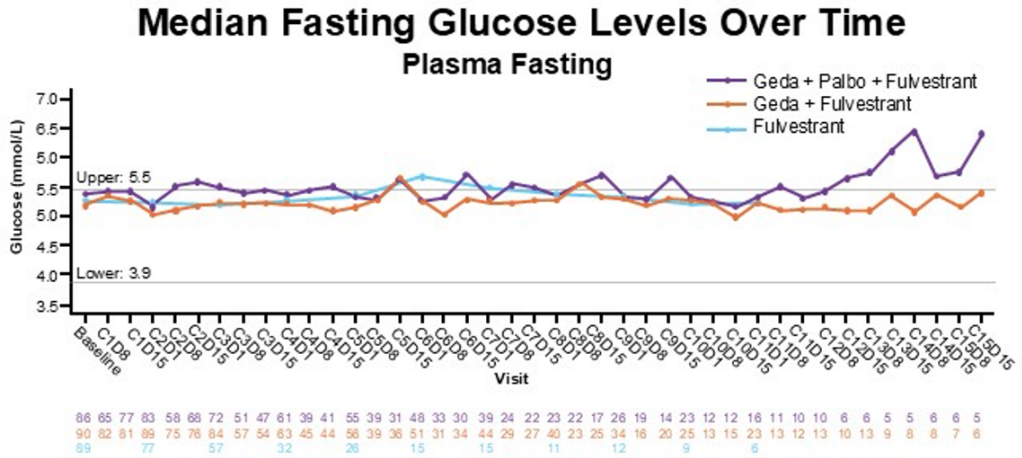
STOMATITIS: TIME TO FIRST ONSET. SAFETY ANALYSIS SET, WEEKS 1-24

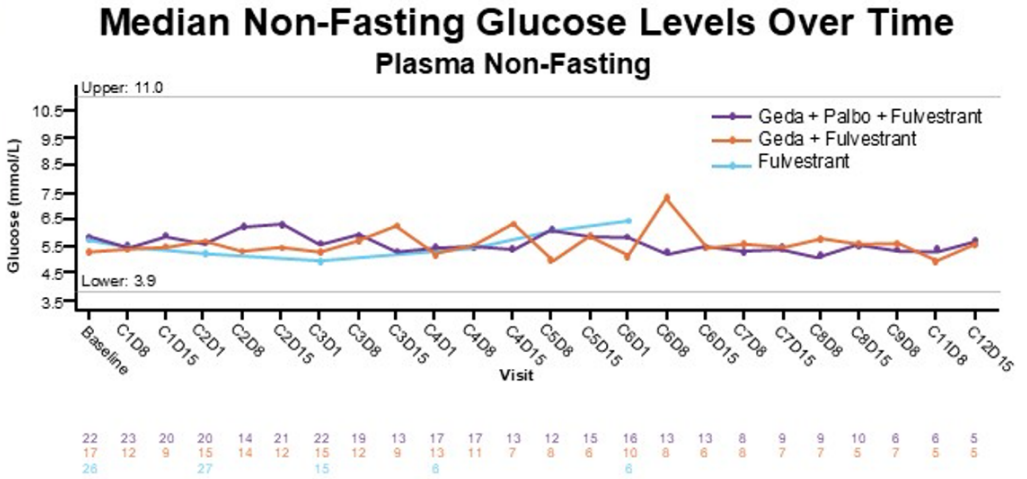


MEDIAN GLUCOSE LEVELS WERE STABLE

Hyperglycemia, n (%)	Geda + Palbo + Fulvestrant (n=130)	Gedatolisib + Fulvestrant (n=130)	Fulvestrant (n=123)
All grades	12 (9.2)	15 (11.5)	0
HbA1c (%), median (range)	n=91	n=89	n=72
Baseline (B)	5.4 (4.1-6.4)	5.4 (4.0-6.3)	5.3 (4.0-6.3)
End of treatment (EOT)	5.9 (4.3-8.8)	5.9 (4.5-14.1)	5.5 (4.6-6.8)
Change, B to EOT	0.5 (-1.6 - 2.9)	0.6 (-0.7 - 8.2)	0.2 (-0.6 - 1.3)

Gedatolisib did not produce clinically relevant hyperglycemia and had no dose reductions or withdrawals due to hyperglycemia





Abbreviations: B, baseline; C, cycle; EOT, end of treatment; Geda, gedatolisib; HbA1c, hemoglobin A1c; Palbo, palbociclib

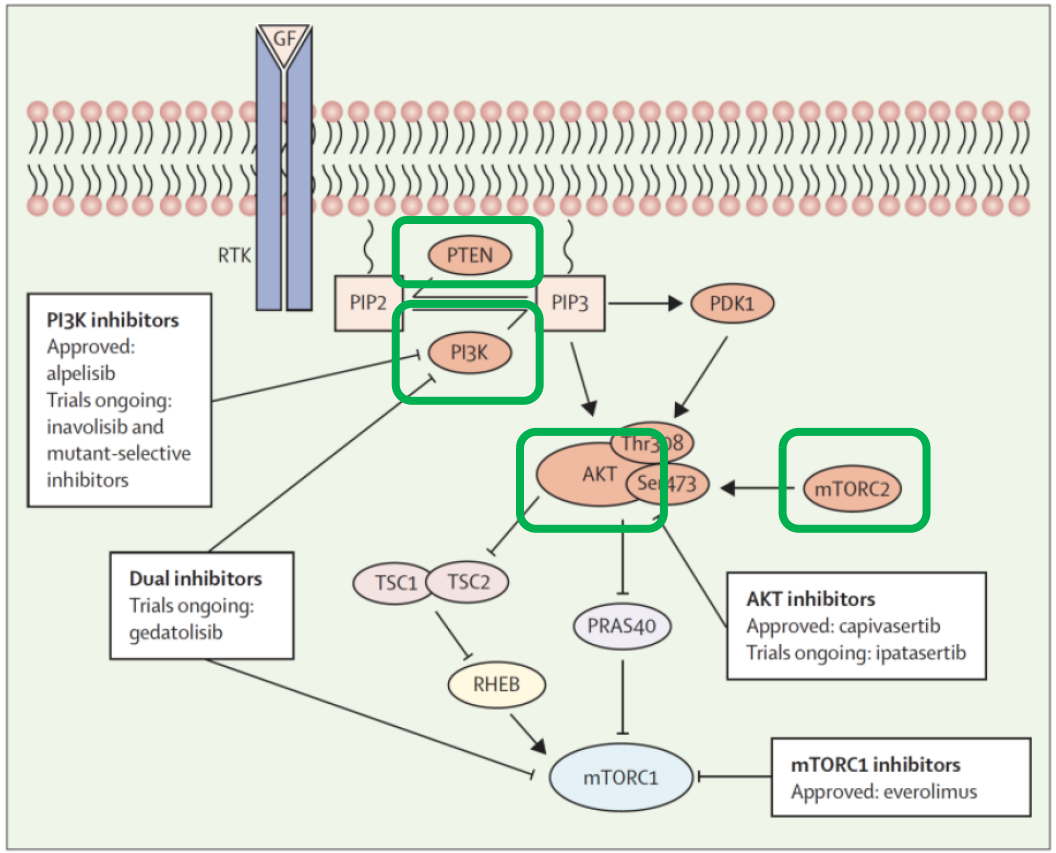
MECHANISMS OF RESISTANCE

HOW TO OVERCOME RESISTANCE?

- USE OF TRIPLETS
- NEW PI3K INHIBITORS
  - ALLOSTERICS INHIBITORS
  - COVALENTS INHIBITORS
- AKT INHIBITORS

THE PI3K/AKT PATHWAY

	HR+/HER2-	HER2+	TNBC
PIK3CA mut	30-50%	30-35%	7-10%
PTEN dysreg	6%	~20%	~15%
AKT1 mut	5%	~2%	~1%



Physiological functions:

- Cell growth and proliferation
- Cell survival and apoptosis inhibition
- Metabolism Regulation: glucose and lipid metabolism
- Neural development and function
- Angiogenesis
- Muscle growth and maintenance
- Immune system regulation

Narrow therapeutic index

Browne IM et al. Lancet Oncol. 2024 Apr:25(4): e139-e151 | TCGA Nature 490:61-70. 2012: Ciriello G. Cell 163:506-19. 2015: Nik-Zainal S. Nature 534:47-54. 2016: Pereira B. Nat Commun 7:11479. 2016

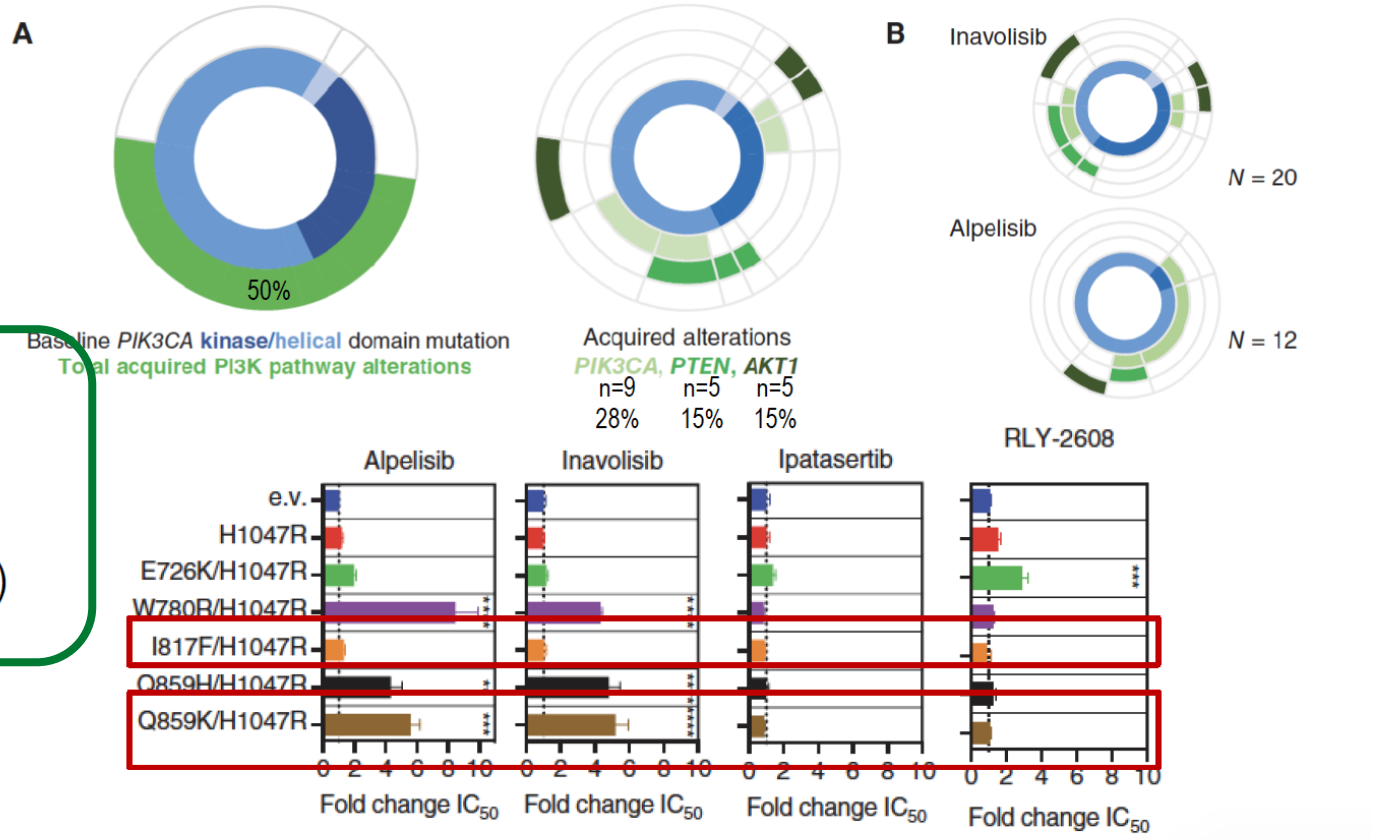
ADDRESSING MECHANISMS OF RESISTANCE

Alterations in the PI3K pathway other than *PTEN* loss mediate resistance to PI3Kα inhibitors

Prospective study of patients treated with inavolisib and alpelisib

N=39

- Paired ctDNA baseline / at PD (n=32)
- Alpelisib and inavolisib (plus fulvestrant)
- Acquired alterations in the PI3K pathway:
  - ***PTEN*** alterations (15%)
  - ***AKT1*** activating mutations (15%)
  - Secondary *PIK3CA* resistance mutations in the catalytic pocket (28%)

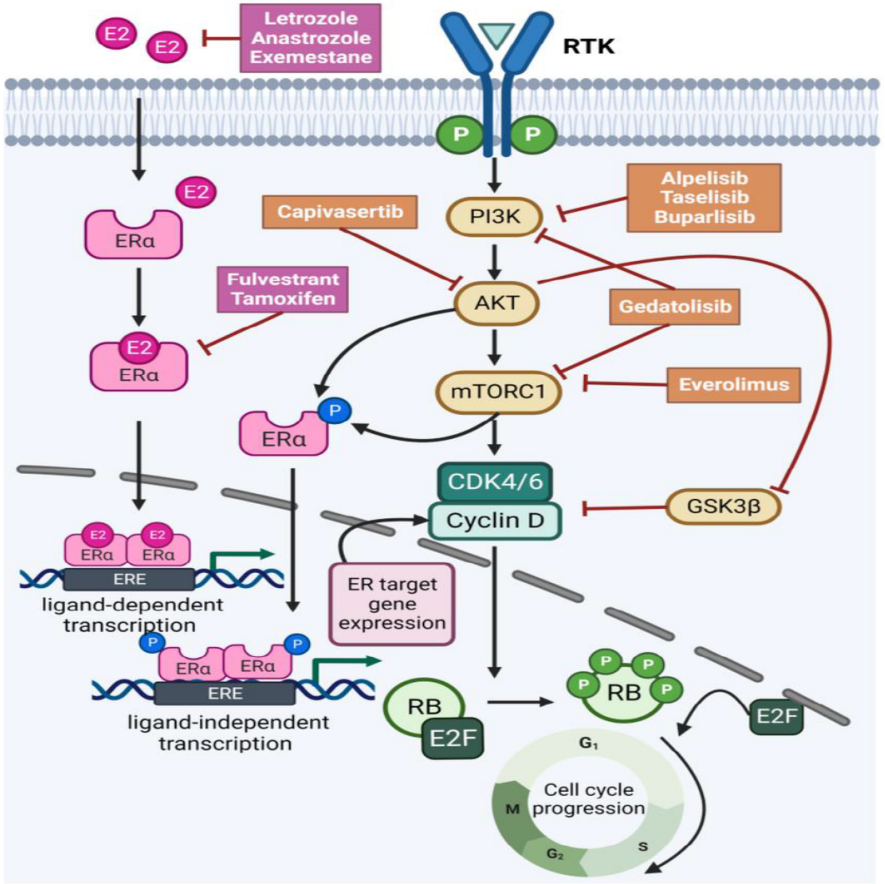


Vaklavas C et al. Cancer Discov 2024

RATIONALE FOR TRIPLE COMBINATION

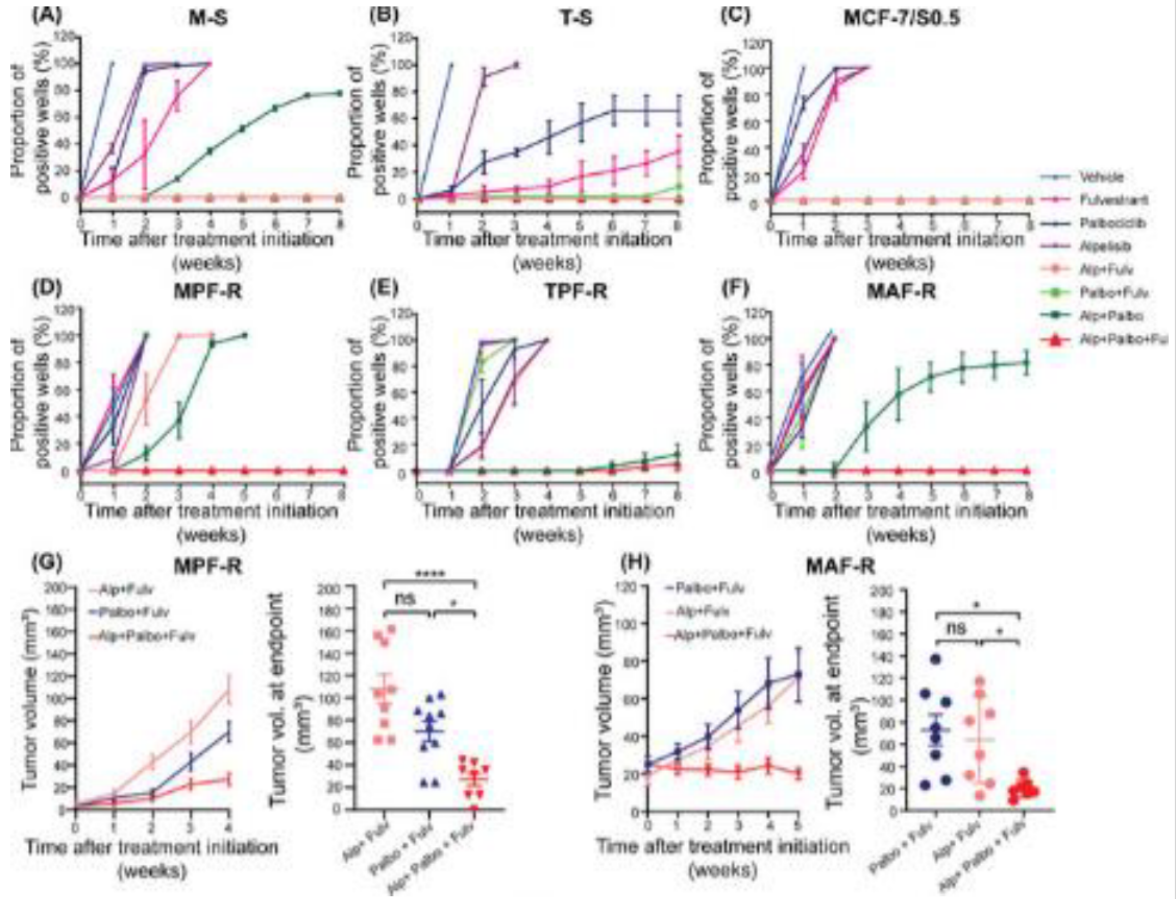
- PI3K activating mutations are the most common (30-40%) finding in endocrine resistant BC
- AKT activation can be caused AT mutations. PTEN loss or upstream PI3K oncogenic mutations.

- **In preclinical models, blocking all three nodes simultaneously - ER, CDK4/6, PI3K – produced synergistic anti-tumor effects, whereas sequential or single-pathway inhibition allowed tumors to adapt and develop resistance.**



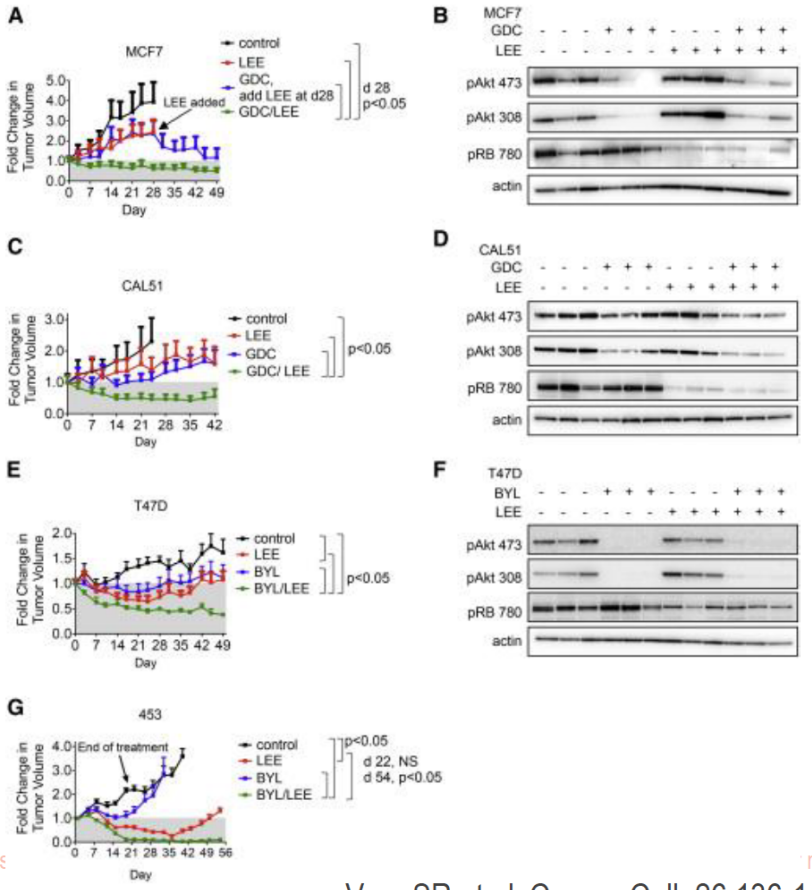
RATIONALE FOR TRIPLE COMBINATION

- Delayed Resistance in Models
  - Triple combination of fulvestrant (ER downregulator) + palbociclib (CDK4/6i) + alpelisib (PI3Kα inhibitor) **prevented or significantly delayed the emergence of resistance** in ER+ cell line xenografts and PDX
- Pathway Downregulation
  - cells that became resistant to one doublet (ET+CDK4/6 or ET+PI3K) remained sensitive to the triplet, whereas alternating between doublets could not overcome resistance



CAN WE IMPROVE THERAPEUTIC TARGETING BY TRIPLET THERAPY?

- CDK4/6 Inhibitors Sensitize PIK3CA Mutant Breast Cancer to P13K Inhibitors
- Combining PI3Ki and LEE011 Overcomes Intrinsic and Acquired Resistance In Vivo



Vora SR et al. Cancer Cell. 26:136-149 2014

SELECTED TRIPLET COMBINATIONS TARGETING ER, CDK4/6, AND PI3K/AKT/MTOR

	TRINITI-1	IPATUNITY 150	NCT03006172	NCT02684032
N	104	20	36 (Arm E, F)	103 (59 Arm C, D)
Phase	I/II	I/III	I/Ib	Ib (dose expansion)
	HR+/HER2- ABC after progression on CDK4/6i	HR+/HER2- ABC after progression on first-line ET or primary endocrine-resistant	Primary endocrine-resistant, PIK3CA-mutated, HR+/HER2− ABC	Previously treated HR+/HER2−ABC; CDK4/6i-pretreated for arms C and D
Treatment arm	Exemestane + Ribociclib + Eeverolimus	Fulvestrant + Palbociclib + Ipatasertib	Fulvestrant + Palbociclib + Inavolisib	Fulvestrant + Palbociclib + Gedatolisib (weekly)(arm C) Fulvestrant + Palbociclib + Gedatolisib (3weeks on, 1 week off)(arm D)
ORR (%) (95% CI)	8.4 (3.7–15.9)	55 (32–77)	40	32 (16–52) 63 (42–81)
CBR (%) (95% CI)	41.1 (31.1–51.6)	95	58	79 (59–92) 96 (81–100)
Median PFS (months) (95% CI)	5.7 (3.6–9.1)	Not mature	Not Reported	5.1 (3.4–7.5) 12.9 (7.4–16.7)

RATIONALE FOR TRIPLE COMBINATION

ET + CDK4/6i + AKT Inhibition

Fulvestrant + CDK4/6 i + Capivasertib

CAPItello-292: A phase Ib/III study of capivasertib, palbociclib and fulvestrant vs placebo, palbociclib and fulvestrant in HR+/HER2− advanced breast cancer

ET + CDK4/6 + PI3K/AKT/mTOR Inhibition

Fulvestrant + Palbociclib + Inavolisib

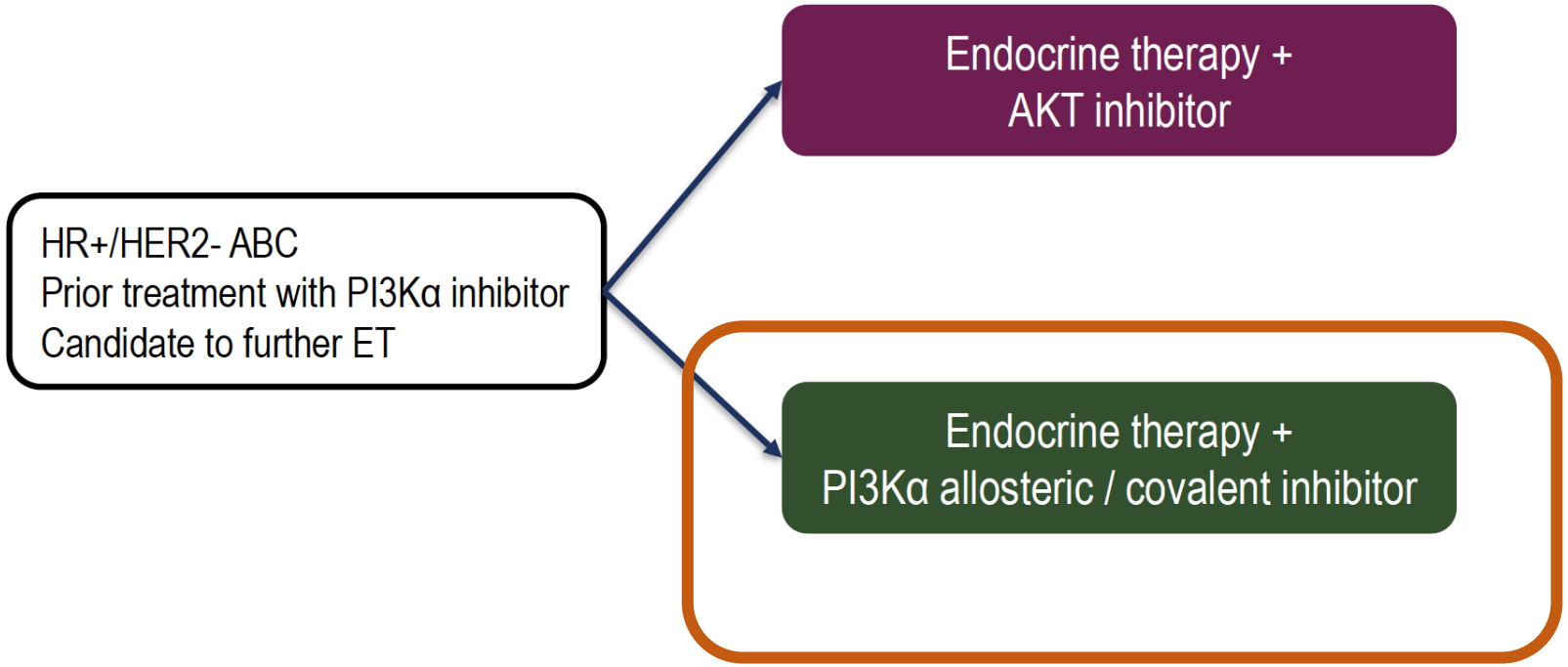
INAVO120 study design

ET +CDK4/6 + PI3K+mTOR Inhibition

Fulvestran+ Palbociclib+Gedatolisisb

VIKTORIA

TREATMENT AFTER PROGRESSION TO PI3KA INHIBITORS



clinical trials needed!

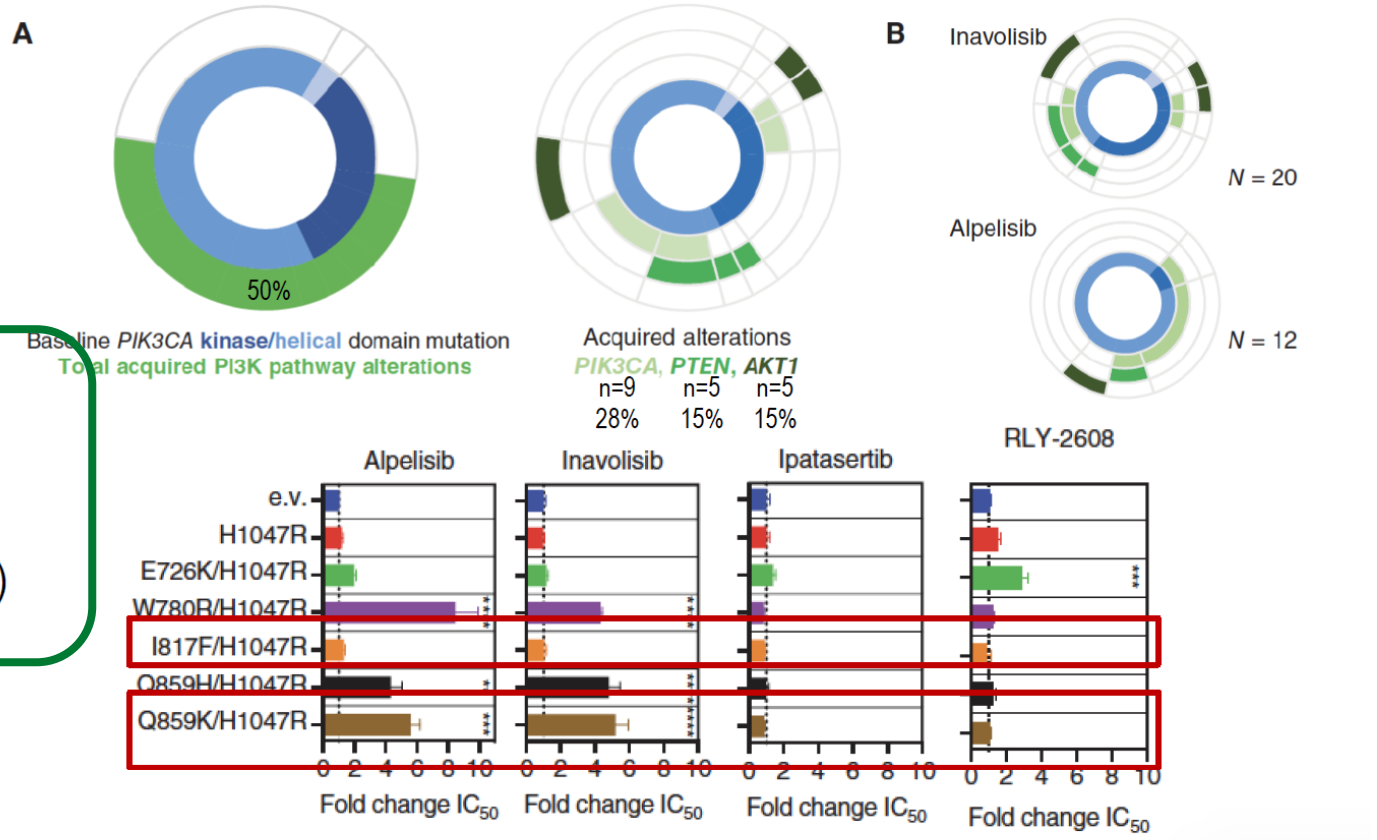
ADDRESSING MECHANISMS OF RESISTANCE

Alterations in the PI3K pathway other than *PTEN* loss mediate resistance to PI3Kα inhibitors

Prospective study of patients treated with inavolisib and alpelisib

N=39

- Paired ctDNA baseline / at PD (n=32)
- Alpelisib and inavolisib (plus fulvestrant)
- Acquired alterations in the PI3K pathway:
  - ***PTEN*** alterations (15%)
  - ***AKT1*** activating mutations (15%)
  - Secondary *PIK3CA* resistance mutations in the catalytic pocket (28%)



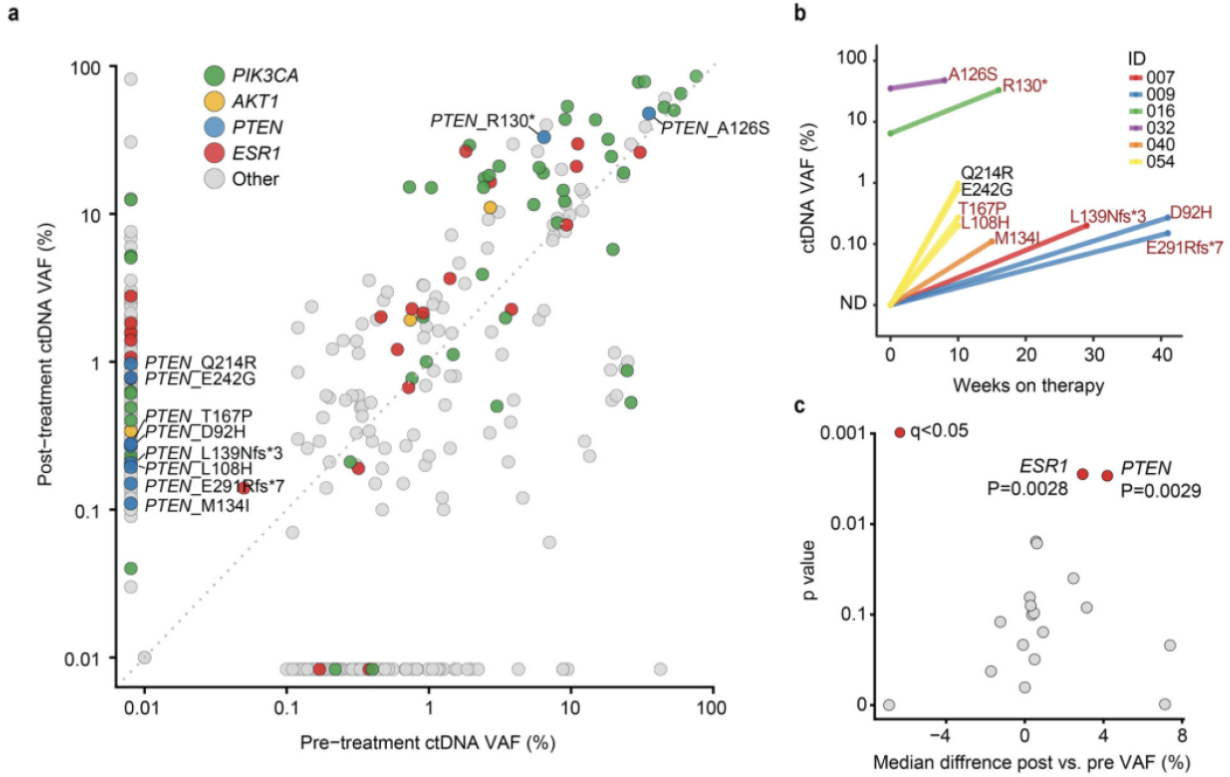
Vaklavas C et al. Cancer Discov 2024

ADDRESSING MECHANISMS OF RESISTANCE

Loss of *PTEN* function mediates resistance to PI3Kα- specific inhibitors

Phase I Alpelisib + AI (NCT01870505)
N=51

- ctDNA baseline / at PD
- ***PTEN*** mutations in 25% of acquired resistance to alpelisib
- ***ESR1*** mutations also enriched at PD sample



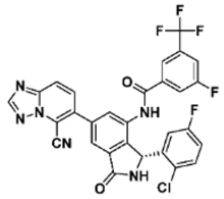
Razavi P et al. Nat Cancer 2020;1(4):382–393

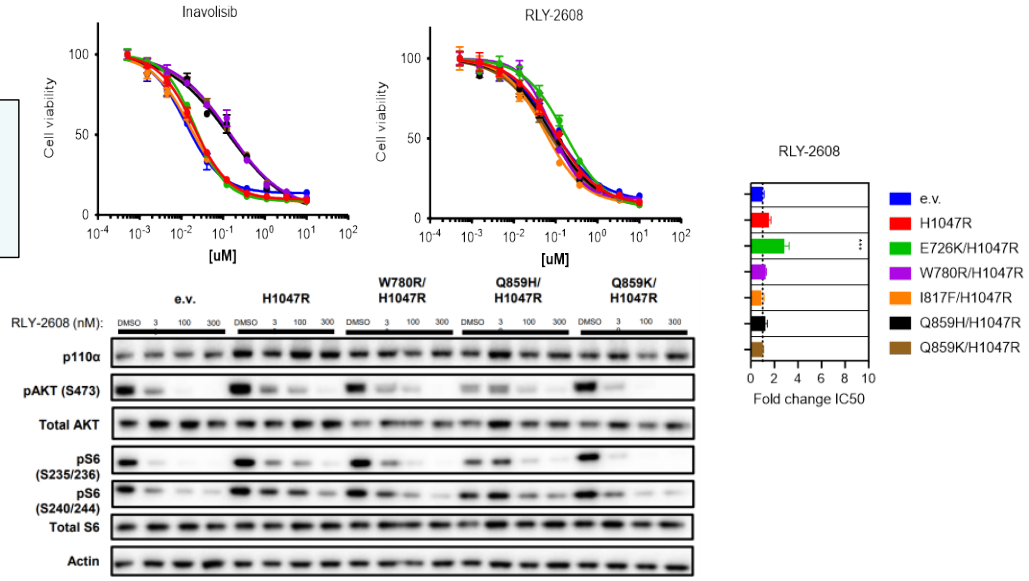
Allosteric mutant selective PIK3CA inhibitors overcome resistance due to acquired PIK3CA mutations

- Reactivation of PI3K signaling represents a dominant mode of acquired resistance to alpelisib and inavolisib, present in nearly half of patients and **involving acquired PTEN loss, activating AKT1 mutations and secondary PIK3CA mutations**.
- **Acquired secondary PIK3CA mutations drive resistance by altering affinity of alpelisib and inavolisib for PI3K-alpha**.

- **Los nuevos inhibidores alostéricos de PI3K y de AKT pueden superar la resistencia provocada por estas alteraciones adquiridas de PIK3CA**

RLY-2608:
Pan-mutant selective allosteric PIK3CA inhibitor





Andreas Varkaris, SABCS 2023

SELECTED OTHER PI3K AGENTS IN DEVELOPMENT

PI3K inhibitor	Company	Type	Status
CYH33	Haihe Biopharma	PI3Ka inhibitor	Phase 2
JS105	Junshi Biosciences	PI3Ka inhibitor	Phase 1/ 2
Serabelisib	Faeth Therapeutics	PI3Ka inhibitor	Phase 2
TOS-358	Totus Medicines	PI3Ka inhibitor	Phase 1
RLY-2608	Relay Therapeutics	Pan mutant selective PI3Ka inhibitor	Phase 3 planned
CGT6297	Cogent	PI3Ka H1047R mutant specific	Preclinical
OKI-219	OnKure	PI3Ka H1047R mutant specific	Phase 1
LOXO-783	Eli Lilly	PI3Ka H1047R mutant specific	Discontinued
LY4045004	Eli Lilly	PI3Ka H1047R and E545K mutant	Preclinical
BBO-1023	BridgeBio	PI3Ka:RAS interaction blocker	Phase 1

Las mutaciones de PI3K más frecuentemente expresadas fueron la H1047R en 19% y E542K 15%

STX-478 MUTANT SELECTIVE PI3KA INHIBITOR

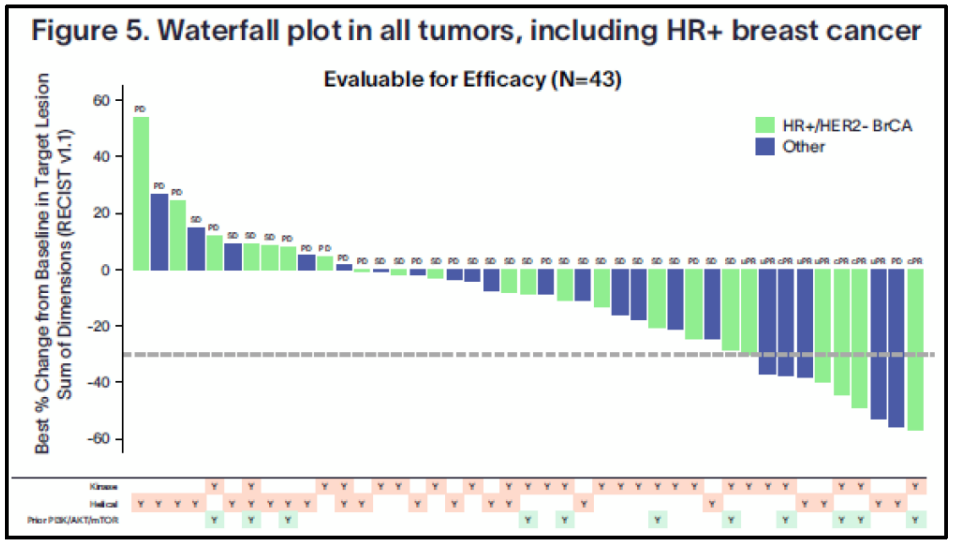
STX-478 is an allosteric, oral, CNS-penetrant, that targets mutant PI3Kα

Ph 1/ 2 study - Monotherapy

- PIK3CA helical or kinase domain mutant advanced solid tumors (including BC)
- Fasting glucose < 140 mg/dL and HbA1c < 7.0%
- Type 2 DM on meds permitted
- Prior PI3K/AKT/mTORi permitted if stopped due to intolerance

CDK 4/6i treated* HR+/HER2- MBC (n=29)
Prior fulvestrant/SERD: 72%
Prior chemo 90%
Prior PI3K/Akt/mTORi: 41%

Safety: No grade ≥3 hyperglycemia, diarrhea and rash
Hyperglycemia: all grades: 23%
Fatigue: all grades 30% G3: 8%
Rash: all grades 10%
Diarrhea: all grades 15%



✓ Encouraging efficacy
Monotherapy ORR exceeds approved PI3K pathway inhibitors
Activity against PIK3CA kinase and helical domain mutations

✓ Improved safety profile
Decrease in hyperglycemia, rash, and diarrhea compared to other PI3 inhib

Juric D et al. SABCS 2024

LOXO-783: ALLOSTERIC PI3Kα H1047R-SELECTIVE INHIBITOR

Phase I Trial PIKASSO-01: LOXO-783 as monotherapy and in combination with ET

N=193 (163 with HR+/HER2- breast cancer)

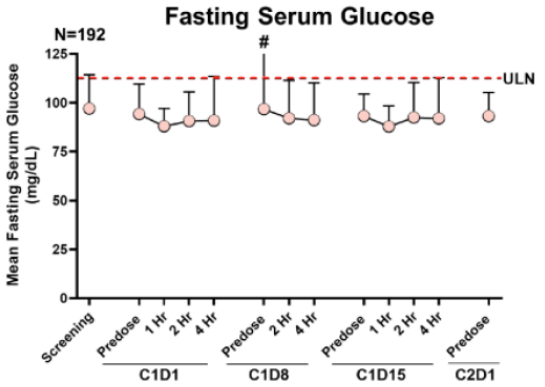
- Prior therapies: median 2 (1-7)
- Prior CDK4/6i 76%; SERD 42%; chemo/ADC 71%; mTOR/PI3K/AKT inhibitor 7%

Efficacy: ORR

- Single agent (n=31): 3%
- LOXO-783 + ET (n=79): 6%
- LOXO-783 + Paclitaxel (n=17): 24%
- LOXO-783 + ET + Abemaciclib (n=18): 17%

Treatment-Emergent AEs (≥25%), All Doses and Patients (N=193)[a]

	LOXO-783 (n=45)		LOXO-783 + ET (n=104)[b]		LOXO-783 + Paclitaxel (n=20)		LOXO-783 + ET + Abemaciclib (n=24)	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Diarrhea	34 (76)	4 (9)	93 (89)	6 (6)	17 (85)	1 (5)	17 (71)	5 (21)
Nausea	14 (31)	-	32 (31)	1 (1)	7 (35)	-	11 (46)	-
Anemia	12 (27)	4 (9)	25 (24)	7 (7)	12 (60)	4 (20)	7 (29)	-
Fatigue	11 (24)	1 (2)	37 (36)	1 (1)	7 (35)	1 (5)	9 (38)	-
Vomiting	8 (18)	-	13 (13)	1 (1)	4 (20)	-	9 (38)	-
Neutropenia	6 (13)	1 (2)	13 (13)	-	15 (75)	11 (55)[e]	11 (46)	6 (25)
WBC decreased	4 (9)	-	6 (6)	1 (1)	7 (35)	6 (30)	4 (17)	3 (13)
Arthralgia	4 (9)	-	16 (15)	-	5 (25)	-	1 (4)	-
Neuropathy peripheral[c]	3 (7)	-	6 (6)	-	9 (45)	1 (5)	-	-
AEs of special interest								
Rash[d]	9 (20)	-	22 (21)	1 (1)	3 (15)	-	4 (17)	-
Hyperglycemia	2 (4)	-	3 (3)	-	-	-	2 (8)	-
Dose holds due to TEAEs	13 (29)		28 (27)		18 (90)		15 (63)	
Dose reductions due to TEAEs	4 (9)		6 (6)		8 (40)		5 (21)	
Discontinuations due to TEAEs	3 (7)		2 (2)		5 (25)		1 (4)	



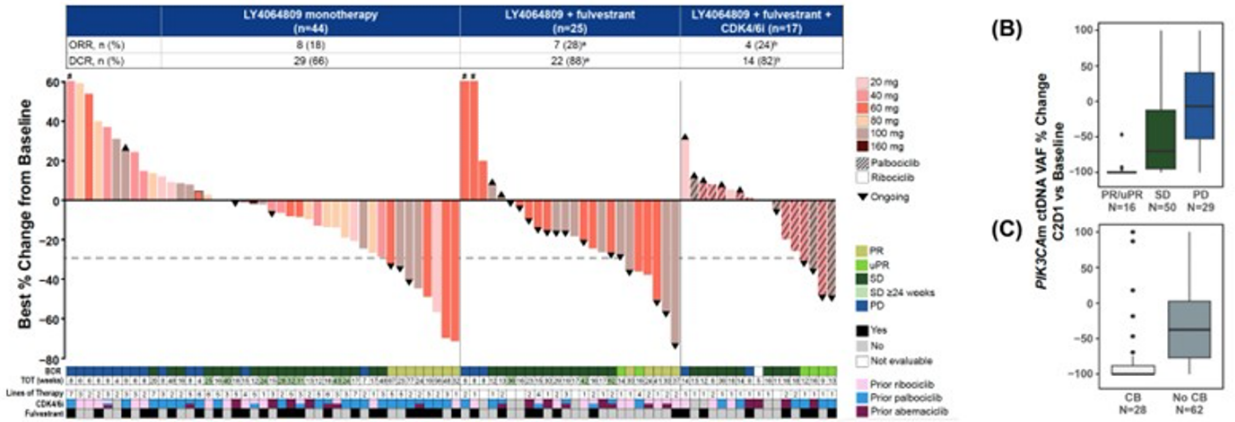
Jhaveri K et al. SABCS 2024

ALLOSTERIC MUT-SELECTIVE PI3KA-I: LY4064809

N=121 HR+/HER2- breast (205 included)

- Median 2 (0-7) prior therapies for MBC
- CDK4/6i 84%; SERD 51%; chemo/ADC 31/11%; mTOR/PI3K/AKT inhibitor 8%

AEs of interest	All	G3
Hyperglycemia	31%	<1%
Nausea	30%	<1%
Diarrhea	25%	<1%
ALT/AST increase	24%	8%
Rash	4%	-
Dose reductions	9%	

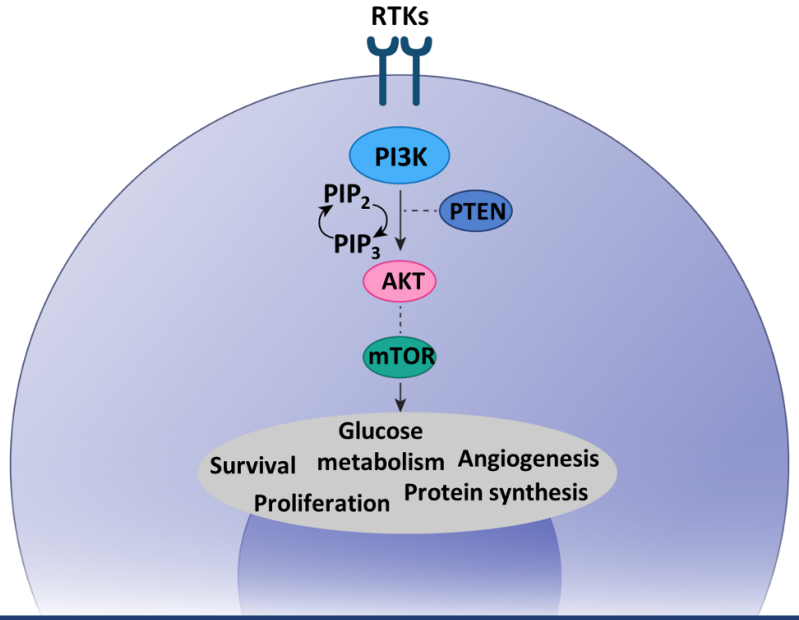


PIKALO-2: Phase III trial of LY4064809 in combination with endocrine therapy and CDK4/6 inhibitors (NCT07174336)

Juric D et al. ESMO 2025

RLY-2608 - THE 1ST MUTANT-SELECTIVE PI3KA INHIBITOR FOR HR+/HER2- BREAST CANCER

Mutant PI3Kα occurs in approximately 40–47% of HR+ BCs[1-3]



Alterations in PI3K signaling are frequently observed in breast cancer[4,5] and are associated with poor prognosis in cancer[6]

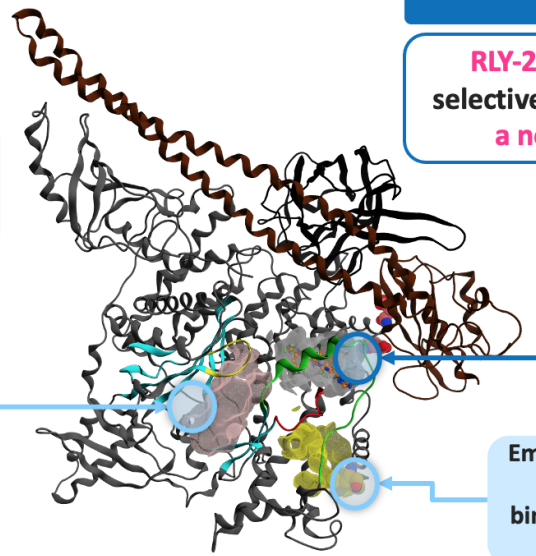
RLY-2608's novel MOA selectively targets mutant PI3Kα[7]

RLY-2608

RLY-2608, a pan-mutant–selective PI3Kα inhibitor, binds a novel allosteric site

Non–mutant-selective PI3Kα inhibitors (alpelisib, inavolisib) bind the orthosteric (active) site

Inhibit both WT and mutant PI3Kα



Emerging H1047R-specific PI3Kα inhibitors bind *only* H1047R hotspot mutation

Non-selective downstream pathway inhibitors (capivasertib, everolimus) do not bind PI3Kα

RLY-2608: ALLOSTERIC PI3Kα INHIBITOR

Phase I ReDiscover Trial

N=118 (64 treated at RP2D)

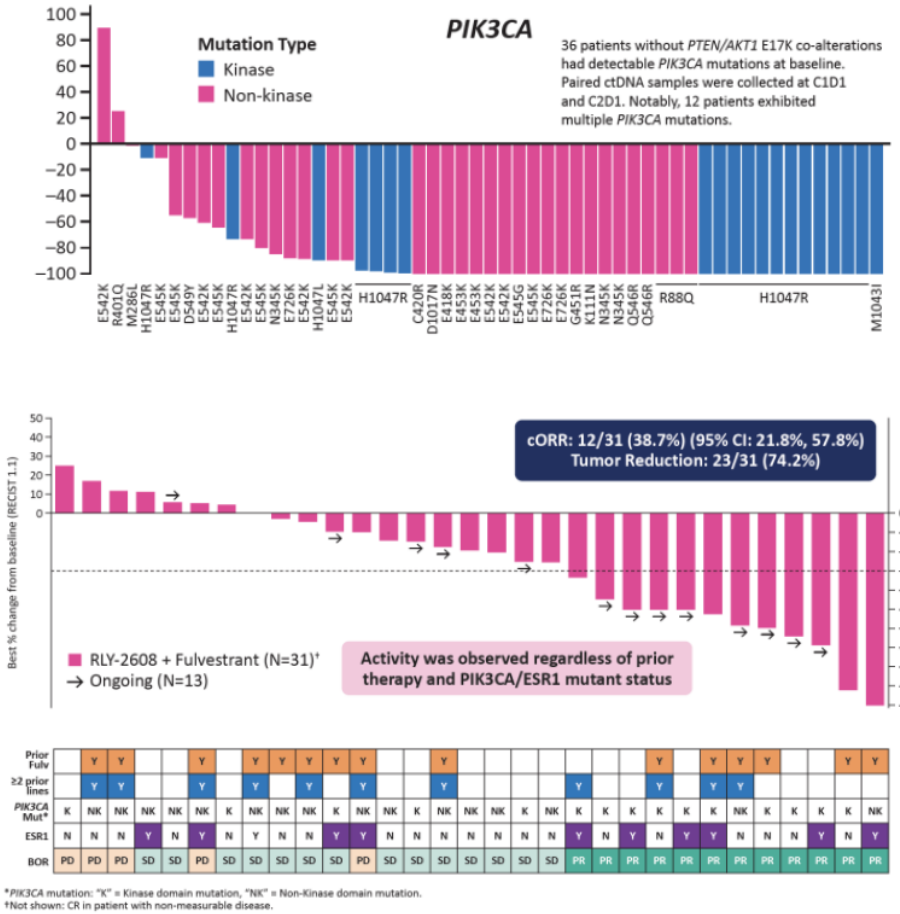
- Median prior lines of therapy: 1 (48% 2+)
- Prior therapies: CDK4/6i 100%; Fulvestrant/novel SERD 56%; chemo/ADC 25%
- PTEN / AKT1mut 21%

		All Patients (N=118)		600mg BID (RP2D, N=64)	
		All Grades	Grade 3	All Grades	Grade 3
Any TRAE, %		92.4	25.4	93.8	31.3
TRAEs ≥15% of 600 mg BID	Hyperglycemia*	42.4	2.5	46.9	3.1
	Nausea	41.5	0.8	50.0	1.6
	Fatigue*	40.7	8.5	35.9	9.4
	Creatinine Increased	34.7	0.8	34.4	1.6
	Diarrhea	30.5	1.7	35.9	3.1
	Decreased Appetite	16.9	0	20.3	0
	Headache	15.3	0.8	20.3	0
	Hypokalemia*	15.3	1.7	17.2	1.6
	Vomiting	12.7	0	15.6	0
Other select TRAEs	Rash*	11.9	0.8	10.9	1.6
	Stomatitis	3.4	0.8	4.7	0
No Grade 4–5 TRAEs					

*Hyperglycemia includes the MedDRA v26.0 Preferred Terms (PT): Hyperglycemia, Blood Glucose Increased, Glucose Tolerance Impaired; Fatigue includes the PTs: Fatigue, Asthenia; Hypokalemia includes the PTs: Hypokalemia and blood potassium decreased; Rash includes the PTs: Rash, Rash Macular, Rash Maculo-Papular.

Median **PFS 9.2 months** (95% CI: 5.8–18.4) across mutation types

Rapid decline in mutant ctDNA at RP2D across mutations



Saura C et al. SABCS 2024

RLY-2608: ALLOSTERIC PI3Kα INHIBITOR

Phase III ReDiscover-2 Trial

Eligibility Criteria:

- HR+/HER2- advanced Breast Cancer
- Any *PIK3CA* mutation with no known PTEN or AKT mutation
- HbA1c <7% and fasting plasma glucose <140 mg/dL at baseline
- 1 prior CDK4/6 inhibitor in either metastatic or adjuvant[1] setting
- Up to 1 prior chemotherapy[2] (no prior ADC)
- 1 or 2 prior endocrine therapies
- 6 months or longer duration of therapy on frontline ET regimen

R 1:1

N=540

RLY-2608 (400 mg BID Fed) + fulvestrant

Capivasertib (400 mg BID 4 days on, 3 days off) + fulvestrant

Stratification: PIK3CA mutation type, visceral disease, geography

Key Primary Endpoints (hierarchical): PFS (kinase), PFS (overall)
Key Secondary Endpoint: OS
Additional Secondary Endpoints: ORR, DoR, CBR, QoL

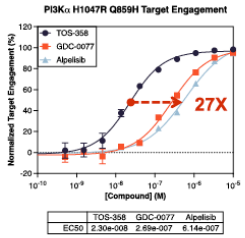
Phase 3 trial initiation expected in mid-2025

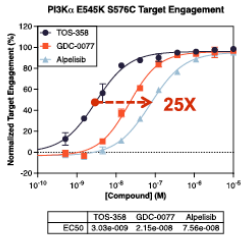
Relay Therapeutics Corporate Presentation, May 5th, 2025

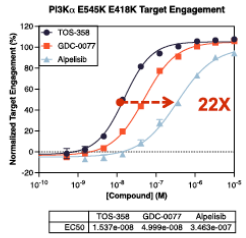
TOS-358: COVALENT PI3Kα INHIBITOR

Phase I Trial (NCT05683418): TOS-358 as monotherapy and in combination with ET

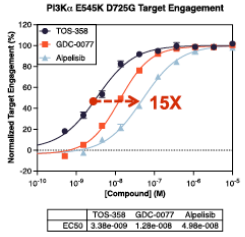
Inavolisib resistant mutations

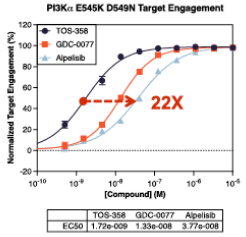


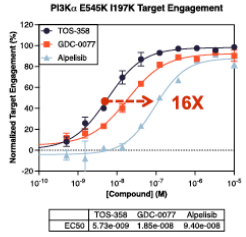


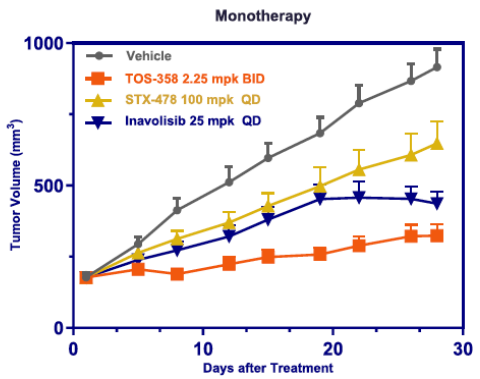


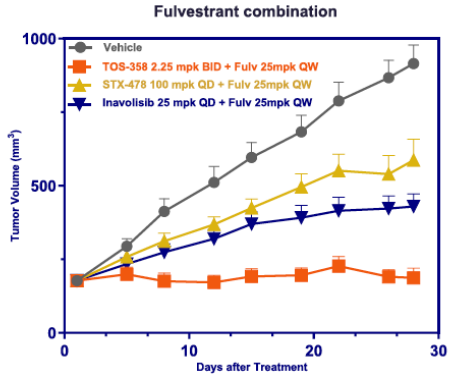
Alpelisib resistant mutations







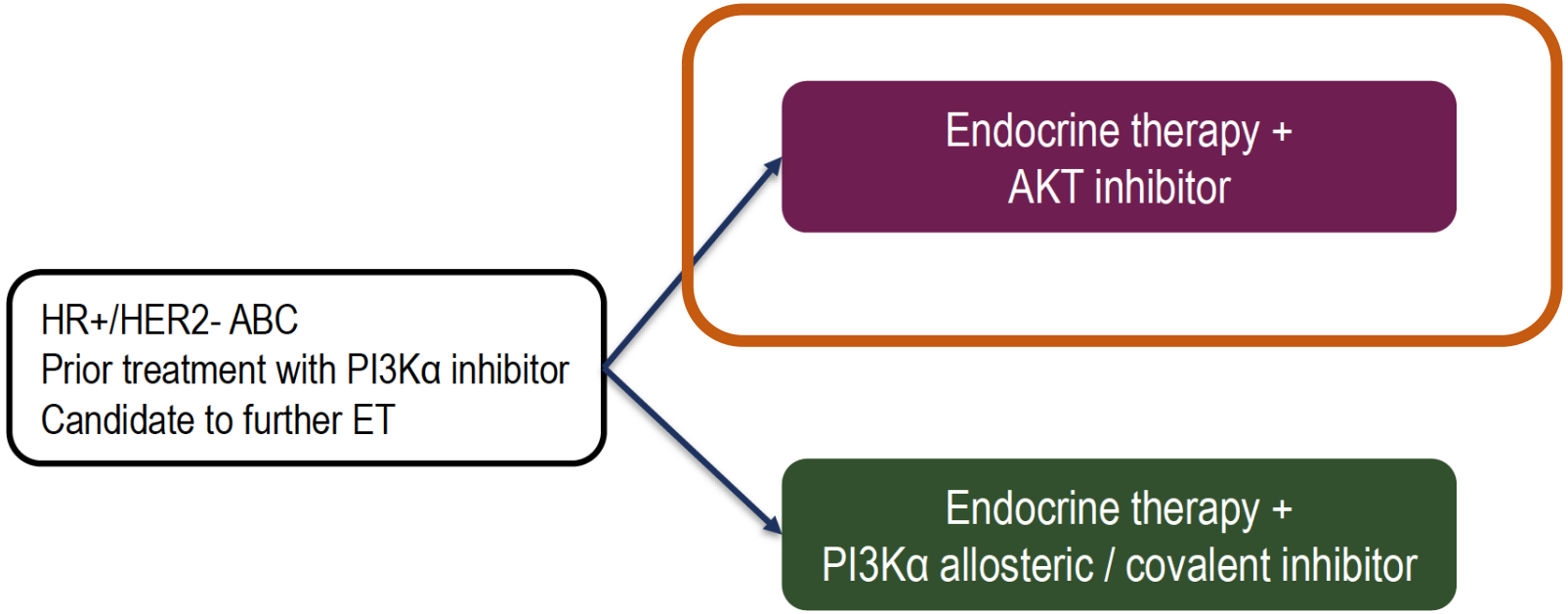




	Patients who received 5 or 8 mg BID (N=25)					
Preferred term	**Any Grade**		**Grade 1/2**		**Grade 3**	
	N	%	N	%	N	%
Hyperglycemia	13	52%	12	48%	1*	4%
Dyspepsia	3	12%	3	12%	0	0%
Diarrhea	2	8%	2	8%	0	0%
Fatigue	2	8%	2	8%	0	0%
Nausea	2	8%	2	8%	0	0%
Decreased appetite	2	8%	2	8%	0	0%
Dry mouth	2	8%	2	8%	0	0%
Asthenia	2	8%	2	8%	0	0%
Glucose tolerance impaired	2	8%	2	8%	0	0%

Courtesy of TOTUS Medicines

TREATMENT AFTER PROGRESSION TO PI3KA INHIBITORS



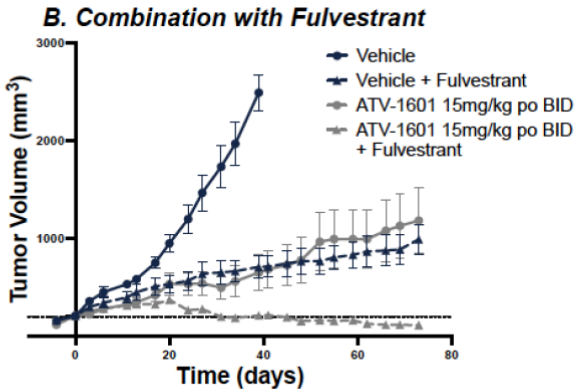
clinical trials needed!

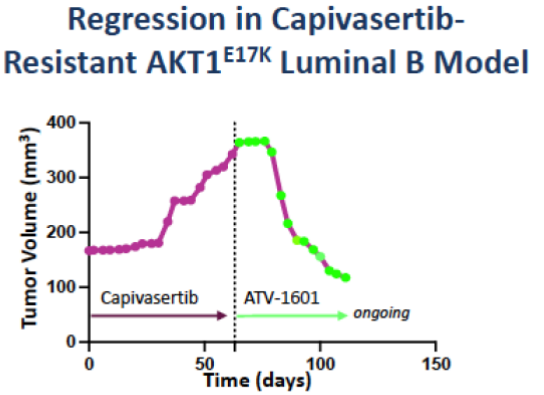
ATV-1601: SELECTIVE ALLOSTERIC INHIBITOR OF AKT1

Higher selectivity for AKT1 over AKT2

Parameter (IC_{50}, uM)	ATV-1601	Capivasertib
$AKT1^{E17K}$	0.06	0.46
AKT2	1.15	0.09
Selectivity $AKT1^{E17K}$/AKT2	20x	<1x
AKT1	0.39	0.06
Selectivity $AKT1^{E17K}$/AKT1	7x	<1x

Activity in $AKT1^{E17K}$ ER+/HER2- Breast Cancer PDX models

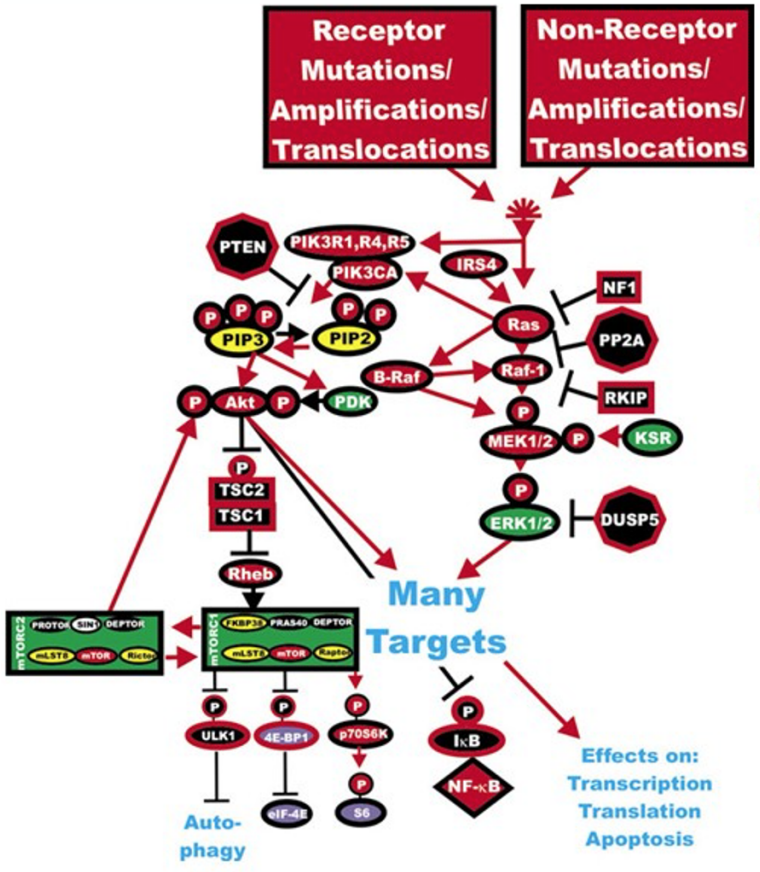


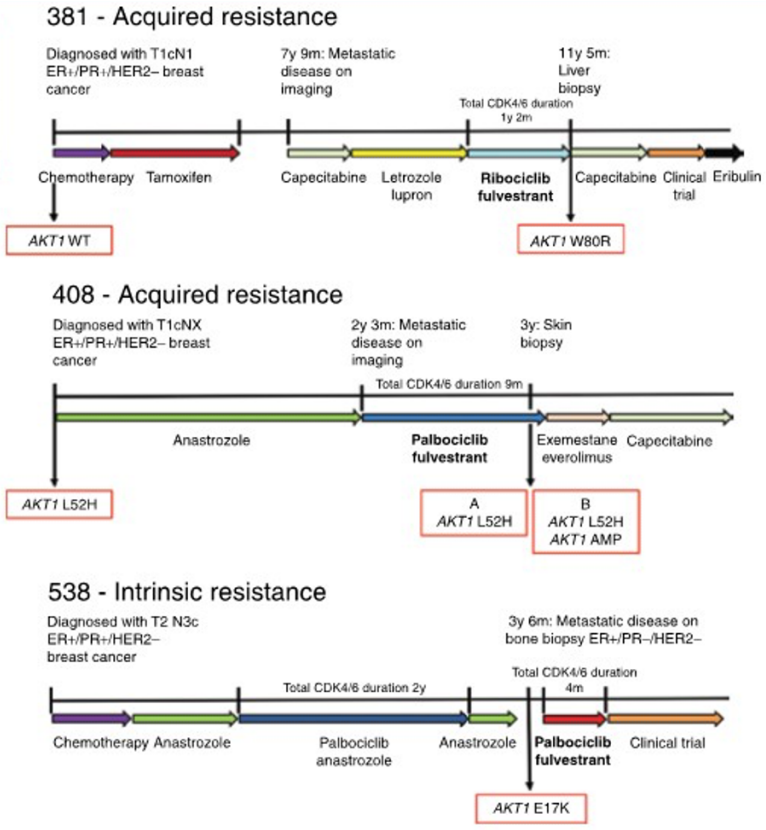


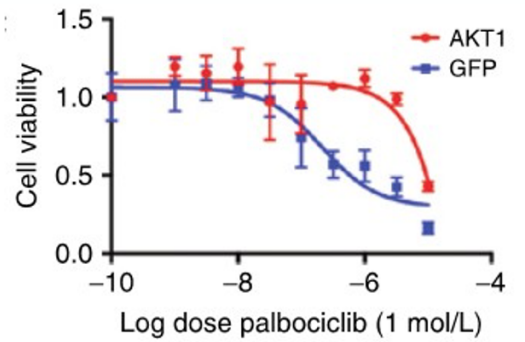
IND enabling and Phase I trial planned

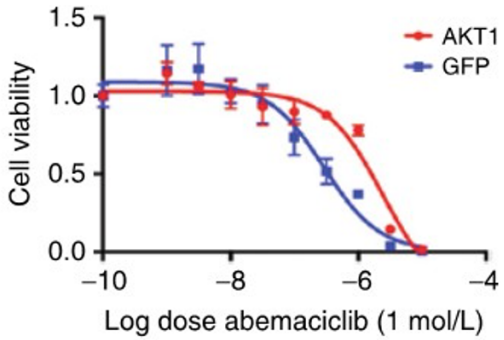
Schinzel C et al. SABCS 2024

AKT1 ONCOGENIC SIGNALING (VIA AKT1 DIRECTLY)





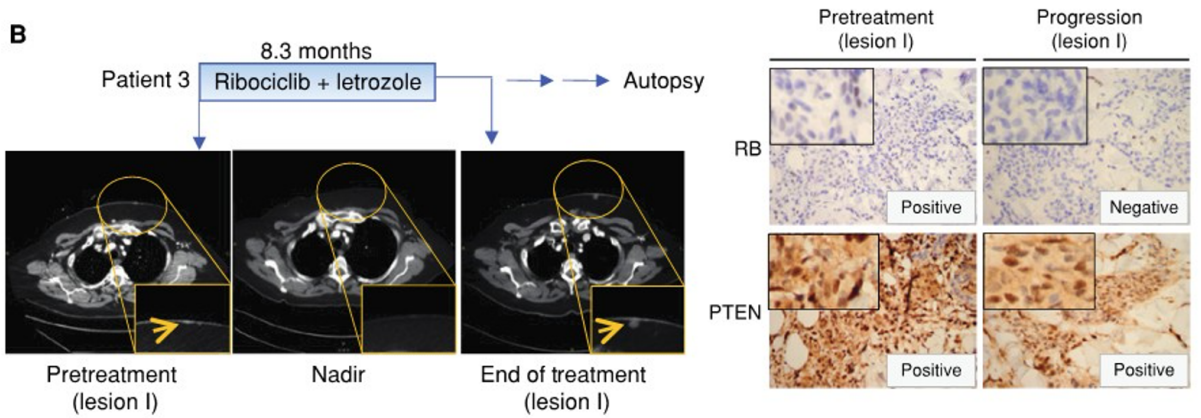


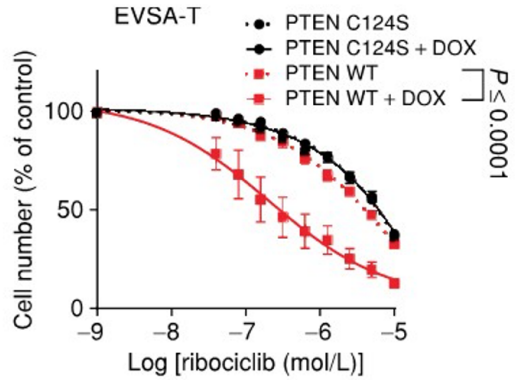


- Multiple distinct AKT1 alterations noted via WES in CDK4/6i resistant tumor biopsies
- AKT1 overexpression provoked CDK4/6i resistance *in vitro*

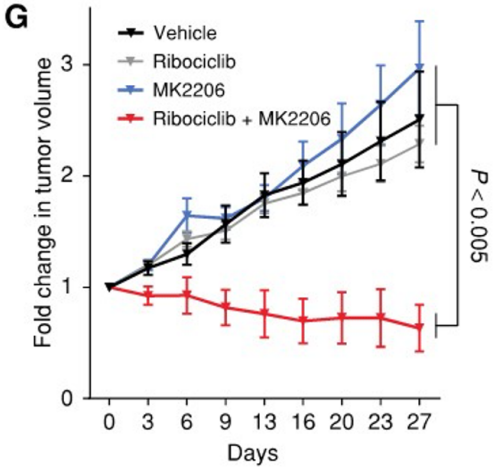
McCubrey JA et al Oncotarget 2012;
Wander SA et al Canc Disc 2020

AKT1 ONCOGENIC SIGNALING (VIA PTEN)



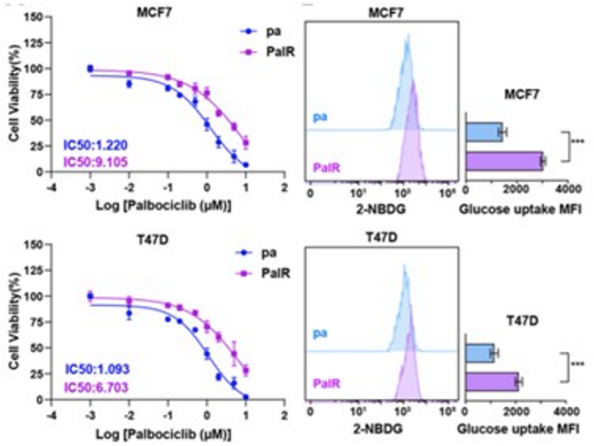


- Tumor specimens following ribociclib resistance demonstrated loss of PTEN expression
- PTEN disruption promoted CDK4/6i resistance *in vitro* via downstream AKT1 activation
- AKT1 inhibition (+CDK4/6i) promoted tumor regression in PTEN-null tumors *in vivo*

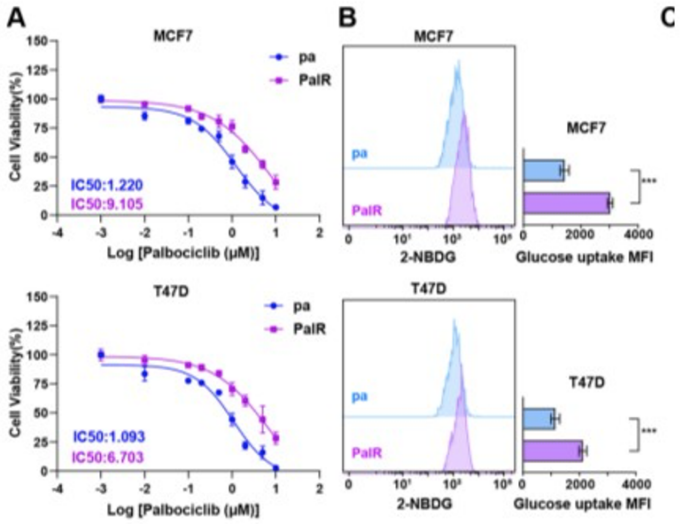


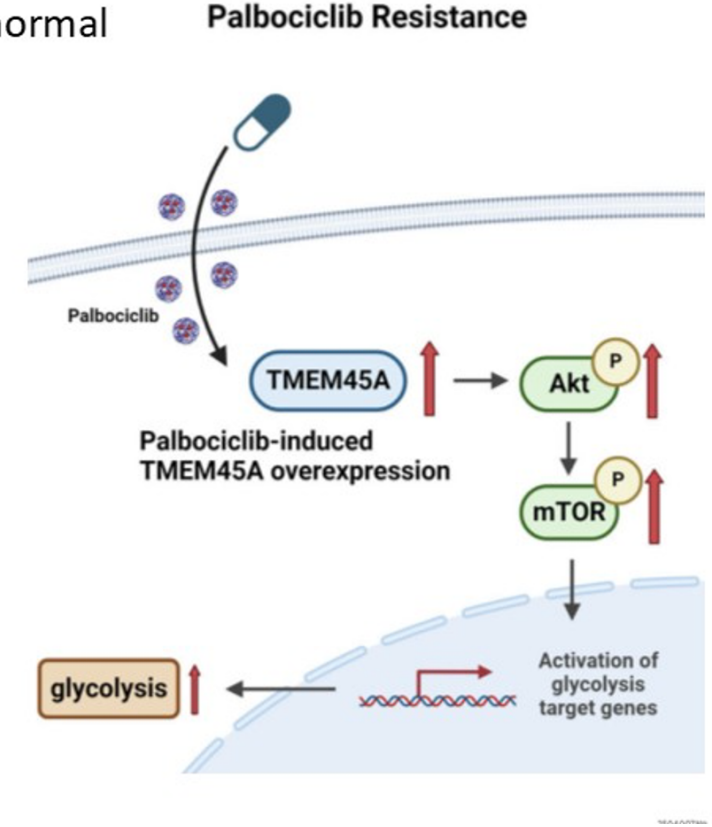
Costa C et al Canc Disc 2020

AKT1 ONCOGENIC SIGNALING (VIA TMEM45A)



- CDK4/6i-resistant cells had increased glycolytic activity
- TMEM45A overexpression
  - Transmembrane protein with abnormal activity in multiple tumor types
- Increased AKT/mTOR activation
- Attenuated via TMEM45A siRNA





Chen C et al Cell Death Disc 2025

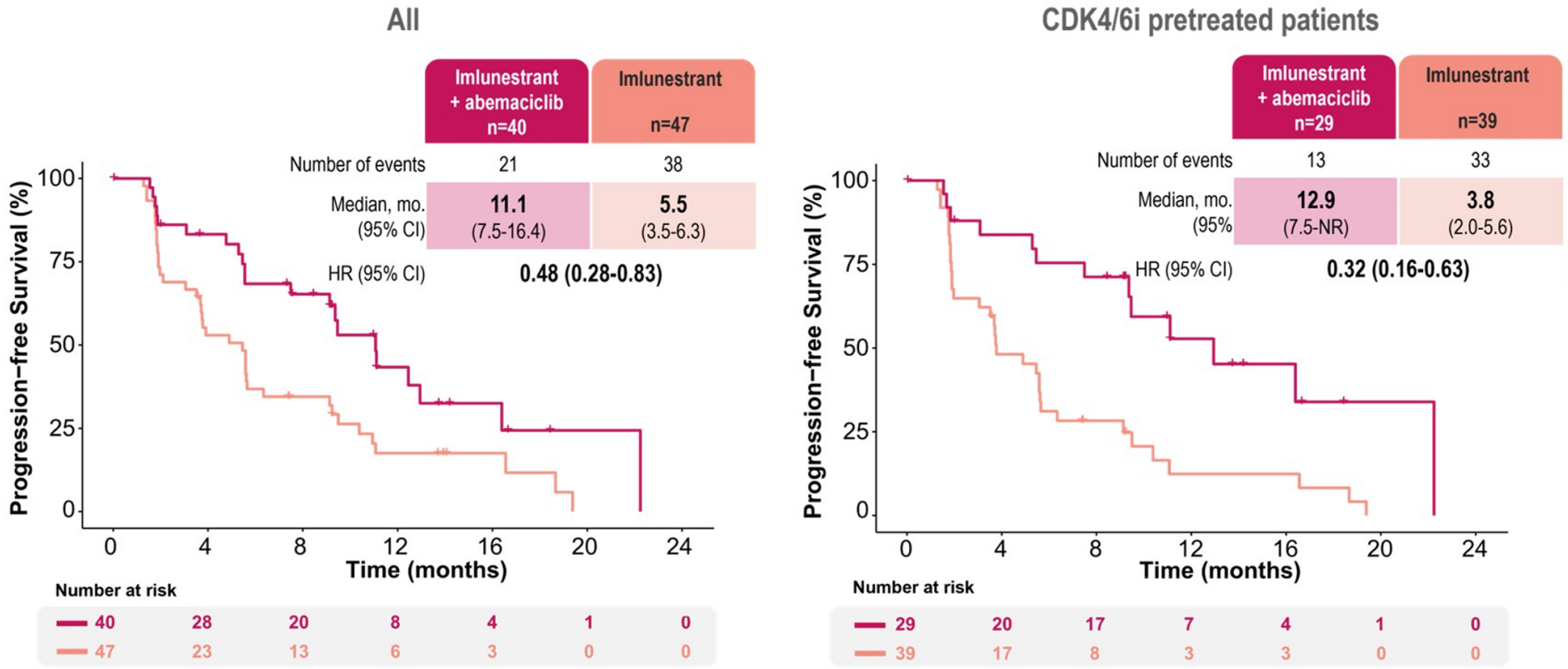
WHAT ABOUT CO-MUTATIONS ?

- Both ESR1 and PIK3CA mutations are prevalent in pretreated ER+ HER2- MBC
- Can co-occur in about 15% of cases

- What is best treatment strategy?

EMBER-3: PFS BY ESR1 AND PI3K-PATHWAY CO-MUTATION STATUS IN ALL PATIENTS AND CDK4/6I PRETREATED PATIENTS

IN PATIENTS WITH BOTH ESR1M AND PI3K-PATHWAY MUTATIONS



EMERALD SUBGROUP ANALYSIS: PFS BY SUBGROUP IN ESR1M PATIENTS WITH ≥12 MO OF CDK4/6I

Subgroup	Patients, n (%)	Median PFS, Mo (95% CI)		HR (95% CI)
		Elacestrant	SoC	
All *ESR1*m	159 (100)	8.6	1.9	0.41 (0.26-0.63)
*ESR1*m with liver and/or lung mets	113 (71)	7.3	1.9	0.35 (0.21-0.59)
*ESR1*m and *PIK3CA*m	62 (39)	5.5	1.9	0.42 (0.18-0.94)
*ESR1*m and *TP53*m	61 (38)	8.6	1.9	0.30 (0.13-0.64)
*ESR1*m and HER2 low	77 (48)	9.0	1.9	0.30 (0.14-0.60)

Bardia. Clin cancer Res. 2024.304299

SUMMARY AND FUTURE PERSPECTIVES

- The PI3K/AKT pathway remains a key therapeutic target in HR+/HER2- advanced breast cancer
- Approved agents offer benefits but are limited by toxicity and acquired resistance
- New-generation allosteric and covalent inhibitors have improved selectivity, may reduce toxicity (which may enhance compliance), and show early signs of efficacy
- Trials must determine best sequencing or combination of ET + CDK4/6i + PI3K/AKT inhibitors in the endocrine sensitive and potentially also resistant setting
- Targeting co-alterations(e.g., PTEN, AKT1 mutations) and integrating ctDNA profiling will be critical to overcome resistance

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025