Memorial Sloan Kettering Cancer Center

PI3K / AKT: Choices, Sequencing, and New Agents

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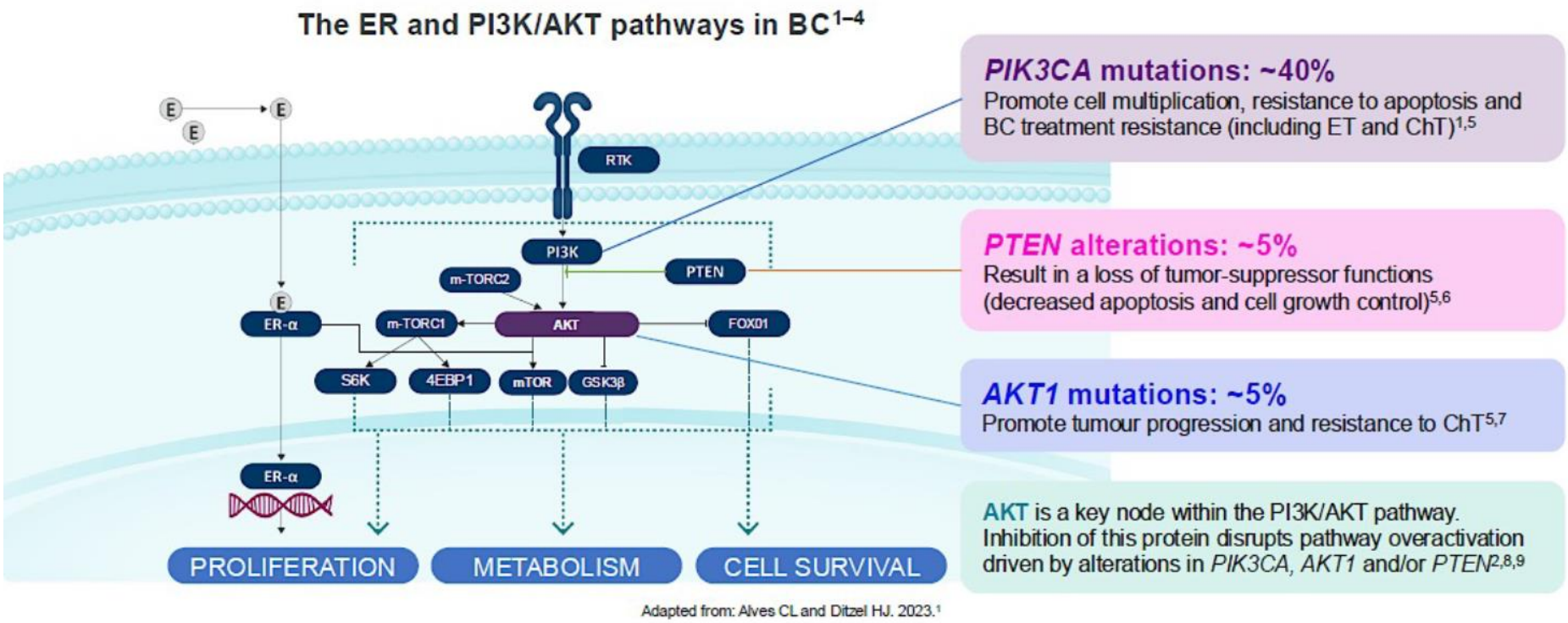
PI3K Pathway in Breast Cancer



FDA approved agents for MBC targeting PI3K pathway

Alpelisib : PIK3CA mutant ER+/HER2- MBC after PD on prior CDK4/6i

Capivasertib: ER+/HER2- MBC post CDK 4/6i w/ PIK3CA, PTEN or AKT1 mutatoins

Inavolisib: PIK3CAm ER+MBC without prior therapy for MBC and quick relapse

Slide credit: *Res to Practice* satellite symposium at SABCS 2024

SOLAR-1 Phase 3 Trial of Alpelisib + Fulvestrant in HR+/HER2– MBC

Key Eligibility Criteria

- Eligible to receive ET after relapse or progression
- Received AI treatment in neo/adjuvant or metastatic setting
- No previous chemotherapy for advanced disease
- No previous fulvestrant or PI3K, AKT, or mTOR inhibitors
- **No type 1 or uncontrolled type 2 diabetes**
- **Fasting glucose ≤140 mg/dL or HbA1c <6.5%[a]**

Primary endpoint: PFS by investigator in patient cohort with *PIK3CA*-mutated cancer
Secondary endpoints: OS in patient cohort with *PIK3CA*-mutated cancer, PFS in patient cohort without *PIK3CA*-mutated cancer, ORR, CBR, safety
Stratification factors: Lung or liver metastases, prior CDK4/6i

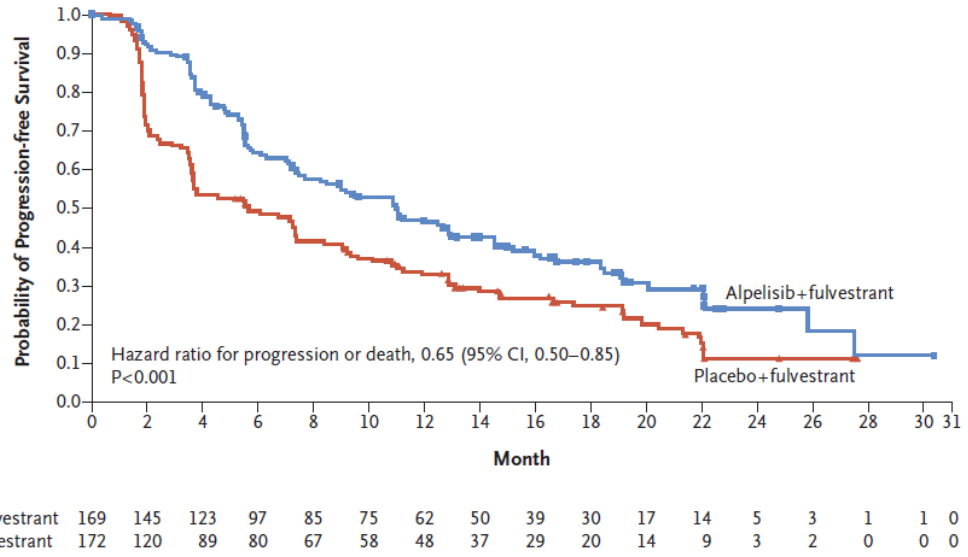
Patient Characteristics, n (%)		With *PIK3CA*mut		Without *PIK3CA*mut	
		A+F (n=169)	P+F (n=172)	A+F (n=115)	P+F (n=116)
Median age (range), years		63 (25-87)	64 (38-92)	62 (39-82)	63 (32-88)
Metastatic sites	Bone only	25%	20%	23%	20%
	Visceral	55%	58%	57%	64%
Endocrine status	Primary	14%	13%	27%	22%
	Secondary	71%	74%	57%	56%
	Sensitivity	12%	11%	14%	17%
Line of treatment in advanced disease	First line	52%	52%	62%	53%
	Second line	47%	48%	37%	46%
Prior treatment	**Any CDK4/6i**	**5.3%**	**6.4%**	**6.1%**	**6.9%**
	Chemotherapy	60%	62%	68%	62%

[a] HbA1c levels was an amendment to the original protocol implemented after the start of the study to lower rates of treatment discontinuation.[2] [b] Administered as intramuscular injection on days 1 and 15 of cycle 1 and on day 1 of subsequent cycles.

1. Andre F, et al. *N Engl J Med*. 2019;380(20):1929-1940. **2.** Rugo HS, et al. *Ann Oncol*. 2020;31(8):1001-1010.

SOLAR-1 Phase 3 Trial of Alpelisib + Fulvestrant in HR+/HER2– MBC

PFS in Patient Cohort With *PIK3CA*-Mutated Cancer

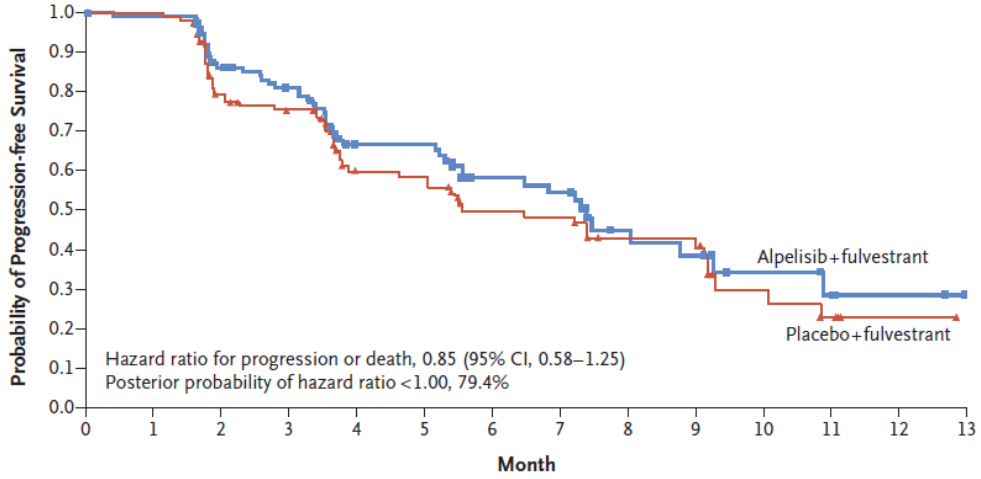


No. at Risk

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

With PIK3CA-Mutated Cancer	A+F (n=169)	P+F (n=172)
12 mo PFS rate	46.3%	32.9%
Median PFS, mo (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
Adjusted HR (95% CI)	0.65 (0.50-0.85)	
P value	<0.001	

PFS in Patient Cohort Without *PIK3CA*-Mutated Cancer



No. at Risk

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

Without PIK3CA-Mutated Cancer	A+F (n=115)	P+F (n=116)
12 mo PFS rate	28.4%	22.2%
Median PFS, mo (95% CI)	7.4 (5.4-9.3)	5.6 (3.9-9.1)
Adjusted HR (95% CI)	0.85 (0.58-1.25)	
Posterior probability of HR <1.00	79.4%	

Andre F, et al. *N Engl J Med*. 2019;380(20):1929-1940.

SOLAR-1 Phase 3 Trial of Alpelisib + Fulvestrant in HR+/HER2– MBC

Most Common AEs (≥20%)[1]

	A+F (n=284)		P+F (n=287)	
AE, %	All grades	Grade 3-4	All grades	Grade 3-4
Any AE	99%	78%	93%	37%
Hyperglycemia	65%	37%	9.4%	1.0%
Diarrhea	60%	7.0%	16%	0.7%
Nausea	47%	2.8%	23%	0.3%
Decreased appetite	36%	0.7%	11%	0.3%
Rash	36%	9.9%	7.0%	0.3%
Vomiting	29%	0.7%	10%	0.3%
Weight decreased	28%	5.3%	2.4%	0
Fatigue	25%	3.5%	18%	1.0%
Stomatitis	25%	2.5%	7.0%	0
Asthenia	23%	2.5%	14%	0
Alopecia	20%	0	2.4%	0

Safety Summary

- AEs of any grade leading to discontinuation of 1 or both treatments in the safety population (both patients with and without *PIK3CA*-mutant cancers) occurred in **75 patients (26.4%)** in the alpelisib + fulvestrant arm and **16 patients (5.6%)** in the placebo + fulvestrant arm[1]
- Safety profile was similar to previous trials of alpelisib + fulvestrant and no new safety signals were observed with longer follow up[1,2]

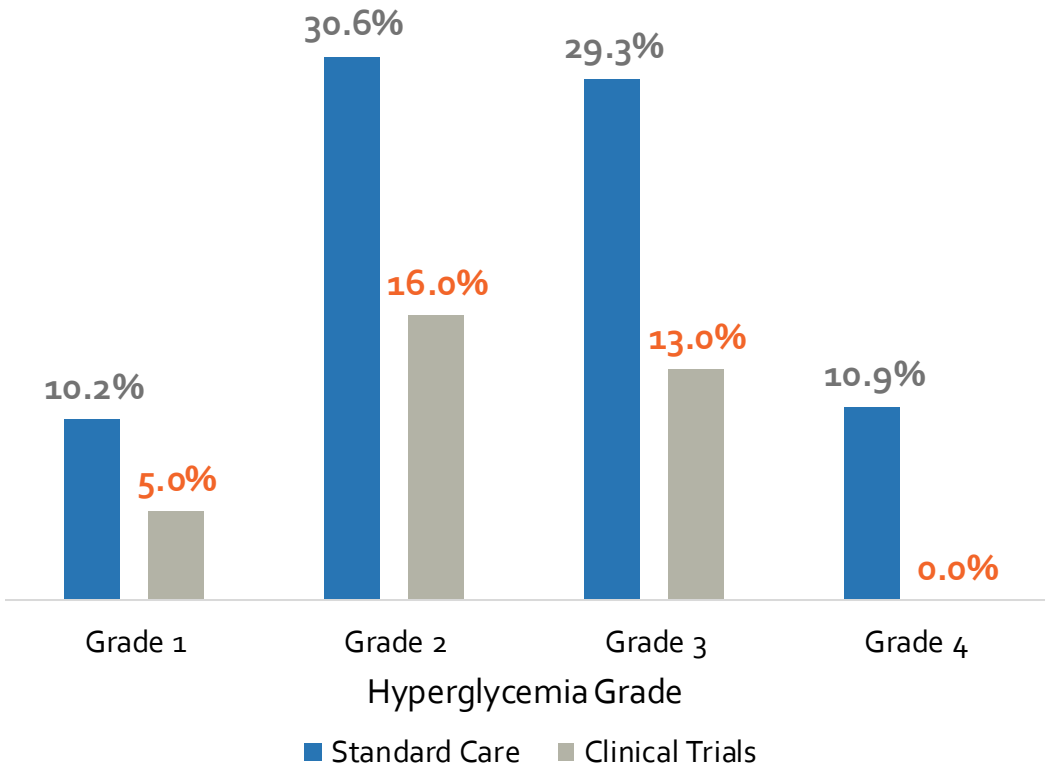
1. Andre F, et al. *Ann Oncol*. 2021;32(2):208-217. **2.** Andre F, et al. *N Engl J Med*. 2019;380(20):1929-1940.

Alpelisib Hyperglycemia Rates in Standard of Care vs Clinical Trials

- Methods/Study Design
  - A **single center** completed a **retrospective cohort study** of adult patients with MBC who received **alpelisib** either as part of standard of care or part of a clinical trial
- Key Findings
  - Hyperglycemia occurred at a **significantly higher rate** in patients receiving **alpelisib as part of standard of care** than in patients enrolled in clinical trials (**80.3%** vs **34.0%**, *P*<0.001)
  - HbA1c in the **prediabetes/diabetes range** was significantly **associated with hyperglycemia occurrence**
  - Hyperglycemia occurrence **did not impact PFS**

	Standard of Care (n=147)	Clinical Trial (n=100)
Hyperglycemia, %	80.3	34.0
P value	<0.001	
Overweight/Obese BMI, %	55.7	48.0
P value	0.09	
HbA1c ≥5.7%, %	30.6	15.0
P value	0.041	

Rates of Hyperglycemia in Patients Treated With Alpelisib as Part of Standard of Care or While on a Clinical Trial

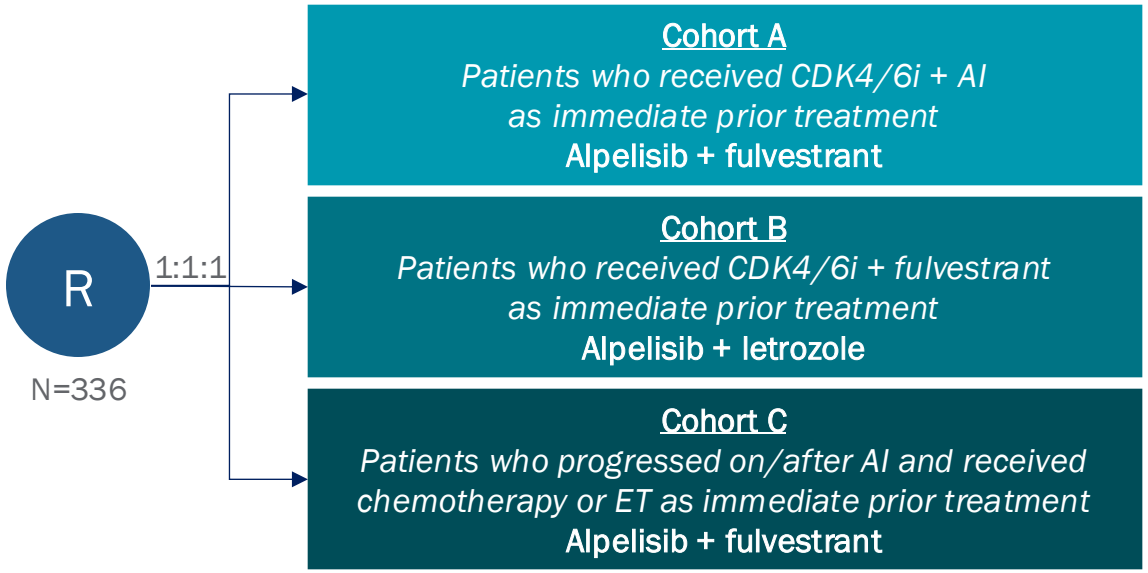


Shen S, et al. *Cancer*. 2023;129(24):3854-3861.

BYLieve Phase 2 Trial of Alpelisib + ET in PIK3CAmut HR+ MBC Post-CDK4/6i

Key Eligibility Criteria

- Men or pre/postmenopausal women with HR+/HER2– MBC
- *PIK3CA*mut in tumor tissue or blood
- Last line of prior therapy: CDK4/6i + ET, systemic CT, or ET



Primary endpoint: Proportion of patients alive without PD at 6 months in each cohort; the primary endpoint was met and clinically meaningful if the lower bound of the CI was >30%
Secondary endpoints: PFS, PFS2, ORR, CBR, DOR, OS, Safety

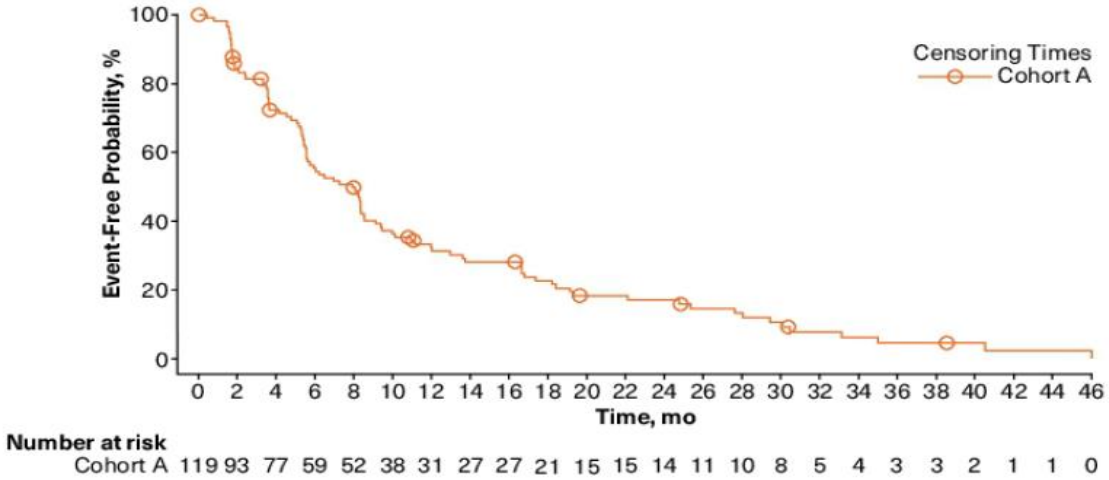
Patient Characteristics		Cohort A (n=127)	Cohort B (n=126)
Median age (range), years		58 (33-83)	61 (37-80)
Metastatic sites	Bone	86%	75%
	Bone only	18%	8.7%
	Visceral	68%	78%
	Lung	34%	37%
	Liver	47%	60%
	Other	6.3%	7.1%
Number of lines of prior therapy in advanced setting, n (%)	0	1.6%	0.8%
	1	80%	52%
	2	18%	45%
	≥3	0.8%	1.6%
Therapy type at last treatment	Targeted	91%	92%
	Hormonal	78%	85%
	Biologics	3.1%	0
	Chemotherapy	0	0.8%

Chia S, et al. ASCO 2023. Abstract 1078.

BYLieve Phase 2 Trial of Alpelisib + ET in PIK3CAmut HR+ MBC Post-CDK4/6i

Cohort A PFS

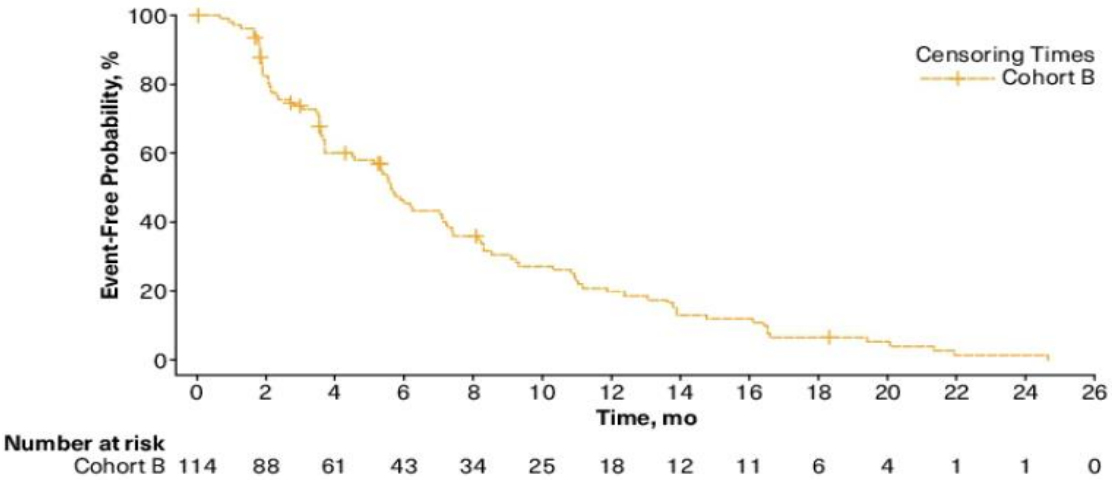
Alpelisib + Fulvestrant in Patients Who Received CDK4/6i + AI



Cohort A PFS	A+F (n=119)
Events, n (%)	98 (82.4)
Median follow-up, mo	5.95
Median PFS, mo (95% CI)	8.0 (5.6-8.6)
Cohort A OS	
Events, n (%)	71 (59.7)
Median follow-up, mo	21.78
Median OS, mo (95% CI)	27.3 (21.3-32.7)

Cohort B PFS

Alpelisib + Letrozole in Patients Who Received CDK4/6i + Fulvestrant



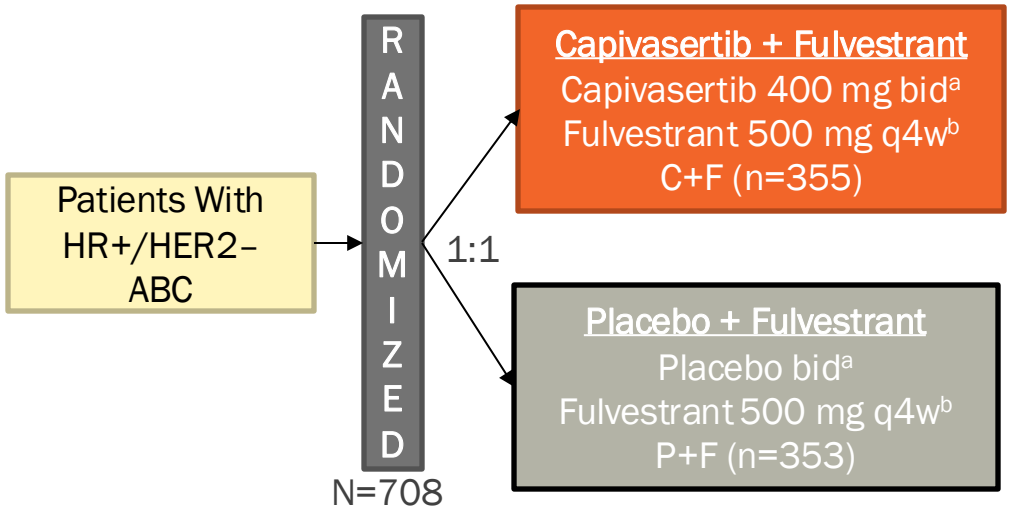
Cohort B PFS	A+L (n=114)
Events, n (%)	97 (85.1)
Median follow-up, mo	5.19
Median PFS, mo (95% CI)	5.6 (3.7-7.1)
Cohort B OS	
Events, n (%)	66 (57.9)
Median follow-up, mo	25.33
Median OS, mo (95% CI)	29.0 (24.5-34.8)

Chia S, et al. ASCO 2023. Abstract 1078.

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Study Design and Patients

Key Eligibility Criteria

- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6i allowed (at least 51% required)
- HbA1c < 8.0%



Dual primary endpoints: PFS by investigator in overall and in AKT pathway-altered tumors[c]
Secondary endpoints: OS, ORR

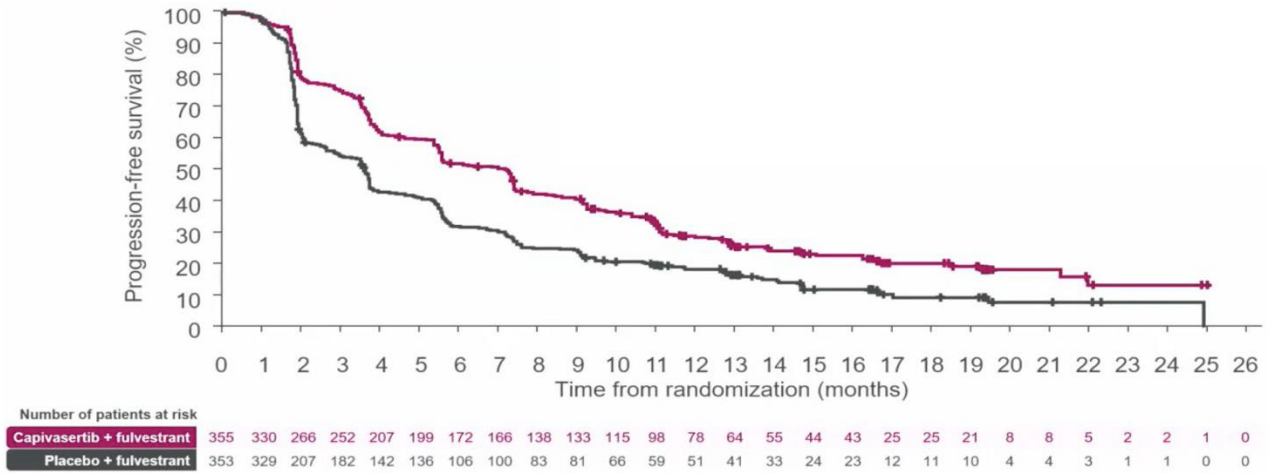
Patient Characteristics, n (%)		Overall Population C+F (n=355)	Overall Population P+F (n=353)	AKT Pathway Altered C+F (n=155)	AKT Pathway Altered P+F (n=134)
Median age (range), years		59 (26-84)	58 (26-90)	58 (36-84)	60 (34-90)
Metastatic sites	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver[d]	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
HR status[e]	ER+/PR+	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
	ER+/PR–	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
	Unknown	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine resistance	Primary	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
	Secondary	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)
Prior endocrine therapy for ABC	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Prior CDK4/6i for ABC		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Prior CT	(Neo)adjuvant	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)
AKT pathway alteration		155 (43.7)	134 (38.0)	-	-

[a] 4 days on, 3 days off. [b] Cycle 1, days 1 & 15; then q4w. [c] AKT pathway-altered tumors: ≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration. [d] Baseline stratification factor. [e] One patient in the C+F group was ER negative.

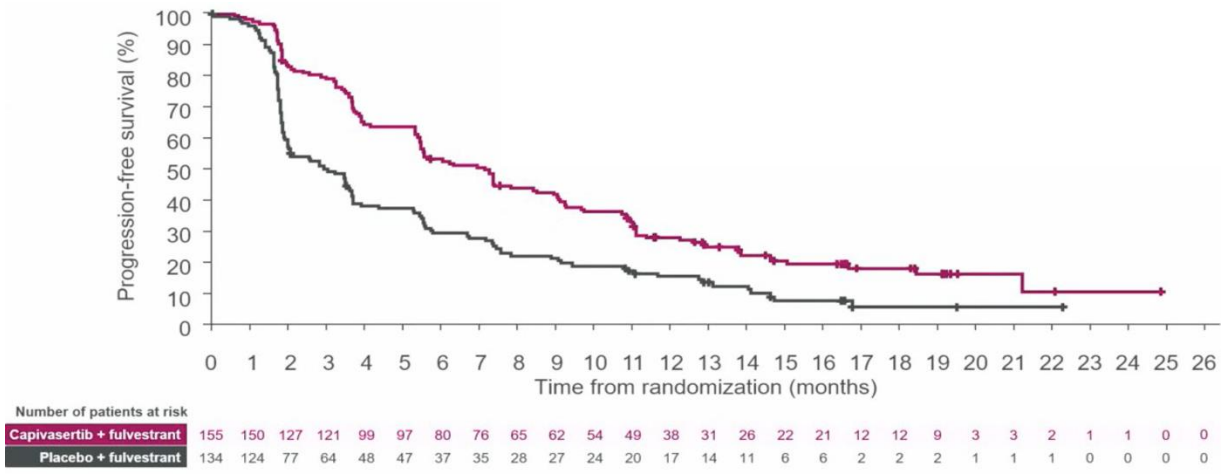
Turner NC, et al. SABCS 2022. Abstract GS3-04.

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Primary Endpoint

PFS by Investigator in Overall Population



PFS by Investigator in the AKT Pathway-Altered Population



Overall Population	C+F (n=355)	P+F (n=353)
PFS events	258	293
Median PFS, mo (95% CI)	7.2 (5.5-7.4)	3.6 (2.8-3.7)
Adjusted HR (95% CI)	0.60 (0.51-0.71)	
Two-sided *P* value	<0.001	

Overall Population	C+F (n=155)	P+F (n=134)
PFS events	121	115
Median PFS, mo (95% CI)	7.3 (5.5-9.0)	3.1 (2.0-3.7)
Adjusted HR (95% CI)	0.50 (0.38-0.65)	
Two-sided *P* value	<0.001	

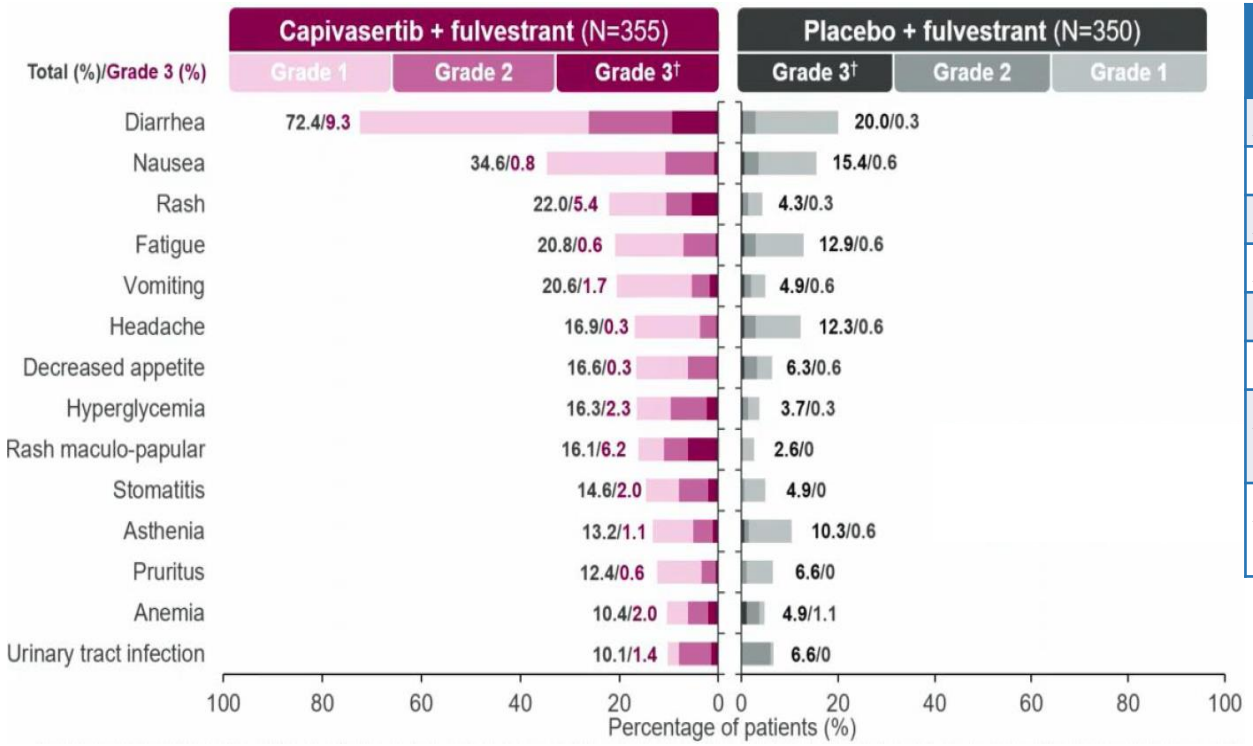
- PFS benefit was observed in all key subgroups, including regardless of prior use of CDK4/6i and liver metastases

HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6i and geographic region.

Turner NC, et al. SABCS 2022. Abstract GS3-04.

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Safety

AEs (>10% of Patients)



Safety Summary, n (%)	C+F (n=355)	P+F (n=350)
Any AE	343 (96.6)	288 (82.3)
Serious AE	57 (16.1)	28 (8.0)
AE leading to death[a]	4 (1.1)	1 (0.3)
AE leading to discontinuation	46 (13.0)	8 (2.3)
Discontinuation of C/P only	33 (9.3)	2 (0.6)
Discontinuation of both C/P and F	13 (3.7)	6 (1.7)
AE leading to dose interruption of C/P only	124 (34.9)	36 (10.3)
AE leading to dose reduction of C/P only	70 (19.7)	6 (1.7)

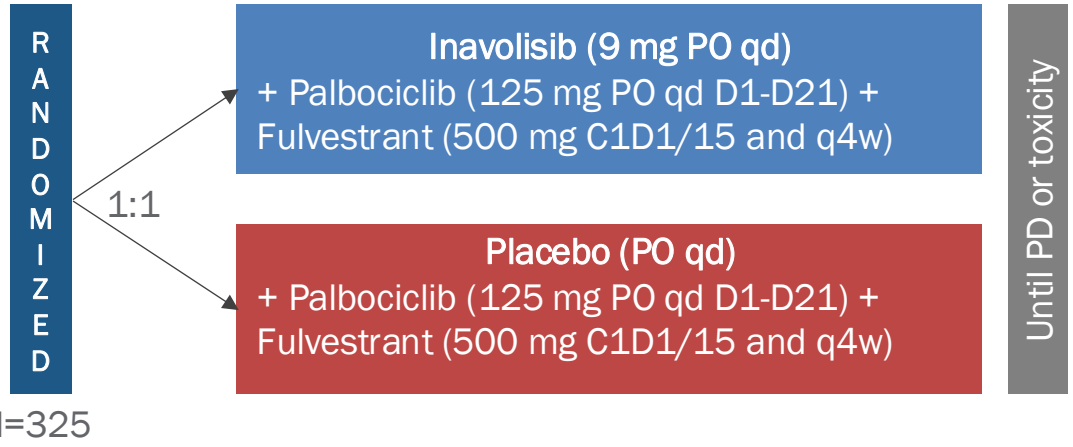
[a] Grade 5 events included acute myocardial infarction, cerebral hemorrhage, pneumonia aspiration, and sepsis (all n=1) in the C+F group and COVID-19 (n=1) in the P+F group. No grade 5 events were classified as related to C/P by local investigator. The safety analysis population included all patients who received at least 1 dose of the study drug.

Turner NC, et al. SABCS 2022. Abstract GS3-04.

Phase 3 INAVO120 Trial of Inavolisib in PIK3CAmut HR+/HER2– MBC

Key Eligibility Criteria

- *PIK3CA*mut, HR+, HER2– ABC by central ctDNA or local tissue/ctDNA test[a]
- Measurable disease
- Progression during/within 12 months of adjuvant ET completion; no prior therapy for MBC
- Fasting glucose <126 mg/dL and HbA1c <6.0%



N=325

Primary endpoint: PFS by investigator
Secondary endpoints: OS (if PFS is positive), ORR, BOR, CBR, DOR, PROs

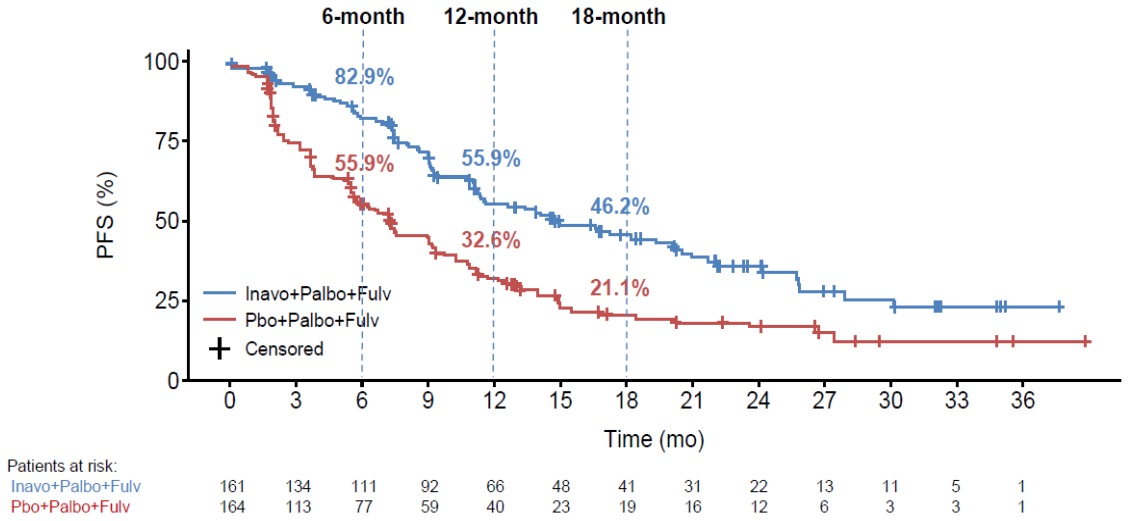
Patient Characteristics, %		Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
Median age (range), years		53.0 (27-77)	54.5 (29-79)
Race	Asian	38%	38%
	Black/African American	0.6%	0.6%
	White	58%	59%
ECOG PS	0	62%	65%
	1	37%	35%
Postmenopausal at randomization		57%	63%
Visceral disease		82%	78%
ER and PgR status	ER+/PgR+	70%	69%
	ER+/PgR–	28%	27%
Endocrine resistance	Primary	33%	35%
	Secondary	67%	64%
Prior (neo)adjuvant Chemo		82%	84%
Prior (neo)adjuvant ET	AI only	37%	43%
	Tamoxifen only	51%	45%
	AI and tamoxifen	11%	12%
Prior adjuvant CDK4/6i		1.9%	0.6%

[a] 301 patients (92.6%) were enrolled by ctDNA testing (284 central, 17 local); 24 (7.4%) were enrolled by local tissue testing.

Jhaveri K, et al. SABCS 2023. Abstract GS03-13.

Phase 3 INAVO120 Trial of Inavolisib in PIK3CAmut HR+/HER2– MBC

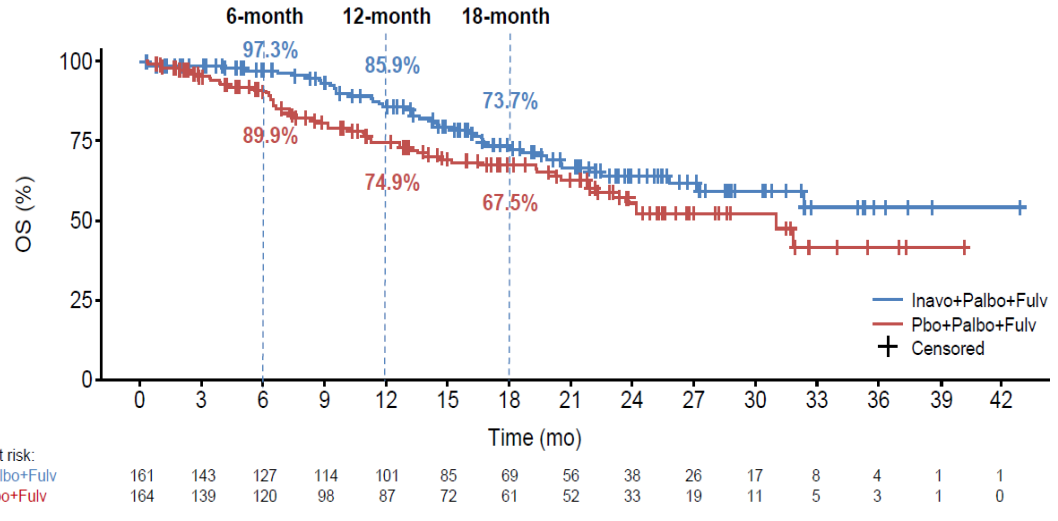
PFS (Investigator Assessed)



Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

OS (Interim Analysis)[a]



Patients at risk:

Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

PFS	Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
PFS events, n (%)	82 (50.9)	113 (68.9)
Median PFS (95% CI), mo	15.0 (11.3-20.5)	7.3 (5.6-9.3)
Stratified HR (95% CI)	0.43 (0.32-0.59)	
P value	*P*<0.0001	

OS	Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
Events, n (%)	42 (26.1)	55 (33.5)
Median OS (95% CI), mo	NE (27.3-NE)	31.1 (22.3-NE)
Stratified HR (95% CI)	0.64 (0.43-0.97)	
P value	*P*=0.0338	

Data cutoff date: September 29, 2023. Median follow-up: 21.3 months.

[a] The prespecified boundary for OS (*P*=0.0098 or HR=0.592) was not crossed at this interim analysis.

Jhaveri K, et al. SABCS 2023. Abstract GS03-13.

Phase 3 INAVO120 Trial of Inavolisib in PIK3CAmut HR+/HER2– MBC

AEs ≥20% Incidence in Either Group, %	Inavo + Palbo + Fulv (n=162)		Pbo + Palbo + Fulv (n=162)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Neutropenia	89%	80%	91%	78%
Thrombocytopenia	48%	14%	45%	4%
Anemia	37%	6%	36%	2%
Stomatitis/Mucositis	51%	6%	27%	0
Hyperglycemia	59%	6%	9%	0
Diarrhea	48%	4%	16%	0
Nausea	28%	<2%	17%	0
Rash	25%	0	17%	0
Decreased appetite	24%	<2%	9%	<2%
Fatigue	24%	<2%	13%	<2%
COVID-19	23%	<2%	11%	<2%
Headache	21%	<2%	14%	<2%
Leukopenia	17%	7%	25%	11%
Ocular toxicities	22%	0	13%	0

Overview of AEs, %	Inavo + Palbo + Fulv (n=162)	Pbo + Palbo + Fulv (n=162)
Any AEs	99%	100%
Grade 3-4 AEs	88%	82%
Grade 5 AE[a]	4%	1%
Serious AE	24%	11%
Leading to discontinuation	7%	0.6%
Inavolisib/placebo	6%	0.6%
Palbociclib	5%	0
Fulvestrant	3%	0
Leading to dose modification/ interruption of treatment	83%	75%
Inavolisib/placebo	70%	35%
Palbociclib	77%	72%
Fulvestrant	32%	21%

[a] None of the grade 5 AEs were reported as related to study treatment by investigators.

Jhaveri K, et al. SABCS 2023. Abstract GS03-13.

Summary of AKTi / PI3Ki Adverse Effects

	Alpelisib + Fulvestrant				Capivasertib + Fulvestrant	
	SOLAR-1[1] (n=284)		BYLieve[2] (Cohorts A+C, n=253)		CAPItello-291[3] (n=355)	
Median treatment duration, mo	5.5		NR		5.4	
Discontinuations due to AEs, %	26.4%		NR		13%	
Dose reductions due to AEs, %	NR		NR		20%	
Most Common AEs (≥25%), %	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any AE	99%	78%	99%	69%	97%	42%
Hyperglycemia	65%	37%	64%	27%	16%	2.3%
Diarrhea	60%	7.0%	59%	4.3%	72%	9.3%
Nausea	47%	2.8%	44%	1.2%	35%	0.8%
Decreased appetite	36%	0.7%	31%	3.6%	17%	0.3%
Rash	36%	9.9%	36%	12%	38%	12%
Vomiting	29%	0.7%	25%	1.6%	21%	1.7%
Weight decreased	28%	5.3%	NR	NR	NR	NR
Fatigue	25%	3.5%	33%	2.4%	21%	0.6%
Stomatitis	25%	2.5%	29%	1.6%	15%	2.0%

1. Andre F, et al. *Ann Oncol*. 2021;32(2):208-217. **2.** Chia S, et al. ASCO 2023. Abstract 1078.
3. Turner NC, et al. *N Engl J Med*. 2023;388(22):2058-2070.

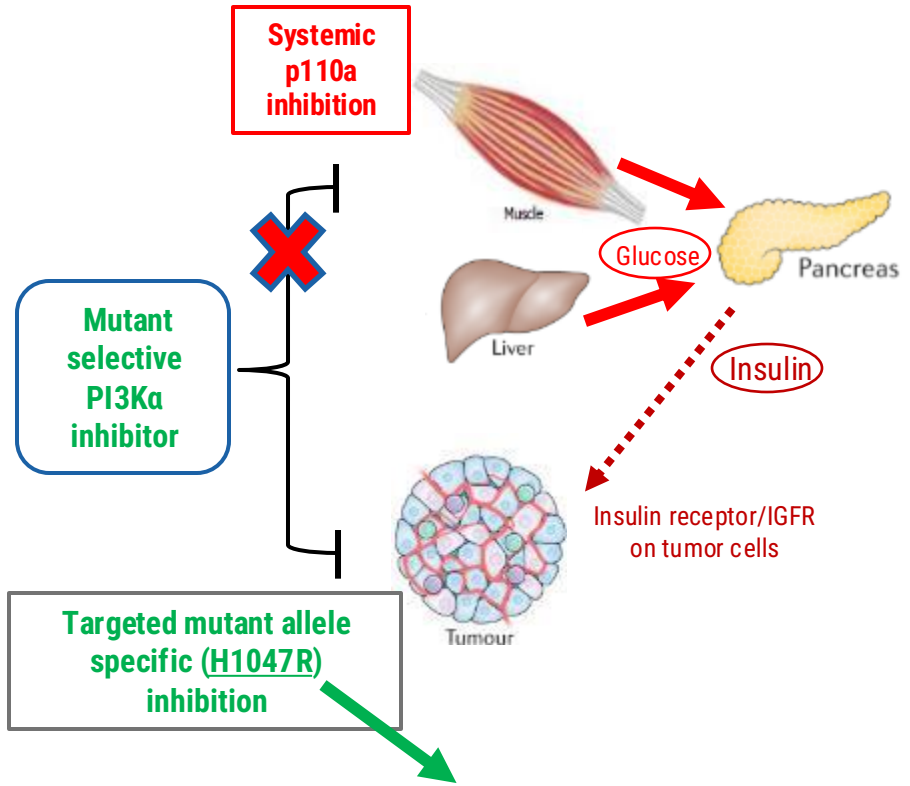
Tumor/Mutant Selective PI3Kα Inhibitors

Selective targeting of oncogenic PI3K activation without inhibiting normal PI3K function in host tissues

Selective tumor targeting of PI3Kα H1047R should:

- Permit higher and uninterrupted dosing
- Permit continuous and more complete target engagement
- Enable long-term dosing with novel combination regimens (CDK4/6 inhibitors, etc)

Increased efficacy and improved safety



p110a kinase (exon 20 p.**H1047R**) domain mutation occurring **~15% of breast cancer**

Dent R. Presented at: ESMO Breast Cancer 2021; May 5-8, 2021; Virtual; Kalinsky K, et al. Clin Cancer Res. 2009;15:5049-5059.

LOXO-783: H1047-mutant selective PI3K inhibitor

- ER+/HER2- MBC: 85%
- mTNBC: 11%
- Other solid tumors: 5%

- Prior ET+ CDK4/6i: 76%
- Prior SERD: 42%
- Prior chemo/ADC: 71%
- Prior PI3K pathway inh: 7%

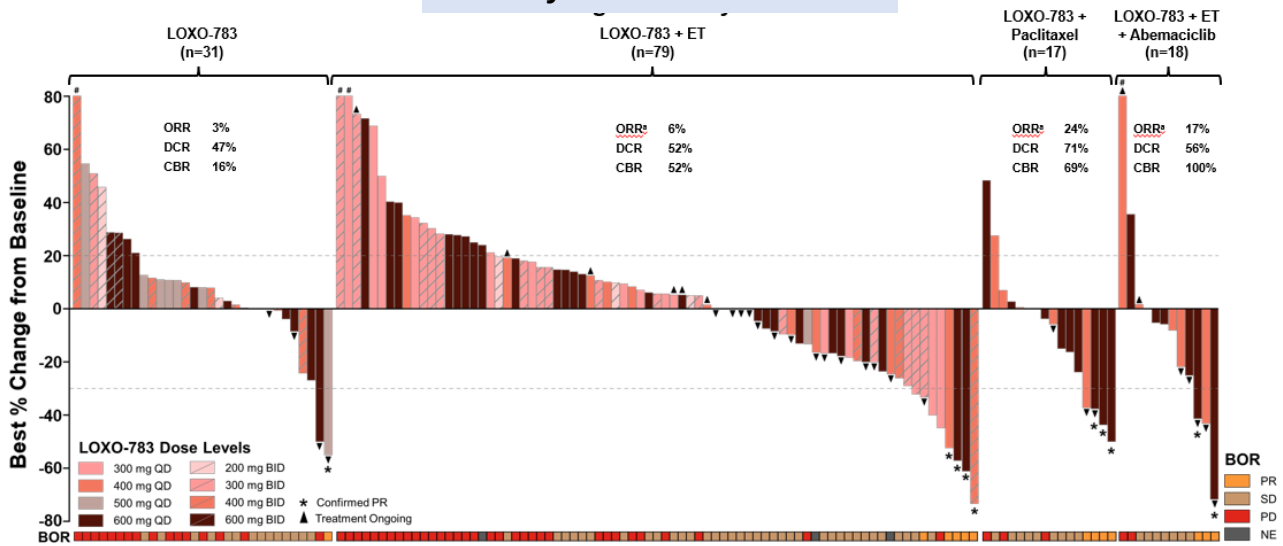
Efficacy

	LOXO-783 (n=31)	LOXO-783 +ET (n=79)	LOXO-783 + paclitaxel (n=17)	LOXO-783 +ET+ abema (n=18)
ORR (%)	3	6	24	17
DCR (%)	47	52	71	56
CBR (%)	16	52	69	100

Safety

Hyperglycemia: all grades:3-8%; G≥3:none
Rash: all grades 15-20% G≥3: 1% (w/ET)
Fatigue: all grades 24-38% G≥3: 1-5%
Diarrhea: all grades 71-89%; G≥3: 5-21%

Efficacy data with LOXO-783



LOXO-783

- ✓ Limited efficacy as monotherapy or w/ET only
- ✓ Demonstrated proof of concept of mutant selectivity - no hyperglycemia
- ✓ High rates of diarrhea observed limit the utility in clinic
- ✓ Not moving forward w/ this compound

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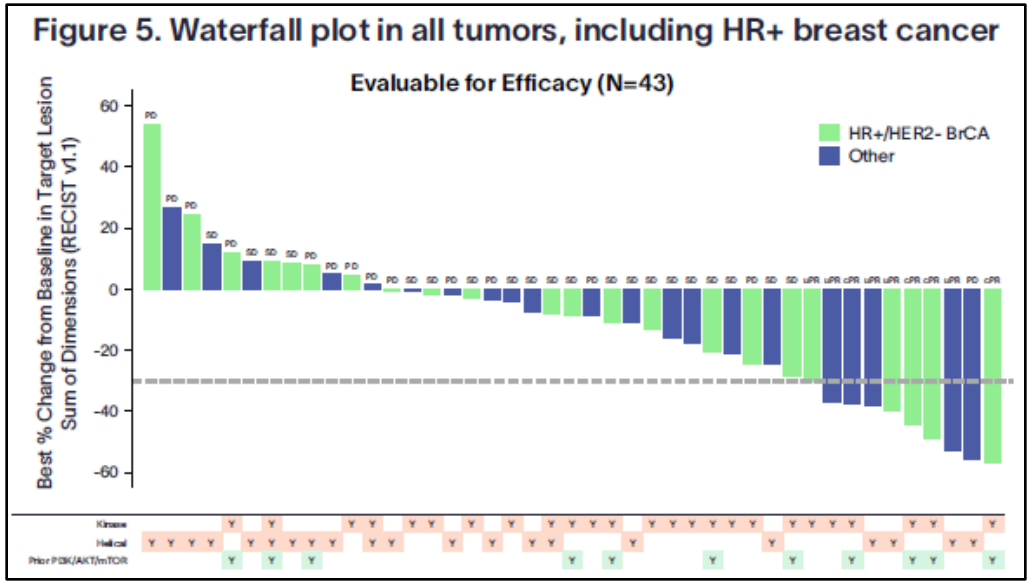
STX-478 Mutant selective PI3Kα inhibitor

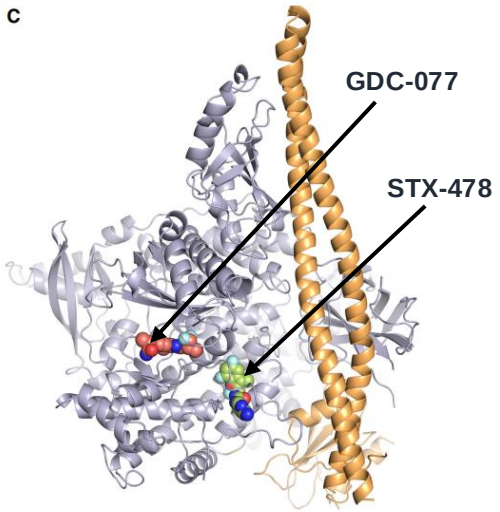
Ph 1/ 2 study - Monotherapy
- PIK3CA helical or kinase domain mutant advanced solid tumors (including BC)
- Fasting glucose < 140 mg/dL and HbA1c < 7.0%
- Type 2 DM permitted
- Prior PI3K/AKT/mTORi permitted if stopped due to intolerance

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 or rash

Hyperglycemia: all grades: 23%
Fatigue: all grades 30% G3: 8%
Rash: all grades 10%
Diarrhea: all grades 15%





Structure of PI3Kα bound to GDC-077 (ATP binding site) and STX-478 (allosteric site)

STX-478 monotherapy

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

✓ Good safety profile
Limited toxicities in high risk pt popn including those with diabetes

✓ STX-748 combinations under investigation in HR+/HER2- MBC

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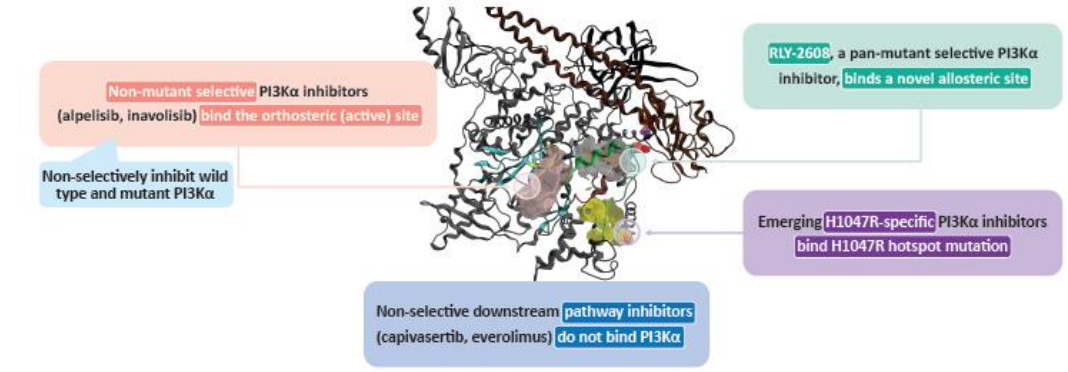
RLY-2608 Pan-mutant selective PI3K inhibitor



RLY-2608 selectively targets mutant PI3Kα, via binding to a novel pocket, distinct from approved orthosteric inhibitors and emerging inhibitors that target only H1047R

ReDiscover: RLY-2608+fulv in HR+/HER2- MBC with ≥1 PIK3CA mutations

- prior ET+ CDK 4/6i for EBC/MBC
- ≤1 line of chemo for MBC

Prior fulvestrant/SERD: 51%
Prior chemo: 25%
ESR1m: 29%

Efficacy

- *Confirmed ORR*: 39%
  - ORR: 67% (kinase domain mutations)
- *Median PFS*: 9.2 months
- *Median PFS:* 11.4 months in 2L patients

Safety: No G4 or 5 TRAE

Hyperglycemia: all grades: 47%; G3: 3.13%
Fatigue: all grades 36% G3: 9.4%
Rash: all grades 36% G3: 9.4%

RLY-2608+ fulvestrant

✓ Durable efficacy

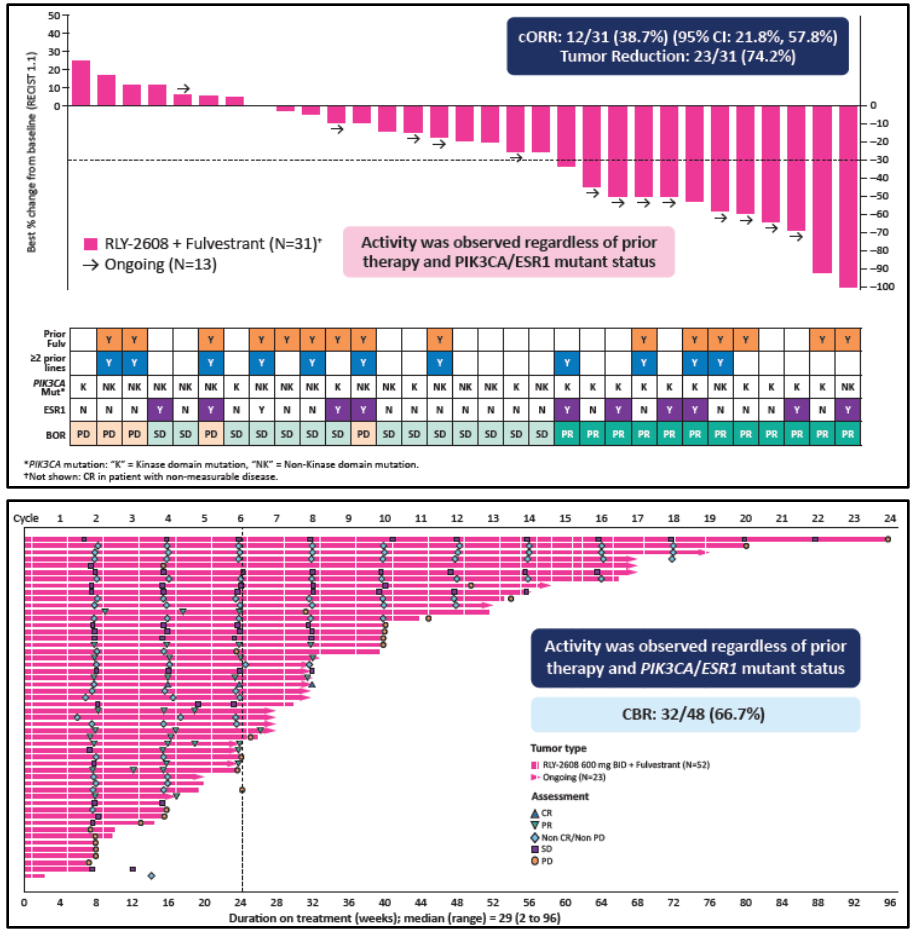
Activity observed regardless of prior therapy and ESR1/PIK3CA mutation status

✓ Favorable safety profile

Elimination or minimization of AEs more frequently seen with alpelisib, capivasertib etc

✓ Ph 3 trial of RLY-2608 + fulv vs capivasertib + fulv planned

Efficacy data with RLY-2608 (RP2D 600mg BID) + fulvestrant
no BL PTEN or AKT comutations in these pts (N=52)



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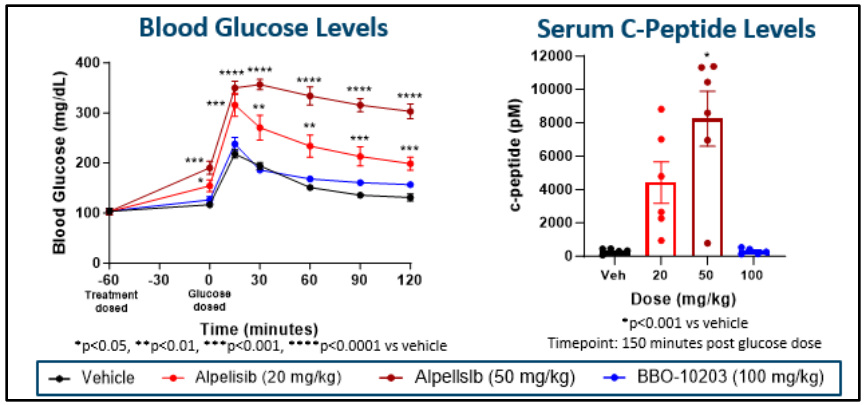
BBO-10203 selective blocker of PI3Kα:RAS interaction

BBO-1023

- Selective inhibitor of the physical interaction between PI3Kα (not β, δ, or γ) and RAS which is critical for malignancy
- Covalently binds PI3Kα on cysteine 242 in the Ras binding domain, which prevents the interaction of PI3Kα with RAS
- Does not inhibit kinase activity of PI3Kα

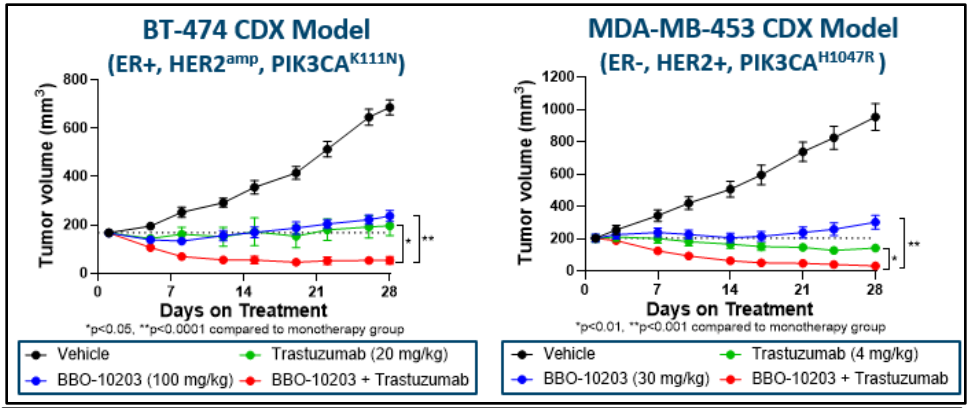
No hyperglycemia or hyperinsulinemia in an oral glucose tolerance test



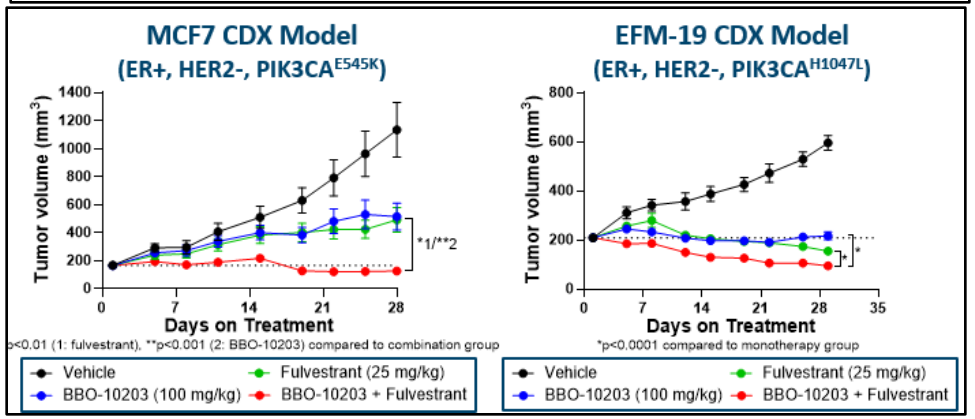
- ✓ **BBO-10203** blocks RAS-mediated activation of PI3Kα, strongly inhibits pAKT signaling in tumor cells without affecting glucose metabolism
- ✓ Shows robust monotherapy activity and combination activity with SOC in HER2+ or HER2- breast cancer models with PI3Kα mutations
- ✓ Phase 1 BREAKER-101 (NCT06625775) trial is underway

BBO-10203 monotherapy and combination activity in BC models

HER2+



ER+/HER2-



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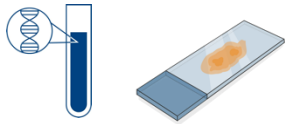
Novel PI3K Inhibitor Development

PI3K inhibitor	Type	Status
CYH33	PI3Kα inhibitor	Phase 2
JS105	PI3Kα inhibitor	Phase 1/ 2
Serabelisib	PI3Kα inhibitor	Phase 2
TOS-358	PI3Kα inhibitor	Phase 1
RLY-2608	PI3Kα mutant selective	Phase 1
RLY-5836	PI3Kα mutant selective	Discontinued
STX-478	PI3Kα mutant selective	Phase 1
CGT6297	PI3Kα H1047R mutant specific	Preclinical
OKI-219	PI3Kα H1047R mutant specific	Phase 1
LOXO-783	PI3Kα H1047R mutant specific	Discontinued
LY4045004	PI3Kα H1047R and E545K mutant	Preclinical

Incorporating AKT/PI3K Inhibition into Treatment Paradigm for HR+/HER2– MBC



- NGS – *PIK3CA*, AKT pathway, *ESR1*
- Germline
- ER/PR/HER2

1st LINE	2nd LINE	3rd LINE	4th LINE
ET + CDK4/6i	ET + AKTi	ET + AKTi	ET + PI3Ki
	ET + PI3Ki	ET + PI3Ki	ET + mTORi
	ET + mTORi	ET + mTORi	
(Inavolisib + Palbociclib + ET)	ET + CDK4/6i		PARPi
ET	ET SERD	ET SERD	ET
Chemo	T-Dxd / Chemo	T-Dxd / Chemo	T-Dxd / Chemo

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