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Real-world clinical outcomes and genomic insights for patients with PIK3CA-mutant metastatic breast cancer following progression on CDK4/6 inhibitor therapy

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BACKGROUND AND OBJECTIVES

- Upfront management of hormone receptor-positive (HR+) / HER2- metastatic breast cancer (mBC) typically includes combination therapy with an antiestrogen and a CDK4/6 inhibitor (CDK4/6i). After disease progression, several treatment options are approved for use in the second-line setting.
- *PIK3CA* mutations (PIK3CAmut) are detected in approximately 40% of HR+ mBC and are actionable therapeutically. The emergence of targeted therapies for mBC with PIK3CAmut, *ESR1* mutations (ESR1mut), and those with dual mutant disease has made therapy decisions following progression on a CDK4/6i increasingly complex.
- **Here we assessed treatment selection for patients with PIK3CAmut mBC post-CDK4/6i, examining clinical outcomes and associated genomic findings via circulating tumor DNA (ctDNA).**

METHODS

- Patients tested with Guardant360 (G360; a ctDNA sequencing assay) since November 2023 (capivasertib approval date) were identified in Guardant INFORM, a real-world clinical-genomic dataset which combines de-identified genomic results with associated claims data. Eligible patients had mBC and were treated with a CDK4/6i after metastatic diagnosis. Patients with PIK3CAmut detected via ctDNA after CDK4/6i but prior to the start of next line therapy were included.
- Therapy selection following PIK3CAmut detection was assessed. Exposures of interest included treatment with biomarker-approved agents capivasertib (CAPI), alpelisib (ALP), and elacestrant. Line of treatment was captured.
- Baseline and post-progression genomic alterations detected in ctDNA were evaluated (post-progression restricted to within 90 days of therapy discontinuation), as was the presence of dual *PIK3CA* and *ESR1* mutant disease identified on the same G360 test.
- Outcomes analyzed included real-world time to treatment discontinuation (rwTTD), time to next treatment (rwTTNT) and overall survival (rwOS) using the Kaplan Meier method. Log-rank tests and Cox analysis compared time-to-event outcomes.

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RESULTS

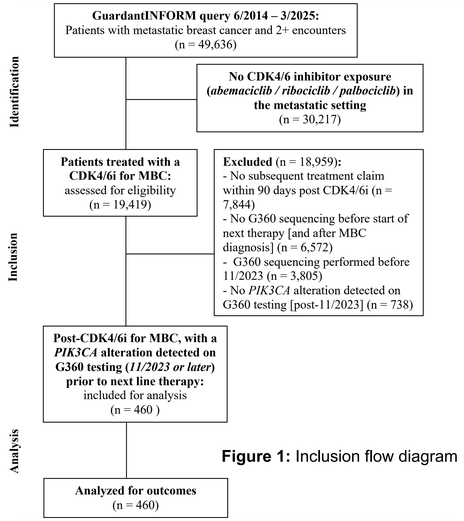


Figure 1: Inclusion flow diagram

Table 1. Cohort characteristics

	PIK3CA mutant cohort		Dual *PIK3CA* + *ESR1* mutant cohort	
Characteristic	**N**	**%**	**N**	**%**
Total N	460		165	
Therapy selection post-CDK4/6i				
Capivasertib regimen	115	25%	28	17%
CDK4/6i-regimen	105	23%	19	12%
AI or fulvestrant monotherapy	73	16%	21	13%
Elacestrant	66	14%	66	40%
Chemotherapy	57	12%	19	12%
Alpelisib regimen	28	6%	10	6%
Other	16	3%	2	1%
Line of therapy at study inclusion				
2nd	221	48%	78	47%
3rd	126	27%	52	32%
4th or later	113	25%	35	21%

Time to next treatment: capivasertib (blue) vs alpelisib (red)

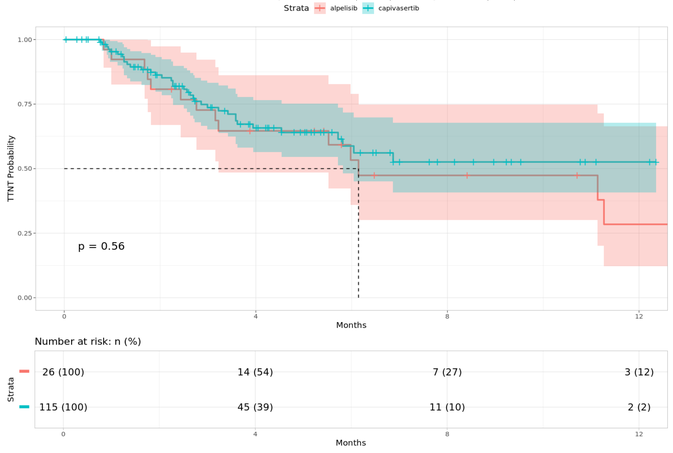


Figure 2: For PIK3CAmut tumors post-CDK4/6i, TTD on next-line capivasertib (blue) vs alpelisib (red); HR 0.82 (95% CI 0.46-1.44). Corresponding table with TTNT and TTD.

Treatment Groups	Alpelisib		Capivasertib		
	total	Median Event Time in Months (95% CI)	total	Median Event Time in Months (95% CI)	Log Rank Test P-value
TTNT	26	6.1 (3.2, NA)	115	NA (5.8, NA)	0.562
TTD	26	5.5 (2.4, NA)	115	6 (4.5, NA)	0.475

Time to next treatment: capivasertib in ESR1mut (blue) vs no ESR1mut (red)

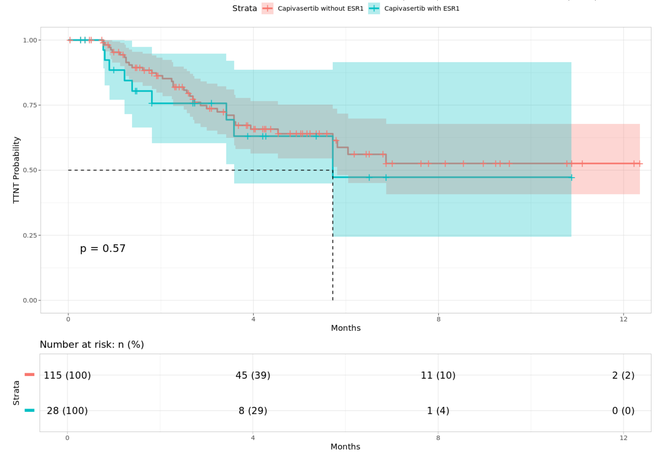


Figure 3: For PIK3CAmut tumors post-CDK4/6i, TTD on next-line capivasertib with co-occurring ESR1mut (blue) vs no ESR1mut (red); HR 1.23 (95% CI 0.63-2.39). Corresponding table with TTNT and TTD.

Treatment Groups	ESR1mut		ESR1wt		
	total	Median Event Time in Months (95% CI)	total	Median Event Time in Months (95% CI)	Log Rank Test P-value
TTNT	28	5.72 (3.58, NA)	115	NA (5.81, NA)	0.574
TTD	28	4.89 (1.84, NA)	115	6.01 (4.5, NA)	0.537

Table 2. Pre- and post-capivasertib ctDNA sequencing: most common alterations detected (>10% frequency before and/or after therapy)

G360 pre-capivasertib (n=115)				G360 post-capivasertib [within 90 days] (n =15)			
Gene	**Alteration type**	**N**	**%**	**Gene**	**Alteration type**	**N**	**%**
PIK3CA	snv	112	97%	PIK3CA	snv	13	87%
TP53	snv	56	49%	TP53	snv	8	53%
ESR1	snv	27	24%	ESR1	snv	2	13%
ARID1A	snv	13	11%	ARID1A	snv	1	7%
CCND1	snv	12	10%	**CCND1**	**snv**	**3**	**20%**
FGFR1	cnv	11	10%	**FGFR1**	**cnv**	**3**	**20%**
KRAS	snv	5	4%	**KRAS**	**snv**	**2**	**13%**

CONCLUSIONS AND FUTURE DIRECTIONS

- In this real-world analysis, patients with PIK3CAmut mBC and CDK4/6i progression were most frequently treated with capivasertib as subsequent therapy when no ESR1mut was identified.
- Dual *PIK3CA* and *ESR1* mutant disease received elacestrant most often.
- Capivasertib responses may differ based upon genomic alterations in baseline ctDNA, including the presence of ESR1mut, though these exploratory findings require additional follow up for data maturity and future validation.
- Though limited by small sample size, differential frequency of *FGFR1*, *CCND1*, and *KRAS* alterations at progression on capivasertib may warrant further investigation.

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