

Exploratory biomarker analysis from a phase 1b/2 trial of zanidatamab + evorpacept in patients with HER2-positive metastatic breast cancer

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Objective

- To evaluate biomarkers of clinical response and potential resistance mechanisms to zanidatamab + evorpacept in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC) previously treated with trastuzumab deruxtecan (T-DXd)



Conclusions

- Zanidatamab + evorpacept showed promising antitumour activity in patients with heavily pretreated HER2-positive mBC, all of whom had received prior T-DXd; greater antitumour activity was observed in patients with centrally confirmed HER2 (ccHER2)-positive disease
- Durable responses in ccHER2-positive disease were largely observed in patients with higher CD47 expression, supporting a CD47-dependent HER2-driven biology that resulted in prolonged progression-free survival (PFS)
- In patients with complete response (CR) or partial response (PR), rapid on-treatment decreases in plasma *ERBB2* copy number and circulating tumour DNA (ctDNA) level, co-occurring with fewer gene alterations in RTK/RAS/PI3K signalling pathways, indicate HER2-driven signalling with limited bypass pathway activation
- Most patients with ccHER2-positive disease remained *ERBB2*-amplified after prior T-DXd, supporting continued use of HER2-targeted therapies, including zanidatamab
- A biomarker-driven approach incorporating CD47 may optimise patient selection for this combination regimen and warrants further study

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Introduction

- There is an ongoing need for novel HER2-targeted regimens, especially chemotherapy-free options, for patients with HER2-positive mBC that progressed on currently available therapies, including T-DXd^{1,2}
- Zanidatamab is a humanised, IgG1-like, HER2-directed, bispecific antibody that has demonstrated promising antitumour activity across multiple HER2-expressing cancers, including HER2-positive mBC³⁻⁷
 - Zanidatamab promotes HER2 clustering and internalisation, inhibits downstream HER2 signalling, and elicits potent immune-mediated effects, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP)³
- CD47 is a cell-surface protein upregulated on tumour cells that interacts with signal regulatory protein (SIRP) α on macrophages to transmit a "don't-eat-me" signal and inhibit phagocytosis⁸
- Evorpacept is a high-affinity CD47 blocker with an inactive fragment crystallisable (Fc) domain designed to block the CD47-SIRP α interaction and enhance ADCP in combination with other therapies while avoiding the toxicity of conventional CD47 blockers⁸
- The antitumour activity of zanidatamab may be enhanced with the addition of evorpacept by combining direct targeting of HER2-expressing tumour cells and ADCP induction by zanidatamab with evorpacept-mediated phagocytic cell activation
- A phase 1b/2 trial (NCT05027139) investigated zanidatamab + evorpacept in patients with locally advanced, inoperable or metastatic HER2-expressing cancers, including mBC⁹

Results

- A total of 24 patients were included in the current analyses (data cutoff: August 1, 2024), including 10 with ccHER2-positive disease
- Three patients received zanidatamab + evorpacept 20 mg/kg, and 21 received zanidatamab + evorpacept 30 mg/kg
- Patients had received a median of 5 (range, 3–7) prior HER2-targeted therapies in any setting, and all patients had prior T-DXd

Table 1. Overall disease response

	All N = 24	ccHER2-positive n = 10	Not ccHER2-positive n = 14 ^a
cORR, n (%)	8 (33.3)	6 (60.0)	2 (14.3)
cBOR, n (%)			
CR	1 (4.2)	1 (10.0)	0
PR	7 (29.2)	5 (50.0)	2 (14.3)
SD	8 (33.3)	2 (20.0)	6 (42.9)
PD	7 (29.2)	1 (10.0)	6 (42.9)
NE	1 (4.2)	1 (10.0)	0
DOR, n (%)	16 (66.7)	8 (80.0)	8 (57.1)
DOR, median (95% CI), mo	20.2 (3.6, NE)	20.2 (5.6, NE)	NE (3.6, NE) ^b
PFS, median (95% CI), mo	3.6 (1.7, 11.0)	8.3 (0.6, NE)	2.8 (1.6, 11.0)

Data cutoff: August 1, 2024. Responses were evaluated in all patients with measurable disease who had 21 post-baseline disease assessment per RECIST v1.1 or who discontinued study treatment due to death or clinical progression.
^aAmong patients without ccHER2-positive disease, 6 had IHC 2+/FISH-negative disease, 5 had IHC 1+/FISH-negative disease, and 3 had IHC 0/FISH-negative disease. ^bMedian DOR was NE because only 2 patients achieved an objective response, and 1 had disease progression while the other did not yet have an event.
cBOR, confirmed best overall response; cccHER2, centrally confirmed human epidermal growth factor receptor 2; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NE, not estimable; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

- Among all patients, the confirmed objective response rate (cORR) was 33% and the median PFS was 3.6 months
- Patients with ccHER2-positive disease had numerically higher cORR and median PFS compared with patients without ccHER2-positive disease

Table 2. Concordance between *ERBB2* amplification status by central tissue-based FISH and plasma ctDNA NGS

<i>ERBB2</i> FISH	<i>ERBB2</i> ctDNA, n			Total n/N (%)
	Amplified	Not amplified	Total	
Positive	6	1 ^a	7	6/7 (86)
Negative	6	7	13	7/13 (54)

Data cutoff: August 1, 2024.
^aOne patient with a FISH-positive tissue sample was negative by ctDNA NGS, possibly due to low tumour fraction below the assay's limit of detection.
ctDNA, circulating tumour DNA; FISH, fluorescence in situ hybridisation; NGS, next-generation sequencing.

- Of 24 treated patients, 20 had baseline plasma ctDNA samples, of whom 12 were *ERBB2*-amplified per ctDNA NGS
- Of 7 patients who were FISH-positive by central tissue assessment at baseline, 6 had *ERBB2* amplification by ctDNA NGS, demonstrating 86% concordance
- Among patients with tumour tissue-negative *ERBB2* amplification status by central FISH testing, 54% (7 of 13) were also negative by NGS of plasma ctDNA samples
- Differences between central tumour tissue and liquid biopsy *ERBB2* amplification status may reflect method differences, tumour heterogeneity, and timing of the tumour sampling, with ctDNA providing the baseline amplification just prior to the first doses of zanidatamab and evorpacept

Table 3. Overall disease response by CD47 expression

Efficacy endpoints	ccHER2-positive		Not ccHER2-positive	
	CD47 expression $\geq 20\%$ (n = 5)	CD47 expression $< 20\%$ (n = 4)	CD47 expression $\geq 20\%$ (n = 4)	CD47 expression $< 20\%$ (n = 7)
CR/PR, n (%)	5 (100)	1 (25)	0	1 (14)
SD/PD, n (%)	0	3 (75)	1 (100)	6 (86)
DOR, median, (95% CI), mo	20.2 (5.6, NE)	NE (NE, NE)	N/A	3.6 (NE, NE)

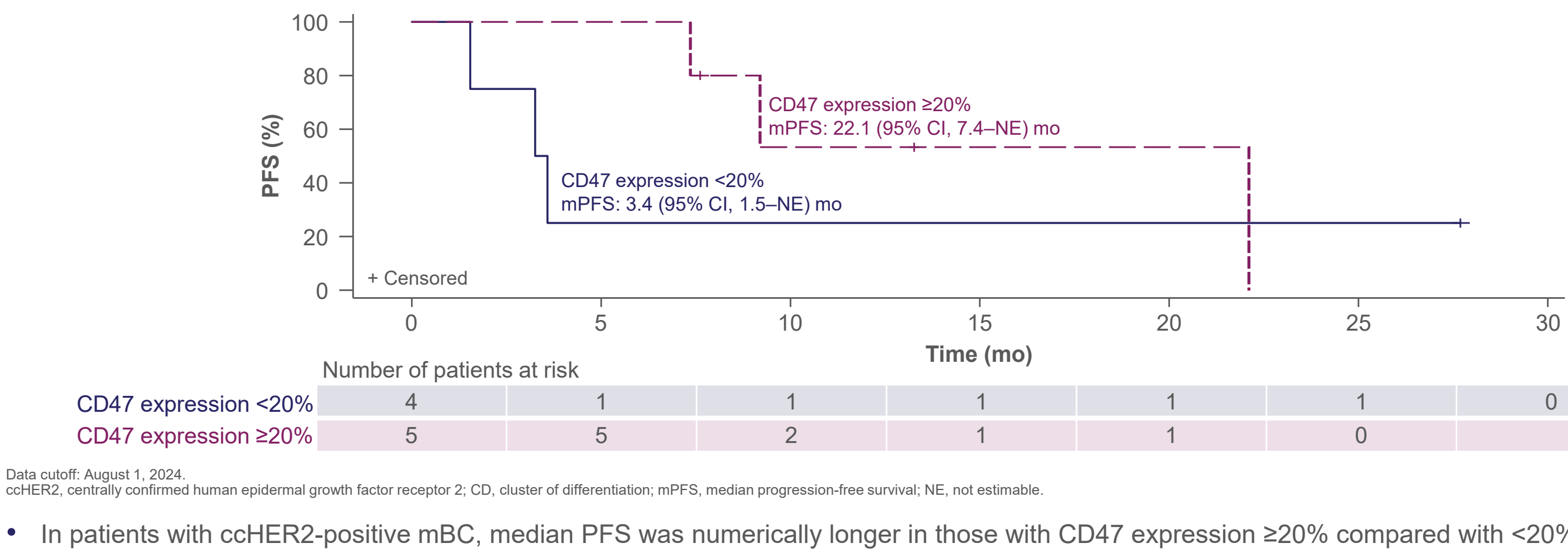
Data cutoff: August 1, 2024. Percentage of CD47 membrane staining of any intensity was classified as $< 20\%$ or $\geq 20\%$.
^accHER2, centrally confirmed human epidermal growth factor receptor 2; CD, cluster of differentiation; CR, complete response; DOR, duration of response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.

- 17 of 24 patient samples were evaluable for CD47 expression (2 samples were not tested, 5 samples failed CD47 testing)
- All 5 patients with ccHER2-positive mBC and CD47 expression $\geq 20\%$ had CR or PR; median DOR was 20.2 months (95% CI, 5.6–not estimable)
- Of the samples tested, CD47 expression $\geq 20\%$ was observed in tissue samples from 5 of 9 (55.6%) patients with ccHER2-positive disease and in 1 of 8 (12.5%) patients without ccHER2-positive disease

Methods

- Patients with HER2-positive (IHC 3+ or IHC 2+/FISH-positive) mBC were enrolled in cohort 1 of a phase 1b/2 trial based on local HER2 testing of archival tissue; HER2 status was retrospectively evaluated by central assessment
- Central HER2 IHC/FISH testing was performed on archival (n = 5) or fresh (n = 19) baseline tumour biopsies using the Dako Herceptest (polyclonalAb) IHC and Abbott PathVysion HER2 DNA Probe FISH kit (HER2/CEP17 ratio ≥ 2.0)
 - HER2 status was retrospectively assessed using fresh tumour biopsies, if feasible
 - In part 1, patients received zanidatamab 1200 mg (< 70 kg) or 1600 mg (≥ 70 kg) + evorpacept 20 mg/kg (part 1A) or 30 mg/kg (part 1B) IV Q2W in 28-day cycles. In part 2, patients received zanidatamab + evorpacept 30 mg/kg
 - The exploratory analyses presented here include patients from part 1 (A and B) and part 2 cohort 1
- Best overall response was assessed by investigators using RECIST version 1.1
- CD47 expression was evaluated by IHC on archival or fresh baseline tumour biopsies using an anti-CD47 antibody (Abcam clone ab218810) on Ventana Benchmark Ultra (IQVIA)
- Plasma ctDNA was collected at baseline (predose on cycle 1 day 1) and during treatment (cycle 2 day 15) and analysed by next-generation sequencing (NGS) using Guardant Infinity (Guardant Health); *ERBB2* amplification was defined as copy number > 2.2
- Molecular response (MR) scores indicate changes in plasma ctDNA levels from baseline and were calculated using tumour fraction (TF) as follows: MR = [(baseline TF – on-treatment TF) / (baseline TF)] – 100

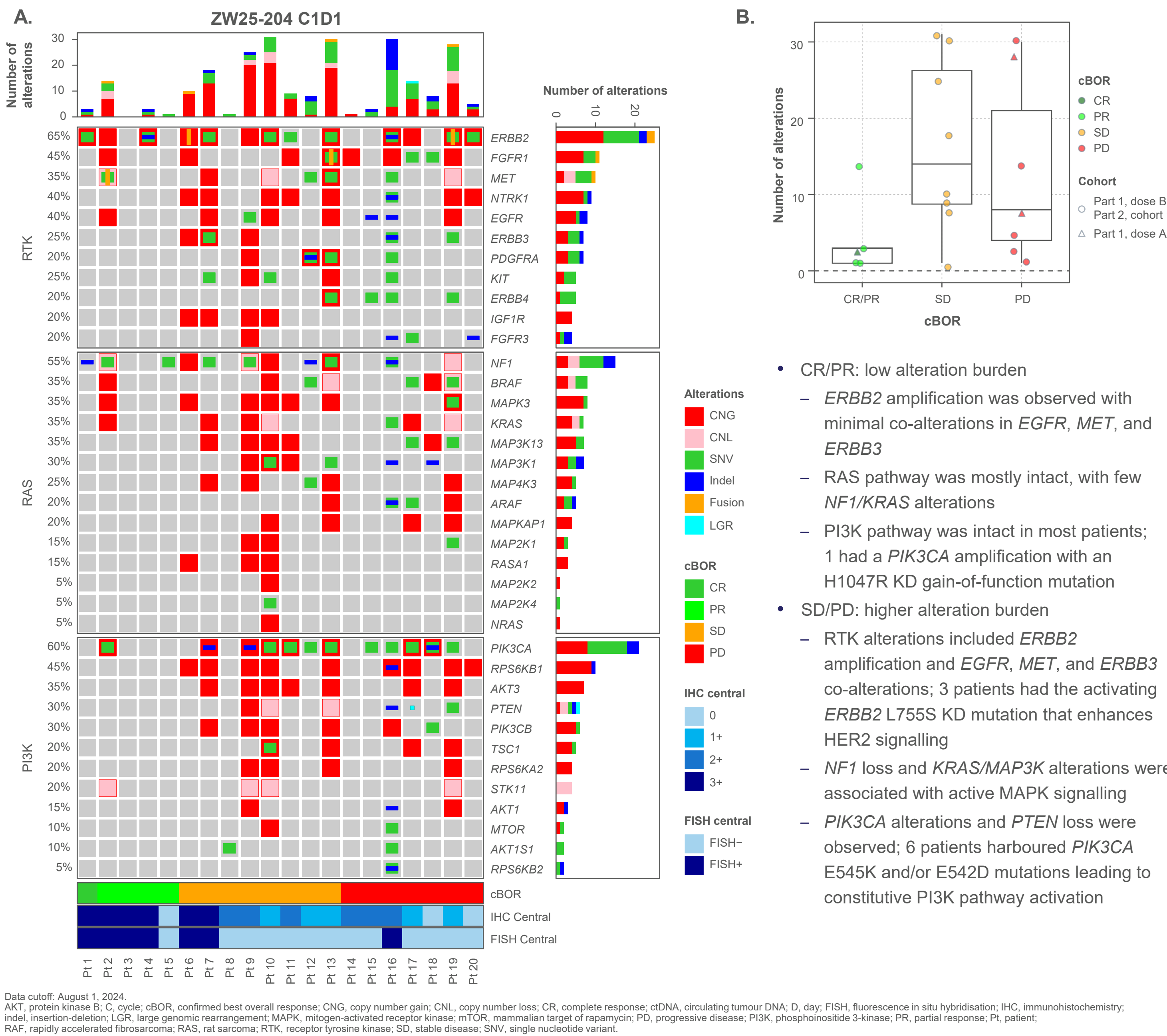
Figure 2. PFS by CD47 expression in patients with ccHER2-positive disease



Data cutoff: August 1, 2024.
ccHER2, centrally confirmed human epidermal growth factor receptor 2; CD, cluster of differentiation; mPFS, median progression-free survival; NE, not estimable.

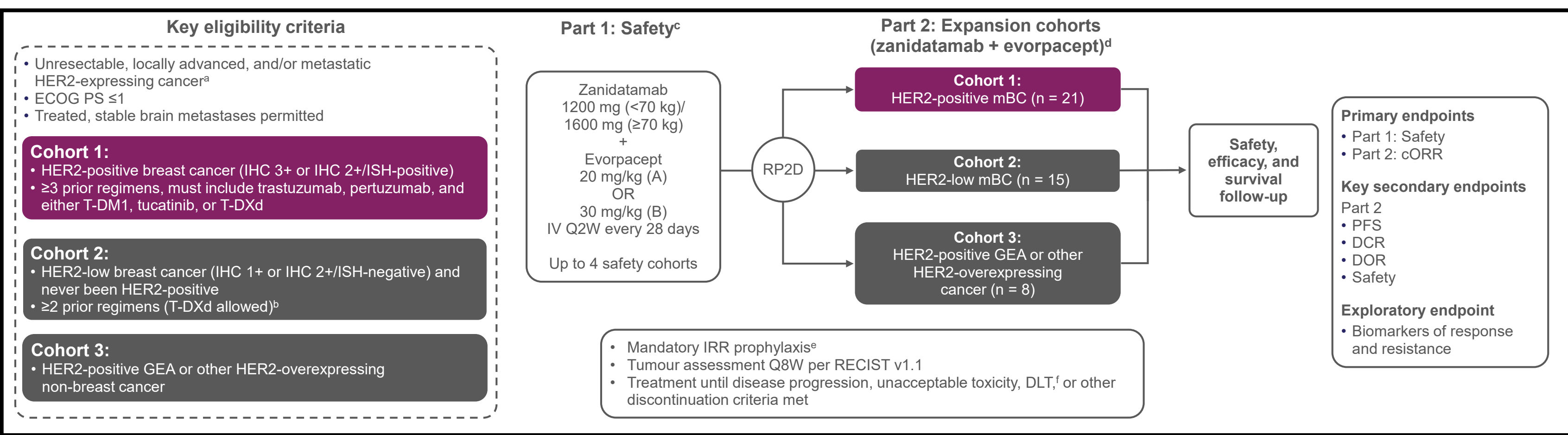
- In patients with ccHER2-positive mBC, median PFS was numerically longer in those with CD47 expression $\geq 20\%$ compared with $< 20\%$

Figure 3. (A) Baseline ctDNA gene alterations across RTK, RAS, and PI3K pathways and (B) number of gene alterations by cBOR



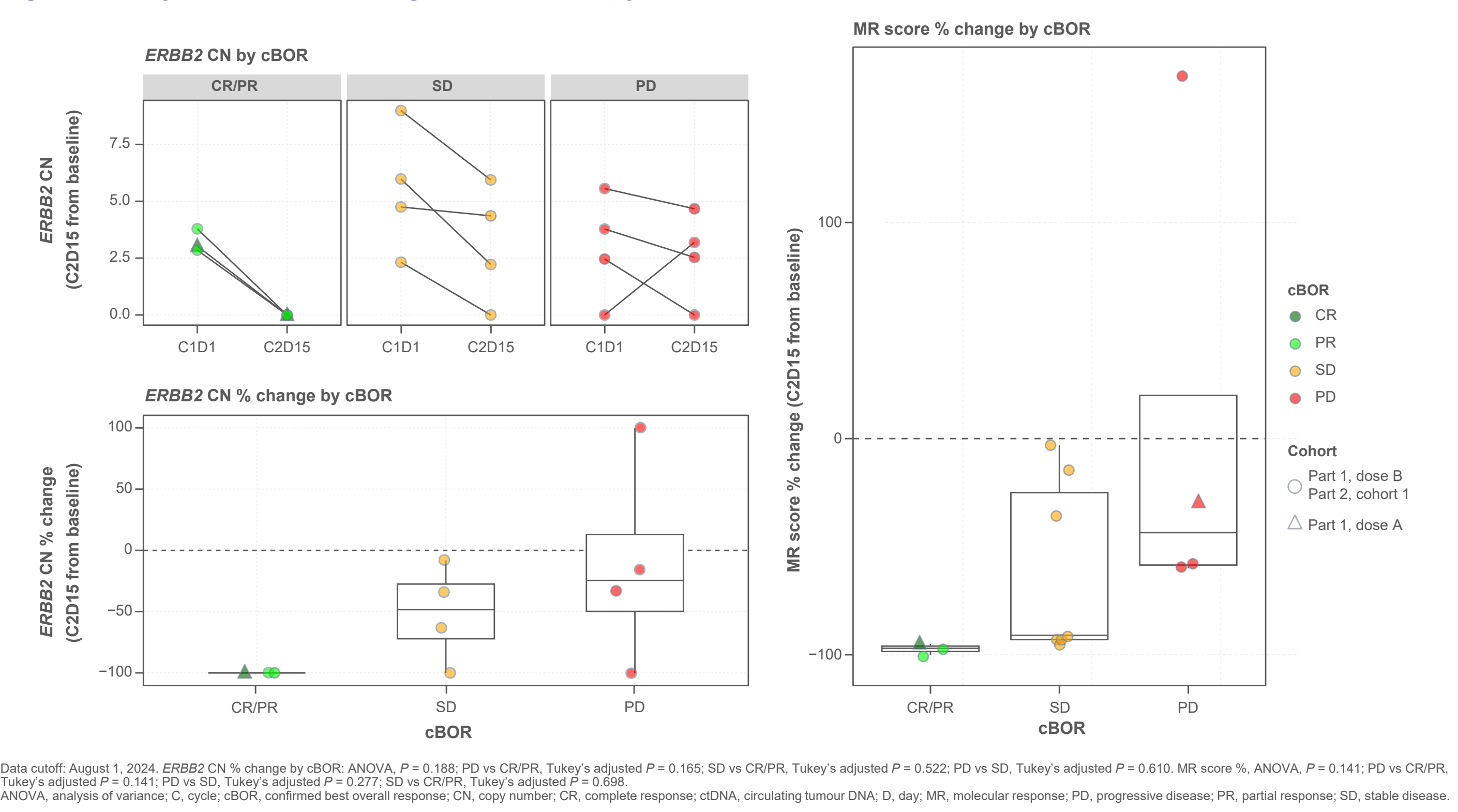
Data cutoff: August 1, 2024.
AKT, protein kinase B; C, cycle; cBOR, confirmed best overall response; CNG, copy number gain; CNL, copy number loss; CR, complete response; ctDNA, circulating tumour DNA; D, day; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; indel, insertion-deletion; LGR, large genomic rearrangement; MAPK, mitogen-activated protein kinase; PD, progressive disease; PI3K, phosphoinositide 3-kinase; PR, partial response; PI, patient; RAS, rat sarcoma; RTK, receptor tyrosine kinase; SD, stable disease; SNV, single nucleotide variant.

Figure 1. Phase 1b/2 study design



Figures adapted from Montero AJ, et al. Poster presented at SABCS 2024. P58-09. Data cutoff: August 1, 2024.
^aFor local or central assessment. ^bPrior HER2-targeted therapies were initially excluded; the protocol was amended to allow prior treatment with T-DXd following its approval in this patient population. ^cIn patients from cohorts 1 and 2. ^dRP2D: Zanidatamab 1200 mg (patients < 70 kg) or 1600 mg (patients ≥ 70 kg) IV Q2W and evorpacept 30 mg/kg IV Q2W on days 1 and 15 of each 28-day cycle. ^eProphylactic treatment included corticosteroids, antiemetics, and antiemetics prior to each zanidatamab infusion. ^fIncluding grade 3 RRE. ^gcORR, confirmed objective response rate; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEA, gastro-oesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRR, infusion-related reaction; ISH, in situ hybridisation; IV, intravenous; mBC, metastatic breast cancer; PFS, progression-free survival; Q2W, once every 2 weeks; Q3W, once every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; T-DXd, trastuzumab deruxtecan; T-DXd, trastuzumab deruxtecan.

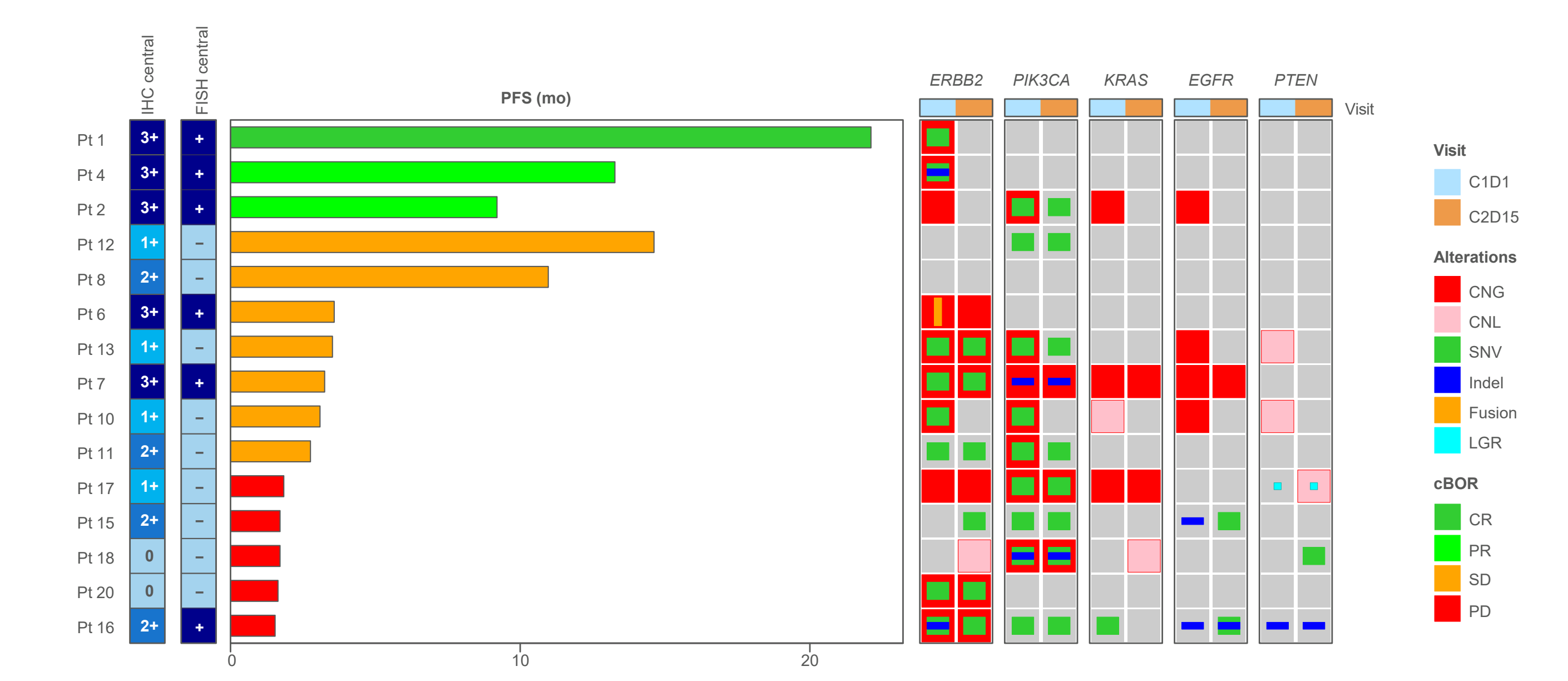
Figure 4. Early on-treatment changes in *ERBB2* copy number and ctDNA



Data cutoff: August 1, 2024. *ERBB2* CN % change by cBOR: ANOVA, $P = 0.188$; PD vs CR/PR, Tukey's adjusted $P = 0.165$; SD vs CR/PR, Tukey's adjusted $P = 0.522$; PD vs SD, Tukey's adjusted $P = 0.610$. MR score % change by cBOR: ANOVA, $P = 0.141$; PD vs SD, Tukey's adjusted $P = 0.141$; PD vs CR/PR, Tukey's adjusted $P = 0.698$. ANOVA, analysis of variance; C, cycle; cBOR, confirmed best overall response; CN, copy number; CR, complete response; ctDNA, circulating tumour DNA; D, day; MR, molecular response; PD, progressive disease; PR, partial response; SD, stable disease.

- Matched baseline and on-treatment ctDNA samples were available for 14 of 24 patients, of whom 10 had baseline *ERBB2* amplification
- Patients with CR or PR showed $> 90\%$ decrease in *ERBB2* copy number, whereas patients with SD or PD had $< 90\%$ changes
- Patients with CR or PR also had $> 90\%$ reductions in MR score (measure of ctDNA change); those with SD showed variable changes in MR score ranging from 5% to 94% decrease, while those with PD ranged from 40% decrease to an increase of 267%

Figure 5. On-treatment ctDNA gene alterations across RTK, RAS/MAPK, and PI3K/AKT pathways



Data cutoff: August 1, 2024.
AKT, protein kinase B; C, cycle; cBOR, confirmed best overall response; CNG, copy number gain; CNL, copy number loss; CR, complete response; ctDNA, circulating tumour DNA; D, day; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; indel, insertion-deletion; LGR, large genomic rearrangement; MAPK, mitogen-activated protein kinase; PD, progressive disease; PI3K, phosphoinositide 3-kinase; PR, partial response; PI, patient; RAS, rat sarcoma; RTK, receptor tyrosine kinase; SD, stable disease; SNV, single nucleotide variant.

- Patients with CR or PR showed a reduction in detectable alterations
 - In the RTK pathway, on-treatment loss of *ERBB2* alterations was consistent with a reduction of HER2-driven subclones; baseline *KRAS/EGFR* gains were also undetectable
 - In 1 patient, *PIK3CA* amplifications decreased (single nucleotide variant persisted)
- Patients with SD or PD exhibited genomic persistence
 - ERBB2* alterations persisted in all but 1 patient; emergent *ERBB2* alterations were observed in 2 patients
 - PIK3CA*, *KRAS*, *EGFR*, and *PTEN* alterations remained common and largely stable, consistent with signalling alteration with persistent pathway activation