Poster PS8-03

Exploratory biomarker analysis of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) efficacy in human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (mBC) in DESTINY-Breast03

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Objective

- This was the first exploratory biomarker analysis of DESTINY-Breast03 aimed to investigate the potential prognostic and/or predictive value of baseline genomic alterations with T-DXd versus T-DM1 treatment in patients with HER2+ mBC. Genomic alterations at end of treatment (EOT) were also examined to assess their emergence after treatment with T-DXd versus T-DM1

Conclusions

- Based on this comprehensive analysis, genomic alterations at baseline were not identified to be predictive of efficacy of T-DXd compared with T-DM1
- T-DXd maintained superior activity compared with T-DM1 regardless of the presence of predefined detectable baseline genomic alterations relevant to mBC, including phosphoinositide 3-kinase (PI3K), homologous recombination deficiency (HRD), breast cancer gene 1/2 (*BRCA1/2*), and tumor protein 53 (*TP53*)
- Emergence of topoisomerase 1 (*TOP1*) mutations after T-DXd treatment represents a potential mechanism of resistance in a limited number of patients from DESTINY-Breast03. Due to the small number of cases and currently unknown impact of observed mutations on TOP1 function or DXd binding, additional datasets may be beneficial to further characterize the significance of this finding[1,2]

Plain Language Summary

Why did we perform this research?
Trastuzumab deruxtecan (T-DXd) is an anticancer therapy that targets a protein called human epidermal growth factor receptor 2 (HER2) which is highly expressed in approximately 20% of breast cancer cases.[1-3] The treatment benefits and safety of T-DXd were compared with those of trastuzumab emtansine (T-DM1) in the DESTINY-Breast03 trial.[4,5] Patients included in the trial must have had HER2-positive breast cancer that could not be removed by surgery and/or had spread to other areas of the body (metastatic).[4,5] Previous results from DESTINY-Breast03 showed T-DXd to be more beneficial in patients compared with T-DM1.[4,5] The objective of this biomarker analysis was to investigate the effect of T-DXd versus T-DM1 according to genomic alterations present at the start of the trial (before receiving T-DXd or T-DM1 treatment). The emergence of genomic alterations after treatment with T-DXd or T-DM1 was also investigated.

How did we perform this research?
Blood samples were collected from patients in the DESTINY-Breast03 trial at the start and end of trial treatment with either T-DXd or T-DM1. Biomarkers within the samples were measured to determine the presence or absence of a specific gene alteration. Efficacy outcomes were assessed to investigate whether the presence of gene alterations was associated with the clinical effects of T-DXd versus T-DM1 treatment.

What were the findings of this research?
T-DXd consistently demonstrated better treatment benefits compared with T-DM1 across all the biomarker groups analyzed at the start of treatment. At the end of treatment, *PI3KCA* mutations were found to persist after T-DM1 treatment compared with T-DXd. In addition, *TOP1* mutations were found after T-DXd treatment in a small number of patients and may represent a rare mechanism by which T-DXd stops having an effect.

What are the implications of this research?
These results demonstrated that the treatment benefits of T-DXd do not appear to be influenced by the biomarkers assessed in this analysis. Further studies are needed to assess the implications of emerging mutations with treatment.

Where can I access more information?
To learn more about the DESTINY-Breast03 study, you can visit https://clinicaltrials.gov/ct2/show/NCT03529110

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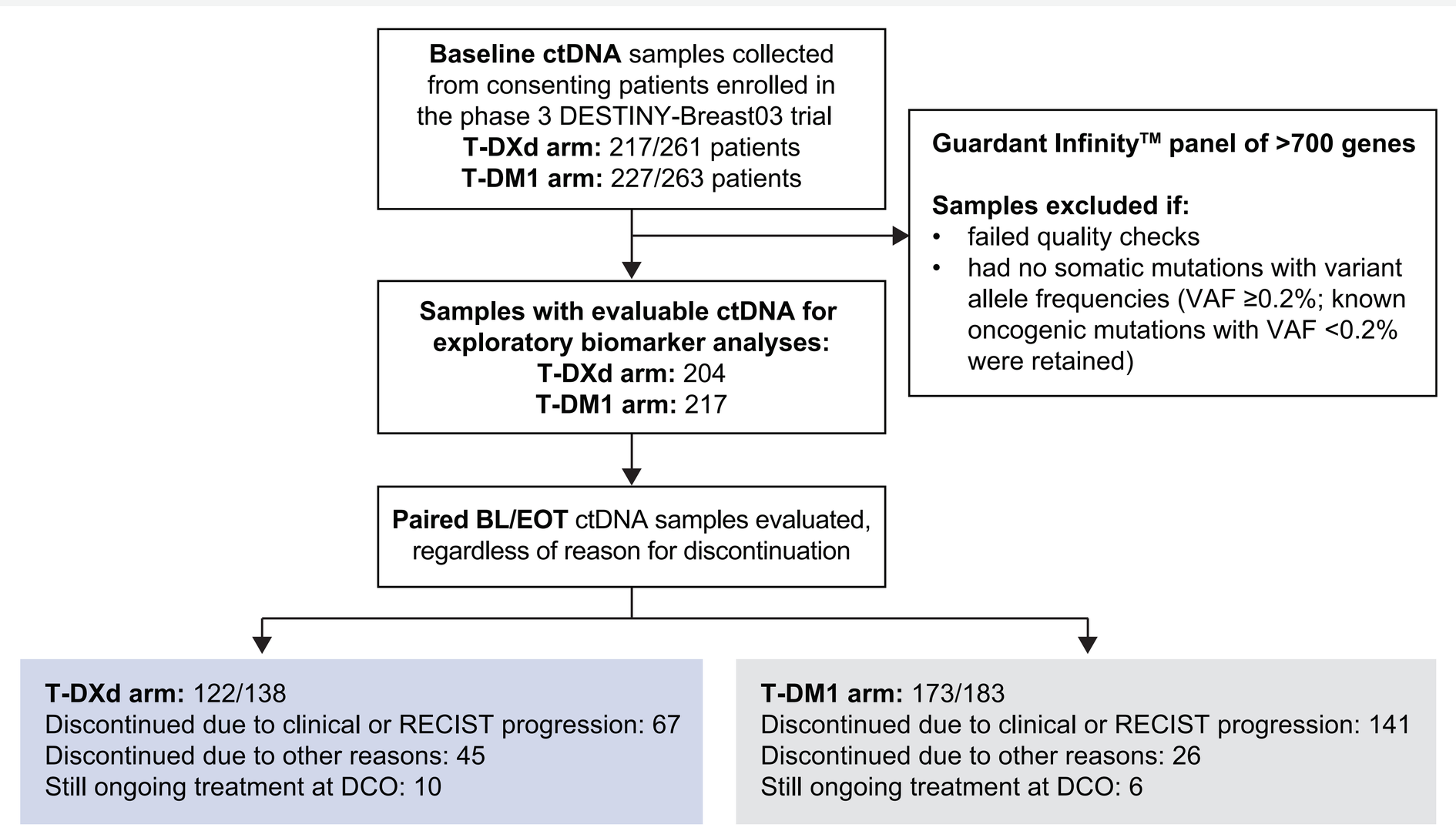
Introduction

- In the randomized DESTINY-Breast03 study (NCT03529110), T-DXd, a HER2-directed antibody-drug conjugate, demonstrated superior efficacy compared with T-DM1 in patients with HER2+ mBC that progressed on or after trastuzumab plus taxane[3]
- During the second interim analysis (data cutoff [DCO] July 25, 2022), T-DXd demonstrated clinically meaningful improvement versus T-DM1, with a median progression-free survival (mPFS) by blinded independent central review (BICR) of 28.8 months versus 6.8 months (hazard ratio, 0.33 [95% CI, 0.26-0.43])[3]
  - Confirmed objective response rate (ORR) by BICR was 79% (21% experiencing a complete response [CR]) with T-DXd versus 35% (10% experiencing a CR) with T-DM1[3]
- Based on DESTINY-Breast03 results, T-DXd was approved for the treatment of patients with HER2+ mBC who have received a prior anti-HER2–based regimen in either the metastatic setting or in the neoadjuvant/adjuvant setting and had developed disease recurrence during or within 6 months of completing therapy[4]
- The cytotoxic payload of T-DXd is a topoisomerase I inhibitor,[5] and molecular biomarkers of DNA damage response and cell proliferation pathways may be useful as prognostic and predictive biomarkers[6,7]

Methods

- Methods of sample collection are shown in **Figure 1**
- In this comprehensive analysis, a Cox proportional hazards model was used to assess any association between baseline biomarker status and differences in T-DXd versus T-DM1 clinical efficacy (mPFS) at a median follow-up of 28.4 months and 26.5 months in the T-DXd and T-DM1 arms, respectively
  - Large genomic rearrangements were excluded
  - Circulating tumor DNA (ctDNA) tumor fraction (maximum variant allele frequency [VAF]) is a known prognostic factor[8] and was associated with PFS in this biomarker analysis. Because of this, ctDNA tumor fraction was tested as a covariate for each Cox proportional hazards model; this did not change the conclusions for each biomarker
  - Copy number variations (CNVs) were generally excluded (except where noted, i.e. *HER2*, phosphatase and tensin homolog [*PTEN*], *BRCA*, and homologous recombination repair) from correlative analysis because these are only detectable above a certain ctDNA tumor fraction threshold. CNVs are reported only in the baseline genomic landscape
  - Alterations observed in <10% of patients were excluded from correlative analysis

Figure 1. Sample collection



Baseline ctDNA samples collected from consenting patients enrolled in the phase 3 DESTINY-Breast03 trial
T-DXd arm: 217/261 patients
T-DM1 arm: 227/263 patients
Guardant Infinity™ panel of >700 genes
Samples excluded if:
failed quality checks
had no somatic mutations with variant allele frequencies (VAF ≥0.2%; known oncogenic mutations with VAF <0.2% were retained)
Samples with evaluable ctDNA for exploratory biomarker analyses:
T-DXd arm: 204
T-DM1 arm: 217
Paired BL/EOT ctDNA samples evaluated, regardless of reason for discontinuation
T-DXd arm: 122/138
Discontinued due to clinical or RECIST progression: 67
Discontinued due to other reasons: 45
Still ongoing treatment at DCO: 10
T-DM1 arm: 173/183
Discontinued due to clinical or RECIST progression: 141
Discontinued due to other reasons: 26
Still ongoing treatment at DCO: 6

- Genetic alterations of interest were reported regardless of statistical significance, including:
  - Median plasma *HER2* adjusted copy number (aCN), adjusted for ctDNA tumor fraction according to published methods,[9] from patients with *HER2* amplified status
  - PI3K pathway alterations defined per the CAPItello-291 trial: activating mutations in *PIK3CA* and *AKT* and inactivating alterations (including deletions) in *PTEN* genes[10,11]
  - *TP53* alterations included single nucleotide variants (SNVs) and insertions/deletions (indels) and were classified as loss of function according to oncoKB™
  - HRD status (cutoff value 0.4) according to the Guardant Infinity pipeline, which incorporates a probabilistic model of genomic and methylation predictors[12]
  - *BRCA1/2* SNVs, CNVs, or indels, including both somatic and germline, classified as loss of function according to Guardant Health functional annotation (Note: germline mutations were not included if not allowed by enrolling country or site)
    - » HRD status is based on an algorithm employed by Guardant Health which is not fully defined by mutational status. This may partially explain why *BRCA*-mutant cases are not fully encapsulated in the HRD-positive subgroup. In addition, samples with monoallelic loss have been reported to have HRD-loss-of-heterozygosity scores which are similar to *BRCA* wild-type cases.[13,14] The majority of *BRCA1/2* alterations in this ctDNA dataset were deletions, with unknown allelic or monoallelic status and may not have a functional impact (ie, are HRD negative)
- For emerging mutations from paired baseline/EOT ctDNA analysis (**Figure 1**):
  - Analysis included only genes with a prevalence ≥5% in either arm at baseline or EOT
  - A McNemar test was applied to determine if the numbers of mutant cases detected at baseline versus EOT were different on a patient level, within each treatment arm
  - Emerging mutations with a significant *P* value of ≤0.05 by McNemar test were tested to identify treatment arm-specific emerging gene alterations by interaction *P* value based on a generalized linear model, including tumor fraction as a covariate[15]
  - Multiple testing correction was conducted using Benjamini-Hochberg procedure in each treatment arm
  - For *TOP1* mutations, all detected *TOP1* SNVs/indels at baseline or EOT were analyzed and reported regardless of prevalence and VAF

Results

Baseline Genomic Landscape

- The DESTINY-Breast03 baseline genomic landscape was representative of HER2+ breast cancer, with most frequent alterations (SNVs, CNVs, and indels) observed in *TP53* (73%), *HER2* (*ERBB2*; 61%), *CDK12* (52%), and *PIK3CA* (48%)
- In this comprehensive analysis, there were no baseline genomic alterations identified that were predictive of efficacy of T-DXd compared with T-DM1
- Several baseline genomic alterations of interest are reported
- The efficacy and baseline characteristics were comparable for the intent-to-treat versus baseline ctDNA evaluable populations (data not shown)

Baseline *HER2* Genomic Status

- Detection rate of *HER2* amplification in ctDNA was 56% (236 of 421 samples), including aneuploidy and focal *HER2* amplification
- *HER2* plasma aCN was higher in the subgroup of patients with HER2 immunohistochemistry 3+ versus immunohistochemistry 2+ tumors (data not shown)
- Efficacy was comparable in both arms regardless of high/low median *HER2* plasma aCN at baseline; a trend towards lower efficacy was more apparent in the T-DM1 arm, which had numerically shorter mPFS and lower ORRs in the low *HER2* plasma aCN subgroup (**Figure 2; Table 1**)
  - Patients without any *HER2* amplification detected in ctDNA (not detected [ND]) tend to have lower ctDNA tumor fraction, which is positively prognostic,[9] as reflected by the efficacy in this subgroup
- Clinical response to T-DXd was similar and remained greater than that of T-DM1 in patients with (T-DXd, n = 20; T-DM1, n = 20) and without (T-DXd, n = 184; T-DM1, n = 197) baseline activating *HER2* alterations

Baseline PI3K Pathway Alteration Status

- T-DXd maintained superior clinical activity compared with T-DM1 regardless of the presence of PI3K pathway alterations (**Figure 3; Table 1**)
- *PIK3CA* mutations have previously been shown to have a prognostic effect, with longer PFS for patients whose tumors expressed wild-type versus mutated *PIK3CA*[16,17]
- Although there is a potential relationship with *PIK3CA* mutation status and T-DM1 efficacy in early BC, T-DM1 appears to be effective regardless of *PIK3CA* mutation status in mBC[18]

Baseline *TP53* Alteration Status

- T-DXd maintained superior clinical activity to T-DM1 regardless of the presence of *TP53* alterations
- Efficacy was comparable in both arms irrespective of *TP53* alteration status (**Figure 3; Table 1**)

Baseline HRD Status

- T-DXd maintained superior clinical activity to T-DM1 regardless of HRD status
- ORR was similar regardless of HRD status in the T-DXd arm and numerically lower in the HRD positive subgroup of the T-DM1 arm; mPFS tended to be shorter in both arms in patients with HRD positive status (**Figure 3; Table 1**)

Baseline *BRCA1/2* Alteration Status

- T-DXd maintained superior clinical activity to T-DM1 regardless of *BRCA1/2* alteration status
- ORRs were similar in the T-DXd arm regardless of *BRCA1/2* alteration status, whereas ORR tended to be lower in patients with *BRCA1/2* alterations in the T-DM1 arm (**Figure 3; Table 1**)
- mPFS tended to be slightly shorter in patients with *BRCA1/2* alterations compared with patients without *BRCA1/2* alterations in both arms

Emerging Mutations at EOT

- The number of patients with *APC* and *ATM* mutations at EOT was higher compared to baseline in the T-DM1 arm based on the McNemar test. In the T-DXd arm at EOT compared with baseline, the number of patients with *CHEK2* mutations was higher and the number of patients with *HER2, GATA3, MED12, PIK3CA,* and *TP53* mutations was lower, per the McNemar test (**Figure 4**)
- *PIK3CA* mutations were retained after treatment in the T-DM1 arm compared with the T-DXd arm, where mutations were less frequent at EOT, based on a generalized linear model accounting for ctDNA tumor fraction (interaction *P* value, 0.014; **Figure 4**)
- Although present at low frequencies in both arms at baseline and EOT (<5.0%), *TOP1* mutations appeared to emerge in 4 patients in the T-DXd arm; no emerging *TOP1* mutations were detected in the T-DM1 arm (**Figure 5**)
  - In the T-DXd arm, multiple emerging *TOP1* mutations were detected in 2 patients with a best overall response of partial response who discontinued due to disease progression
  - All emerging *TOP1* mutations, except one, have unknown significance relating to TOP1 function or inhibitor binding and span the N-terminal, core, and linker domains of TOP1

Figure 2. Efficacy according to baseline *HER2* plasma aCN

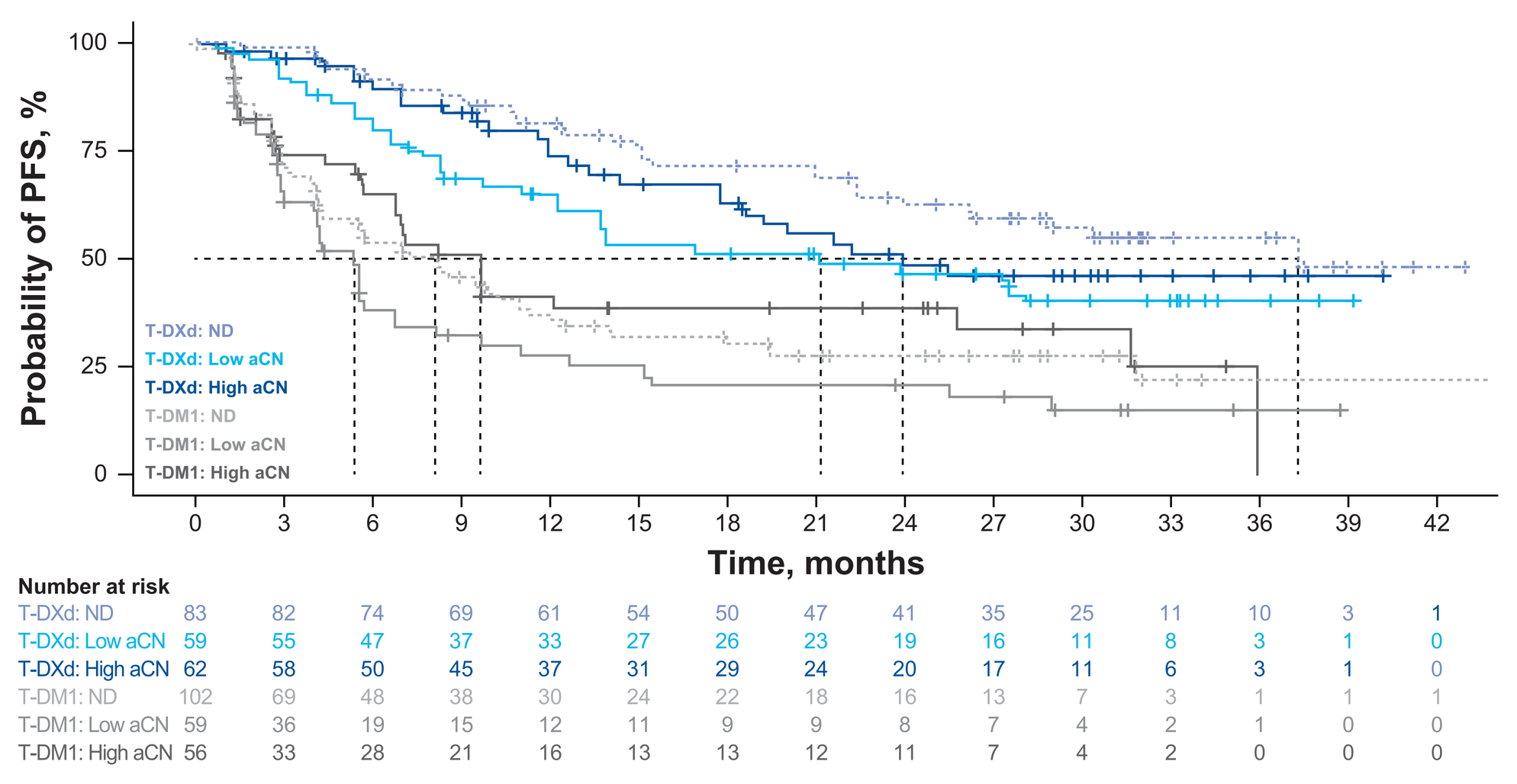
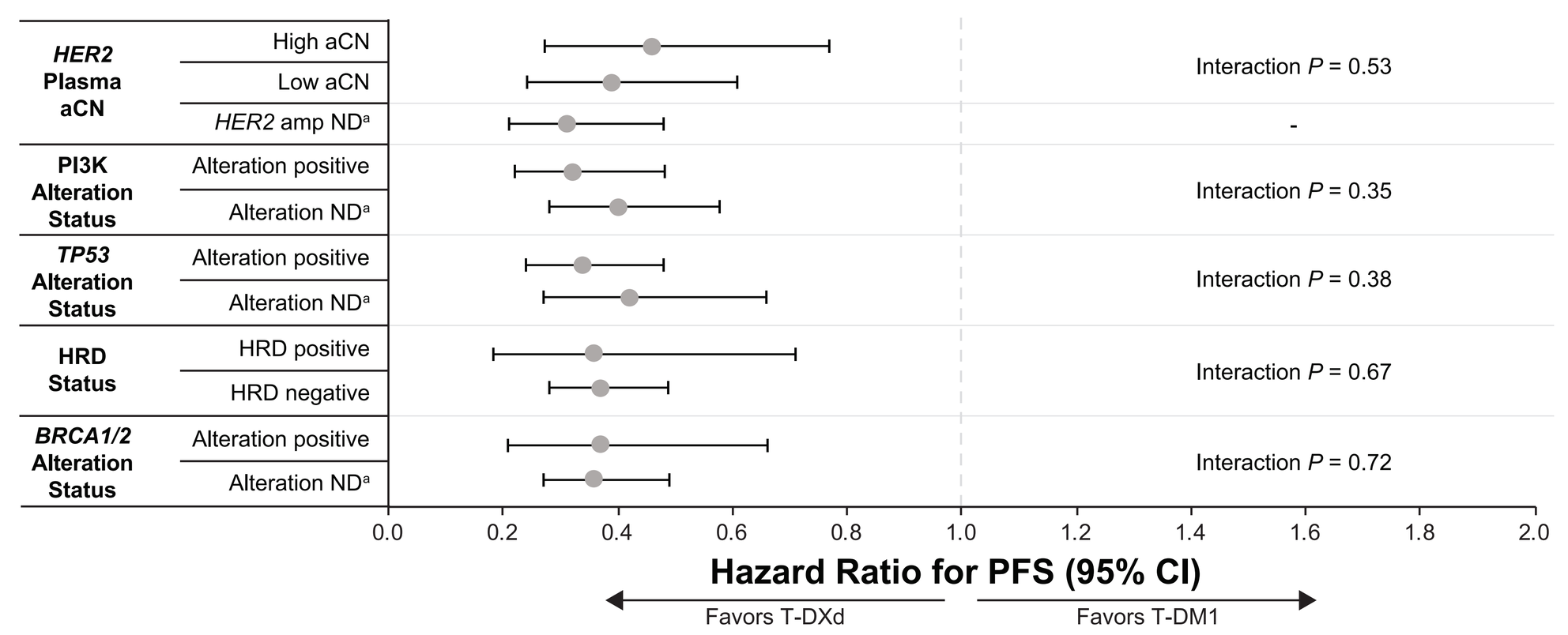


Figure 3. Association of baseline biomarkers and hazard ratio for PFS



HER2 Plasma aCN
High aCN
Low aCN
HER2 amp ND[a]
Interaction P = 0.53
PI3K Alteration Status
Alteration positive
Alteration ND[a]
Interaction P = 0.35
TP53 Alteration Status
Alteration positive
Alteration ND[a]
Interaction P = 0.38
HRD Status
HRD positive
HRD negative
Interaction P = 0.67
BRCA1/2 Alteration Status
Alteration positive
Alteration ND[a]
Interaction P = 0.72
Hazard Ratio for PFS (95% CI)
Favors T-DXd
Favors T-DM1

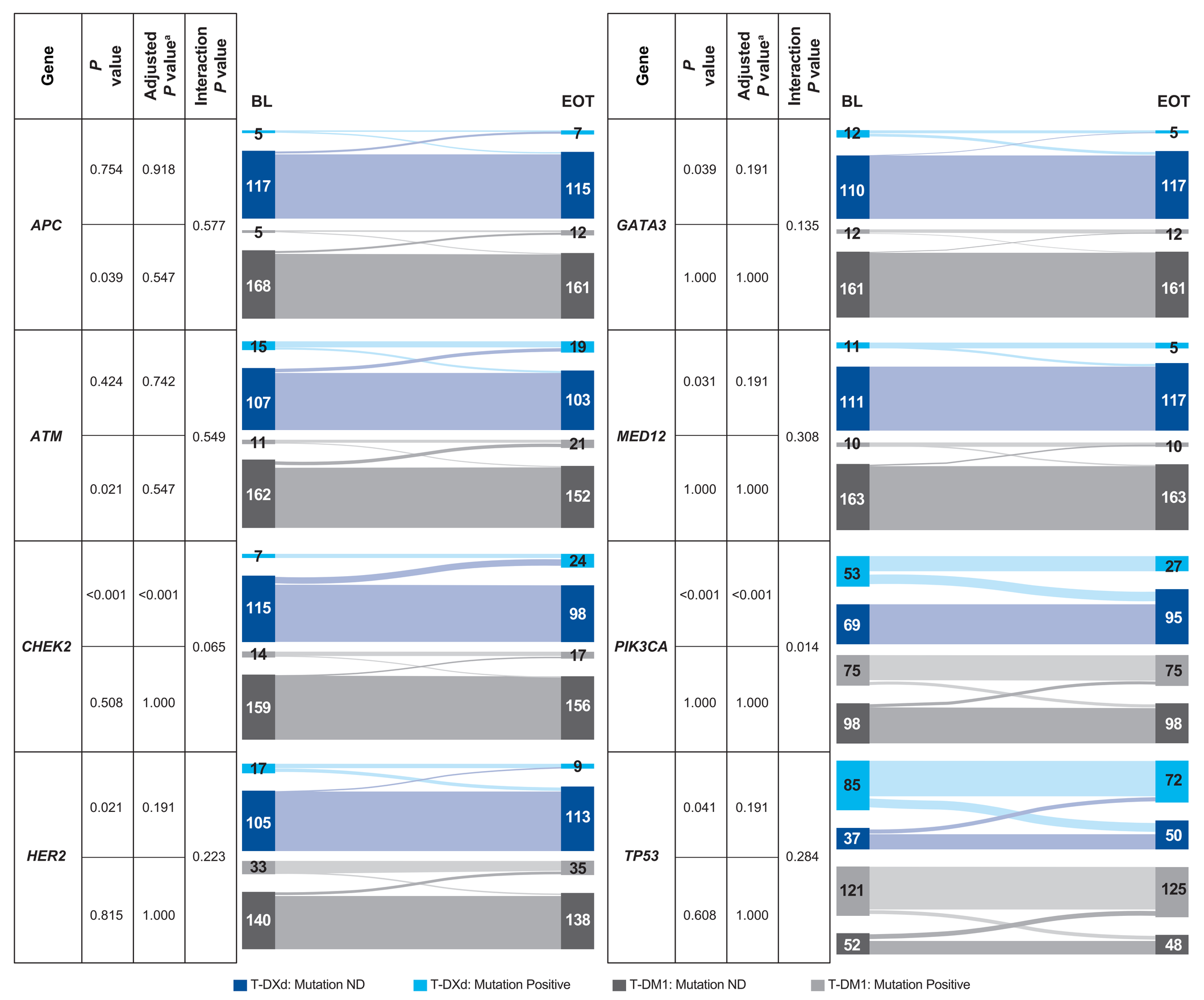
[a]Not detected in samples with analyzable ctDNA.

Table 1. Efficacy according to baseline biomarker status

Biomarker	Status	Treatment Arm, n (%)[a]	ORR (95% CI), %	mPFS (95% CI), months	mPFS Hazard Ratio (95% CI)	mPFS Interaction *P* Value
HER2 Plasma aCN	High aCN	**T-DXd** 62 (30.4)	87.1 (76.1-94.3)	23.9 (18.0-NE)	0.46 (0.27-0.77)	0.53
		T-DM1 56 (25.8)	50.0 (36.3-63.7)	9.7 (6.8-25.7)		
	Low aCN	**T-DXd** 59 (28.9)	81.4 (69.1-90.3)	21.1 (12.3-NE)	0.39 (0.24-0.61)	
		T-DM1 59 (27.2)	35.6 (23.6-49.1)	5.4 (3.0-6.8)		
	HER2 amp ND[b]	**T-DXd** 83 (40.7)	77.1 (66.6-85.6)	37.3 (26.2-NE)	0.31 (0.21-0.48)	-
		T-DM1 102 (47.0)	31.4 (22.5-41.3)	8.1 (4.4-10.9)		
PI3K Alteration	PI3K alteration positive	**T-DXd** 87 (42.6)	80.5 (70.6-88.2)	27.6 (15.0-NE)	0.32 (0.22-0.48)	0.35
		T-DM1 87 (40.1)	33.3 (23.6-44.3)	4.4 (3.2-6.8)		
	PI3K alteration ND[b]	**T-DXd** 117 (57.4)	82.1 (73.9-88.5)	NE (22.1-NE)	0.40 (0.28-0.58)	
		T-DM1 130 (59.9)	40.0 (31.5-49.0)	9.7 (6.8-12.1)		
TP53 Alteration	*TP53* alteration positive	**T-DXd** 123 (60.3)	86.2 (78.8-91.7)	29.0 (21.0-NE)	0.34 (0.24-0.48)	0.38
		T-DM1 137 (63.1)	35.0 (27.1-43.7)	5.6 (4.2-8.2)		
	TP53 alteration ND[b]	**T-DXd** 81 (39.7)	74.1 (63.1-83.2)	27.5 (20.9-NE)	0.42 (0.27-0.66)	
		T-DM1 80 (36.9)	41.3 (30.4-52.8)	8.4 (5.8-14.0)		
HRD Status	HRD positive	**T-DXd** 23 (11.3)	82.6 (61.2-95.1)	12.4 (6.8-NE)	0.36 (0.18-0.71)	0.67
		T-DM1 27 (12.4)	14.8 (4.2-33.7)	2.8 (1.4-4.3)		
	HRD negative	**T-DXd** 181 (88.7)	81.2 (74.8-86.6)	37.3 (23.7-NE)	0.37 (0.28-0.49)	
		T-DM1 190 (87.6)	40.5 (33.5-47.9)	7.1 (5.7-9.7)		
BRCA1/2 Alteration	*BRCA1/2* alteration positive	**T-DXd** 40 (19.6)	80.0 (64.4-91.0)	21.1 (11.9-NE)	0.37 (0.21-0.66)	0.72
		T-DM1 38 (17.5)	26.3 (13.4-43.1)	2.7 (1.5-7.0)		
	BRCA1/2 alteration ND[b]	**T-DXd** 164 (80.4)	81.7 (74.9-87.3)	37.3 (23.7-NE)	0.36 (0.27-0.49)	
		T-DM1 179 (81.1)	39.7 (32.4-47.2)	8.1 (5.6-9.8)		

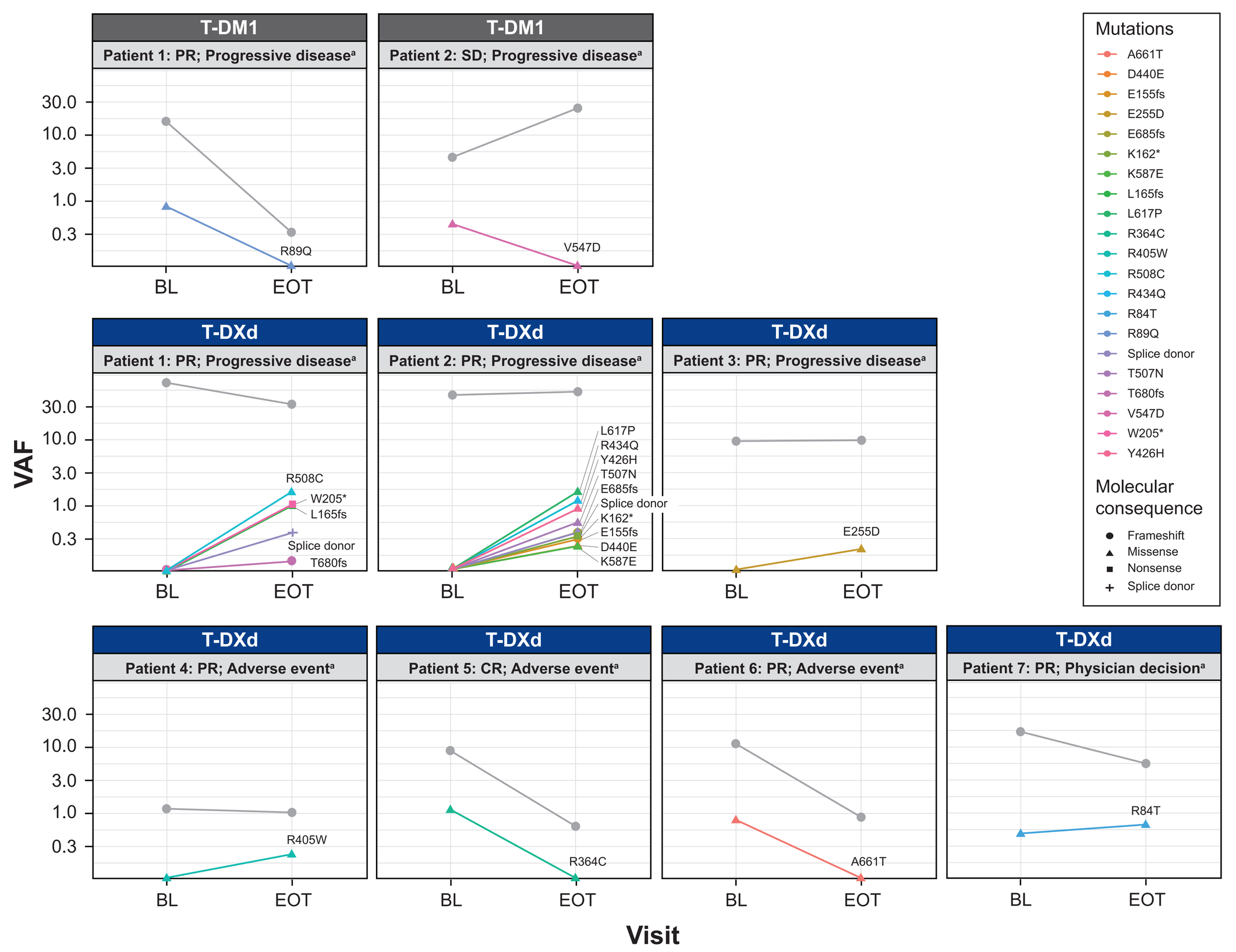
[a]Percentages calculated using 204 and 217 as the denominators for T-DXd and T-DM1, respectively.
[b]Not detected in samples with analyzable ctDNA.

Figure 4. Emerging mutations at EOT



P values were calculated based on the McNemar test.
[a]Multiple testing correction was conducted using Benjamini-Hochberg procedure in each treatment arm.

Figure 5. Emerging *TOP1* mutations at baseline and EOT



Asterisk denotes translation termination. Grey line represents max VAF as tumor fraction.
[a]Confirmed BOR, reason for discontinuation.

Abbreviations

aCN, adjusted copy number; Amp, amplification; *APC*, adenomatous polyposis coli; *ATM*, ataxia-telangiectasia mutated; BC, breast cancer; BICR, blinded independent central review; BL, baseline; BOR, best overall response; *CHEK2*, checkpoint kinase 2; *BRCA1/2*, breast cancer gene 1/2; CNV, copy number variation; CR, complete response; ctDNA, circulating tumor DNA; EOT, end of treatment; *GATA3*, GATA binding protein; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; indels, insertions/deletions; mBC, metastatic breast cancer; *MED12*, mediator complex subunit 12; mPFS, median progression-free survival; ND, not detected; NE, not estimable; ORR, objective response rate; *PTEN*, phosphatase and tensin homolog; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PR, partial response; SD, stable disease; SNV, single nucleotide variant; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; *TOP1*, topoisomerase 1; *TP53*, tumor protein 53; VAF, variant allele frequency.

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Disclosures

Dr. Jacot holds grants/contracts with AstraZeneca, Daiichi Sankyo; has received payment or honoraria for lectures/presentations from AstraZeneca, Daiichi Sankyo, BMS, Novartis, Roche, Eisai, Lilly France, MSD, Pfizer, Seagen; has received support for meeting attendance/travel from AstraZeneca, Chugai Pharma, Eisai, GlaxoSmithKline, Lilly France, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Aventis; and has participated on a Data Safety Monitoring Board/Advisory Board with AstraZeneca, Daiichi Sankyo, BMS, Novartis, Roche, Gilead, Eisai, Lilly France, MSD, Pfizer, Seagen.

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DESTINY Breast03