Poster 7148

Exploratory biomarker analysis of trastuzumab deruxtecan (T-DXd) treatment for HER2-positive (HER2+) metastatic colorectal cancer (mCRC) in DESTINY-CRC02

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Objective

- This exploratory biomarker analysis of DESTINY-CRC02 was conducted to investigate whether baseline genomic alterations in colorectal cancer (CRC)-related genes, expression of genes related to antibody-drug conjugate activity, and molecular response (MR) rates following treatment are associated with trastuzumab deruxtecan (T-DXd) clinical activity in patients with human epidermal growth factor receptor 2–positive (HER2+) metastatic CRC (mCRC)

Conclusions

- The presence of epidermal growth factor receptor (*EGFR*) amplification and an adenomatous polyposis coli (*APC*) mutation were potentially associated with T-DXd efficacy. The effect of these alterations may not be specific to T-DXd, given they have known prognostic effects in CRC and the contribution of each individual alteration was not assessable, due to high overlap
- Adenosine triphosphate binding cassette subfamily B member 1 (*ABCB1*) transporter gene expression was also potentially associated with T-DXd efficacy
- MR analyses suggested that the magnitude of circulating tumor DNA (ctDNA) reduction after 2 cycles of T-DXd treatment was associated with T-DXd clinical response
- Due to the lack of a control arm and the limited sample size of biomarker-defined subgroups, these findings would need validation in a larger study to understand the predictive versus prognostic value of these biomarkers

Plain Language Summary

Why did we perform this research?
Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2 (HER2)-directed antibody-drug conjugate that kills HER2-altered cancer cells. The HER2 protein is abundant in 3-11% of all colorectal cancers (CRC).[1,2] In the DESTINY-CRC02 clinical trial, treatment with T-DXd led to tumor shrinkage in 34% of patients with CRC that had been previously treated and could not be surgically removed or had spread to other body sites (metastatic).[3] This analysis looked at whether patients who participated in DESTINY-CRC02 had alterations in genes relevant to CRC and whether these genetic changes affected the antitumor activity of T-DXd.

How did we perform this research?
To assess whether specific genetic changes were associated with T-DXd treatment outcomes, blood and tumor tissue samples were collected from patients enrolled in the DESTINY-CRC02 trial at the start of trial treatment and/or after 2 treatment cycles with T-DXd. Samples were evaluated to measure gene expression levels and the presence or absence of specific CRC-related genetic alterations. Whether patients with a specific gene alteration or expression level had better or worse clinical outcomes with T-DXd treatment was evaluated.

What are the findings of this research?
A correlation was observed between poorer clinical outcomes and the presence of *EGFR* amplification or *APC* mutations. Higher gene expression of the *ABCB1* transporter was also associated with a poorer response to T-DXd treatment.

What are the implications of this research?
Changes in *EGFR* and *APC* genes and expression levels of the *ABCB1* transporter gene may affect the antitumor activity of T-DXd in patients with metastatic CRC. These findings require validation in a larger study.

Where can I access more information?
To learn more about the DESTINY-CRC02 study, you can visit https://clinicaltrials.gov/study/NCT04744831

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Poster
Supplementary material

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Introduction

- T-DXd, a HER2-directed antibody-drug conjugate, showed clinically meaningful antitumor activity in patients with HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization–positive) mCRC in the randomized phase 2 DESTINY-CRC02 trial[1]
  - Results from the DESTINY-CRC02 trial contributed to the tumor-agnostic accelerated approval of T-DXd by the US Food and Drug Administration for patients with unresectable or metastatic HER2 IHC 3+ solid tumors, including CRC
- Previous exploratory ctDNA analyses of baseline samples in the DESTINY-CRC02 trial investigated *HER2* (*ERBB2*), phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*), and rat sarcoma (*RAS*) mutation status, as well as blood-based tumor mutational burden[1]
  - For these previous analyses, baseline ctDNA samples were available for 118/122 total patients
  - T-DXd had clinical activity in patients with HER2 IHC 3+ status across all key subgroups, including patients with *RAS*-mutant status (subgroup n = 14), a subgroup in which dual HER2 inhibition has little clinical activity[1-3]
- Biomarker analyses of the DESTINY-CRC01 trial indicated T-DXd antitumor activity in patients with baseline activating *RAS*, *PIK3CA*, or *HER2* mutations detected in ctDNA[4]
  - The proportion of patients with activating *HER2* mutations was 15.4% (8/52) in the HER2+ cohort of the DESTINY-CRC01 study
- Numerous prognostic biomarkers have been identified in patients with mCRC, including *EGFR* and *APC* alterations[5,6]
- ctDNA analysis of genomic alterations may improve the precision of targeted therapies in patients with mCRC

Methods

Clinical data

- This exploratory biomarker analysis combined data from patients with HER2+ mCRC enrolled in the 5.4- and 6.4-mg/kg T-DXd cohorts of the DESTINY-CRC02 clinical trial (data cutoff, November 1, 2022)
- The clinical efficacy of T-DXd (objective response rate [ORR] and progression-free survival [PFS]) was compared in patient subgroups with or without detectable genomic alterations and in subgroups defined according to median gene expression cutoffs

RNA sequencing

- Transcriptome analysis was performed on archival tissue samples by RNA sequencing (RNA-seq) with ribosome depletion

ctDNA analyses

- Blood was collected at baseline and after 2 T-DXd treatment cycles (cycle 3, day 1 [C3D1]) for ctDNA analyses performed by Guardant Health
- Genomic landscape was assessed for baseline samples using the Guardant OMNI panel (~500 genes)
  - For the baseline genomic landscape analysis, samples with no gene alterations were excluded from the analysis. Possible germline mutations, synonymous mutations, mutations that are not oncogenic (ie, not considered "likely oncogenic," "oncogenic," or "predicted oncogenic" based on OncoKB) with variant allele frequency (VAF) <0.2, and clonal hematopoiesis of indeterminate potential (CHIP) mutations as reported by Guardant Health were not counted as altered
  - Germline mutations were classified according to the Guardant Health pipeline
- MR was determined using the Guardant OMNI panel described above for baseline samples and the Guardant G360 panel (~74 genes) for C3D1 samples
  - MR was calculated by Guardant Health according to the relative change in mean VAF at C3D1 as compared with baseline
  - Complete MR was defined as 100% reduction in ctDNA levels, partial MR as 50% to <100% reduction in ctDNA levels, and absent MR as <50% reduction in ctDNA levels
- Gene amplification, reported here for *HER2* and *EGFR*, included both focal and aneuploid amplifications, as classified by the Guardant Health pipeline
- *HER2* variants were considered to be activating mutations if they were categorized as "gain-of-function" or "likely gain-of-function" based on OncoKB

Statistical analysis

- Point estimates and two-sided 95% exact binomial CIs were calculated for ORR in each subgroup. Odds ratios (OR) with corresponding 95% CIs were estimated
- The Kaplan-Meier method was used to estimate median event times with two-sided 95% CIs calculated using the Brookmeyer and Crowley method. Hazard ratios (HRs) with corresponding 95% CIs were estimated using Cox proportional-hazards regression models

Results

- 122 patients enrolled in the DESTINY-CRC02 clinical trial comprised the intention-to-treat (ITT) population
  - In the ITT population, median age was 60.2 years (range, 26-84 years); 52.5% of patients were male; and 58.2%, 35.2%, and 6.6% of patients were from Asia-Pacific, Europe, or the United States, respectively
  - The evaluable RNA-seq dataset at baseline included samples from 102 patients
  - Genomic analysis was performed on 120 baseline ctDNA samples
  - MR analysis was performed on 97 samples collected after 2 T-DXd treatment cycles (C3D1), for which paired baseline ctDNA data were also available
- Clinical outcomes for the biomarker-evaluable populations (BEPs) for ctDNA and tissue (RNA-seq) were comparable to the ITT population (**Table 1**)

Baseline ctDNA genomic landscape analysis

- Alterations in *TP53* (84.2%, 101/120), *APC* (77.5%, 93/120), *FLT3* (63.3%, 76/120), and *PREX2* (52.5%, 63/120) were the most common (**Figure 1**)
  - Baseline ctDNA genomic landscape was similar to that reported in the DESTINY-CRC01 study[4]
- 82.5% (99/120) and 15.0% (18/120) of patients had *HER2* amplification or *HER2* activating mutations, respectively
  - Of patients with *HER2* amplification, 87 had focal amplification and 12 had aneuploid amplification
  - **Table 2** shows the correlation between *HER2* gene amplification and HER2 IHC status

Analysis of efficacy by *APC* mutation status and *EGFR* amplification

- 71.7% of patients (86/120) had *APC* mutation when limited to "loss of function" or "likely loss of function"
- Patients with *APC* mutations tended to have lower ORR and shorter median PFS as compared with those with no detectable mutation (**Table 1, Figures 2** and **3**)
- 41.7% (50/120) of patients had *EGFR* amplification; 8 had focal amplification and 42 had aneuploid amplification
- PFS appeared to be shorter in patients with *EGFR* amplification versus patients with no detectable amplification; ORR did not differ significantly between these 2 subgroups (**Table 1, Figures 2** and **3**)
- Patients with *EGFR* amplification also had higher ctDNA levels, which are negatively prognostic,[7] possibly contributing to the observed change in T-DXd efficacy in the *EGFR* amplification group (**Supplemental Figure 1**)
- *EGFR* amplification and *APC* mutation status were largely overlapping; 40/50 (80%) patients with *EGFR* amplification also had *APC* mutations
  - The number of patients with only *EGFR* amplification, only *APC* mutation, or both alterations was small, limiting the ability to sufficiently assess the effect of each alteration on T-DXd efficacy

Analysis of efficacy by transporter gene expression status

- Patients with higher (median or greater) *ABCB1* (P-gp) transporter gene expression tended to have lower ORR and shorter median PFS as compared with those with lower (less than median) gene expression (**Table 1, Figures 2** and **3**)
- The potential association between *ABCB1* transporter gene expression and T-DXd clinical efficacy was more apparent than that observed for gene expression of other transporters, including *ABCC1* (*MRP1*) and *ABCG2* (*BCRP*) (**Supplemental Figure 2**)
  - Higher *ABCC1* gene expression was associated with lower ORR, but no significant effect on PFS was observed
  - *ABCG2* expression did not show an effect on T-DXd clinical activity
- There was no obvious correlation between *ABCB1* and *HER2* gene expression levels (**Supplemental Figure 3**)
- *ABCB1* gene expression levels were comparable across HER2 IHC subgroups (**Supplemental Figure 4**)

Molecular response at C3D1

- Patients with complete MR at C3D1 showed the highest ORR and longest median PFS, while those with absent MR had the lowest ORR and shortest median PFS (**Table 1, Figure 4**)
- ORR and median PFS in patients with partial MR were comparable to the BEP

Table 1. Efficacy according to baseline biomarker status and molecular response

	ORR			PFS		
	ORR (95% CI), %	OR (95% CI)	*P* value[a]	Median (95% CI), months	HR (95% CI)	*P* value[a]
ITT (n = 122)	34.4 (26.1-43.6)	NA	NA	5.7 (4.6-6.9)	NA	NA
BEP (ctDNA) (n = 120)	35.0 (26.5-44.2)	NA	NA	5.7 (4.6-6.9)	NA	NA
BEP (tissue) (n = 102)	32.4 (23.4-42.3)	NA	NA	5.6 (4.6-6.9)	NA	NA
Baseline *APC* mutation status (ctDNA)						
Mut ND (n = 34)	52.9 (35.1-70.2)	0.35 (0.15-0.83)	0.01	8.5 (5.9-NE)	2.8 (1.6-5.0)	< 0.001
Mut (n = 86)	27.9 (18.8-38.6)			5.5 (4.3-5.7)		
Baseline *EGFR* amplification status (ctDNA)						
AMP ND (n = 70)	38.6 (27.2-51.0)	0.68 (0.30-1.56)	NS (> 0.05)	6.9 (5.5-8.2)	1.7 (1.1-2.6)	0.02
AMP (n = 50)	30.0 (17.9-44.6)			4.5 (3.9-5.7)		
Baseline *ABCB1* gene expression (tissue)						
< Median (n = 51)	47.1 (32.9-61.5)	0.24 (0.09-0.64)	0.003	8.1 (5.7-9.8)	2.7 (1.6-4.5)	< 0.001
≥ Median (n = 51)	17.6 (8.4-30.9)			4.2 (2.9-5.5)		
Molecular response at C3D1 (ctDNA)						
BEP (MR) (n = 97)	40.2 (30.4-50.7)	NA	NA	6.7 (5.5-7.4)	NA	NA
CMR[b] (n = 19)	78.9 (54.4-93.9)	NA	NA	8.3 (6.9-NE)	NA	NA
PMR[c] (n = 53)	35.8 (23.1-50.2)	NA	NA	6.8 (5.5-8.2)	NA	NA
AMR[d] (n = 25)	20.0 (6.8-40.7)	NA	NA	4.2 (2.9-5.5)	NA	NA

[a]*P* ≤ 0.05 is the significance threshold; subgroups were compared using the Fisher exact test for ORR and log-rank test for PFS.
[b]CMR = 100% reduction in ctDNA levels.
[c]PMR = 50 to <100% reduction in ctDNA levels.
[d]AMR = <50% reduction in ctDNA levels.

Table 2. *HER2* amplification (ctDNA) versus HER2 IHC status (tissue) at baseline

HER2 IHC status (tissue)	Patients with ctDNA data at baseline				
	Total, n (%)	AMP, n (%)			AMP ND, n (%)
		AMP*	Focal	Aneuploid	
3+	97 (100)	87 (89.7)	80 (82.5)	7 (7.2)	10 (10.3)
2+/ISH+	23 (100)	12 (52.2)	7 (30.4)	5 (21.7)	11 (47.8)
Total	120 (100)	99 (82.5)	87 (72.5)	12 (10.0)	21 (17.5)

AMP* = focal + aneuploidy.

Figure 1. Baseline ctDNA genomic landscape, including top 20 genes with the most alterations and selected genes of interest

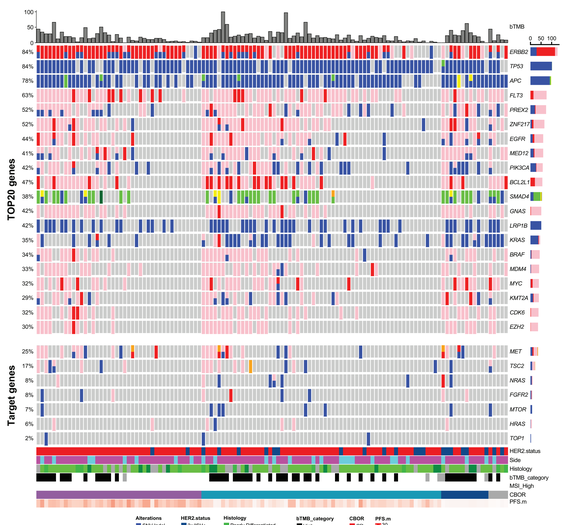


Figure 2. Association of baseline biomarkers and molecular response at C3D1 with ORR

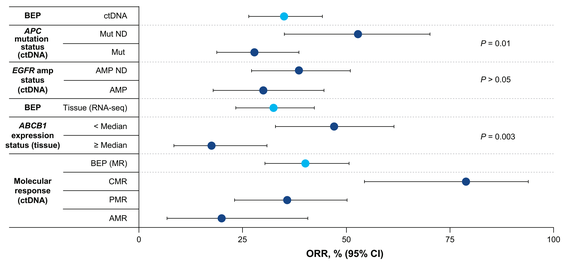


Figure 3. Association of baseline biomarkers with PFS

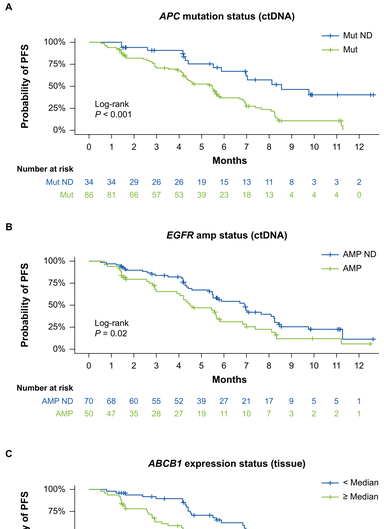
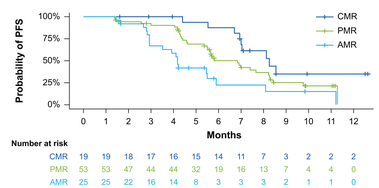


Figure 4. PFS according to molecular response at C3D1



Abbreviations

ABCB1, adenosine triphosphate binding cassette (ABC) subfamily B member 1; ABCC1, ABC subfamily C member 1; ABCG2, ABC subfamily G member 2; AMP, amplification; AMR, absent molecular response; APC, adenomatous polyposis coli; BEP, biomarker-evaluable population; BCRP, breast cancer resistance protein; C3D1, after 2 T-DXd treatment cycles; CMR, complete molecular response; CNV, copy number variation; CRC, colorectal cancer; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; MR, molecular response; MRP1, multidrug resistance protein 1; mut, mutation; NA, not available; ND, not detected; NE, not estimable; NS, not significant; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival; PMR, partial molecular response; T-DXd, trastuzumab deruxtecan; VAF, variant allele frequency.

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