Poster 148P

# DESTINY-PanTumor02 study of trastuzumab deruxtecan (T-DXd) in patients with HER2-expressing solid tumors: exploratory biomarker analyses of HER2 expression and gene amplification in tissue and plasma

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## Objectives

- Evaluate the concordance between local and central human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) testing in the DESTINY-PanTumor02 study
- Assess the concordance between HER2 IHC or erb-b2 receptor tyrosine kinase 2 (*HER2* [*ERBB2*]) gene amplification detected by in situ hybridization (ISH) archival tissue sections and by analysis of plasma circulating tumor (ct)DNA at baseline

## Conclusions

- The observed concordance between local and central HER2 results was 59% (IHC 3+) and 54% (IHC 2+); this was generally consistent with previous reports[1–4]
  - The moderate concordance rate may be attributed to the age of the tissue blocks, tumor heterogeneity, inter-pathologist variability, lack of a standardized test for HER2 in indications other than breast (BC) and gastric (GC) cancer, and variation in HER2 antibodies
- *HER2* amplification was detected in 35% and 18% of samples by ISH and ctDNA, respectively
- The low rate of false positives indicated that the ctDNA assay was specific, but the sensitivity was poor
  - The discrepancy may be ascribed to the sensitivity of the ctDNA assay to detect copy number variants, differences in the time and number of treatments between archival tissue and plasma samples, and as a result of low DNA-shedding tumors in specific indications
- These data support the need for a validated clinical diagnostic test and consistent algorithm to score HER2 across tumor types outside of BC and GC
- ctDNA testing can identify patients with *HER2* amplification; in the event of a negative result, complementary tissue-based IHC and/or ISH methods can be utilized


## Plain language summary

**Why did we perform this research?**
Human epidermal growth factor receptor 2 (HER2) is a growth factor receptor overproduced in some solid tumors. The level of HER2 can be used to identify the most appropriate treatment for some patients. HER2 levels can be measured in tissue or blood samples. Testing blood samples is less invasive and quicker than testing tissue samples. We wanted to understand if different HER2 tests produced matching results for each individual.

**How did we perform this research?**
We looked at HER2 testing methods used for participants in the DESTINY-PanTumor02 study of trastuzumab deruxtecan (T-DXd). T-DXd is an antibody-drug conjugate, which is a chemotherapy with a linker (deruxtecan) joined to an antibody (trastuzumab). Trastuzumab binds to HER2 on cancer cells, where it releases the chemotherapy to kill them. T-DXd is approved for use in HER2-positive breast and gastric cancers.[5] Participants in the study had cancer that had spread from where it started to nearby tissue/lymph nodes, had received one or more treatments that affect the whole body, and had tumors with high levels of HER2.

**What were the findings of this research?**
The tests that examined blood samples typically had a low number of false readings (specific) but failed to detect some positive samples (lacked sensitivity) compared with results from tissue. Different HER2 tests produced different results for the following reasons: they used different methods to interpret the results; there were time differences in samples being taken for testing; and there are differences in how tumors behave.

**What are the implications?**
This study highlights the need for a consistent test to measure HER2 levels across tumor types. Blood sample tests can be used to determine tumor HER2 levels but when there is a negative result, further testing of a tissue sample can be used.

**Where can I access more information?**
For information about DESTINY-PanTumor02, please visit https://clinicaltrials.gov/study/NCT04482309, or see primary data presented at ESMO 2023 (LBA34). Please reach out to Dr. Vicky Makker at makkerv@mskcc.org



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## Introduction

- T-DXd is a HER2-directed antibody-drug conjugate approved in HER2-positive BC and GC, and HER2-mutant non-small cell lung cancer (NSCLC)[5]
- HER2 expression (IHC 3+ or IHC 2+) is seen in a wide variety of other solid tumors[6–8]
- HER2 testing is not routinely conducted outside of BC and GC, and no HER2 assays are currently validated across all solid tumors
- Plasma ctDNA testing allows quick and minimally invasive genomic testing to enable more timely treatment decisions versus tissue-based testing[9]
- We evaluated the concordance between local and central HER2 IHC and between *HER2* amplification detected by ISH archival tissue sections and by analysis of plasma ctDNA at baseline

## Methods

### Patient population

- Patients with locally advanced or metastatic disease
- ≥1 prior systemic treatment or without treatment options
- Prior HER2-directed therapy allowed
- HER2 expressing (IHC 3+ or IHC 2+)* by local or central testing on archival tissue ≤3 years old
- Cohorts:
  1. Endometrial cancers
  2. Cervical cancer
  3. Ovarian cancer
  4. Bladder cancer
  5. Other tumors (excludes tumors from cohorts 1–4, 6, and 7 as well as GC, BC, colorectal cancer, and NSCLC)
  6. Biliary tract cancer
  7. Pancreatic cancer

### Monotherapy treatment

T-DXd 5.4 mg/kg every 3 weeks

### Study type

Open label, multicenter, multicohort, Phase 2

### Enrollment

N≈40 per cohort

### Trial registration #

NCT04482309

### Endpoints

**Primary:**
- Confirmed objective response rate (ORR)†

**Secondary:**
- Duration of response
- Disease control rate
- Progression-free survival
- Overall survival
- Safety and tolerability

**Exploratory:**
- Pharmacodynamic biomarkers

### Testing methods

**HER2 IHC:**
- Assessed locally; antibody not specified in enrollment criteria; scored according to gastric-specific criteria[10]
- Assessed centrally via HER2 HercepTest™ (Dako) and scored according to gastric-specific criteria[10]
- Local and central testing performed on samples from the same tissue block, where possible; different slide sections were used at different timepoints

***HER2* amplification:**
- Evaluated centrally via VENTANA HER2 Dual ISH (Roche) on archival tissue biopsies
- Analyzed in baseline plasma ctDNA using GuardantOMNI™ panel (Guardant Health AMEA)

*The trial design was adaptive, and ≤10 patients per cohort (excluding the other tumor cohorts) with IHC 1+ could be included if ≥3 objective responses had been observed in the first 15 patients with central IHC 3+ or IHC 2+ overexpression by central testing
†Confirmed ORR per Response Evaluation Criteria in Solid Tumours v1.1, as assessed by investigator

## Results

### Biomarker status

- Central HER2 IHC status was available for 255 patients; central *HER2* amplification was evaluated in 223 patients and 260 patients by ISH and ctDNA testing, respectively (**Figure 1**)

### Figure 1. Biomarker status by IHC, ISH, and ctDNA testing

**All patient cohort; N=267**

| Central IHC cohort | | Central ISH cohort | | Plasma ctDNA cohort | |
|---|---|---|---|---|---|
| **IHC status** | **N** | **ISH status** | **N** | ***HER2* amp** | **N** |
| 3+ | 75 | Positive | 78 | Detected | 48 |
| 2+ | 125 | Negative | 145 | Not detected | 212 |
| 1+ | 25 | | | | |
| 0 | 30 | | | | |
| Unknown* | 12 | Unknown* | 44 | Unknown† | 7 |

*Unknown central IHC/ISH test results include patients whose samples were unevaluable (for various technical reasons) and may include patients who did not provide a sample for central testing
†Total shedders = 260; total non-shedders = 5; shedders: tumors release or 'shed' their DNA in the bloodstream. Non-shedders were included as 'not detected'; samples were considered to be non-shedders if no mutations detected, very-low frequency mutations, or only variants of uncertain significance were detected
amp, amplification; ctDNA, circulating tumor DNA; IHC, *HER2*, erb-b2 receptor tyrosine kinase 2 immunohistochemistry; ISH, in situ hybridization

### Agreement between local and central HER2 IHC testing (Table 1)

- The agreement between local and central HER2 IHC score was 59% (51/87) for IHC 3+ and 54% (55/101) for IHC 2+; the observed discordance was >40%
- The agreement between local and central HER2 IHC scores was 73% (138/188) for IHC 3+ and IHC 2+, combined
- Analysis of HER2 IHC scores from only the local sites that used HercepTest™ (Dako) and central HER2 IHC scores showed a higher level of agreement (73% [8/11] for IHC 3+ and 70% [7/10] for IHC 2+)

### Table 1. Agreement* between local and central IHC results

| | | Central HER2 HercepTest™ | | | | | |
|---|---|---|---|---|---|---|---|
| | | **IHC 3+** | **IHC 2+** | **IHC 1+** | **IHC 0** | **IHC unknown†** | **Total** |
| **Local HER2 IHC** | **IHC 1+** | 0 | 1 | 0 | 1 | 0 | 2 |
| | **IHC 2+** | 6 | 55 (54%) | 17 | 23 | 6 | 107 |
| | **IHC 3+** | 51 (59%) | 26 | 4 | 6 | 6 | 93 |
| **Centrally enrolled** | | 18 | 44 | 3 | 0 | 0 | 65 |
| | **Total** | 75 | 126 | 24 | 30 | 12 | 267 |

| | | Central HER2 HercepTest™ | | | | | |
|---|---|---|---|---|---|---|---|
| | | **IHC 3+** | **IHC 2+** | **IHC 1+** | **IHC 0** | **IHC unknown†** | **Total** |
| **Local HER2 HercepTest™** | **IHC 1+** | 0 | 0 | 0 | 1 | 0 | 1 |
| | **IHC 2+** | 0 | 7 (70%) | 2 | 1 | 1 | 11 |
| | **IHC 3+** | 8 (73%) | 2 | 1 | 0 | 1 | 12 |
| | **Total** | 8 | 9 | 3 | 2 | 2 | 24 |

*Defined as the percentage of samples classified with the same IHC score by both local and central testing; agreement was calculated excluding central IHC unknown samples (total IHC 3+ samples excluding unknowns: 87; total IHC 2+ samples excluding unknowns: 101). †Unknown central IHC/ISH test results include patients whose samples were unevaluable (for various technical reasons) and may include patients who did not provide a sample for central testing
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry

### *HER2* amplification by ISH and plasma ctDNA

- *HER2* amplification was identified in 35% of samples by ISH and 18% by ctDNA
- Plasma *HER2* amplification testing was found to have a high specificity (low false-positive rate) but low sensitivity (high false-negative rate) (**Table 2**)

### Table 2. Comparison between plasma *HER2* amplification and ISH+, and plasma *HER2* amplification and HER2 status

| | Central ISH status | | | |
|---|---|---|---|---|
| **Plasma *HER2* amplification status*** | **HER2 ISH+** | **HER2 ISH−** | **ISH unknown‡** | **Total** |
| **Detected** | 32 | 7 | 9 | 48 |
| **Not detected†** | 44 | 136 | 32 | 212 |
| **Data unknown‡** | 2 | 2 | 3 | 7 |
| **Total** | 78 | 145 | 44 | 267 |
| | **PPA§ (95% CI¶) 42% (31, 54)** | **NPA‡ (95% CI¶) 95% (90, 98)** | | |

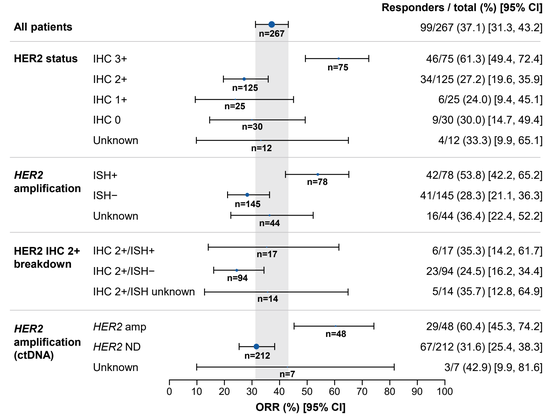
| | Central HER2‖ status | | | |
|---|---|---|---|---|
| **Plasma *HER2* amplification status*** | **HER2+** | **HER2−** | **Unknown‡** | **Total** |
| **Detected** | 35 | 7 | 6 | 48 |
| **Not detected†** | 54 | 140 | 18 | 212 |
| **Data unknown‡** | 3 | 2 | 2 | 7 |
| **Total** | 92 | 149 | 26 | 267 |
| | **PPA§ (95% CI¶) 39% (29, 50)** | **NPA‡ (95% CI¶) 95% (90, 98)** | | |

Blue=true positive; pink=false negative; yellow=false positive; green=true negative
*GuardantOMNI™ ctDNA analysis. Focal amplification of *HER2* detected by ctDNA was used for this analysis: *HER2* adjusted copy number gain over a diploid background (high confidence); GuardantOMNI™ considers as amplified 2.22 copies of *HER2*
†Total shedders = 260; total non-shedders = 5; shedders: tumors release or 'shed' their DNA in the bloodstream. Non-shedders were included as 'not detected'; samples were considered to be non-shedders if no mutations detected, very low-frequency mutations, or only variants of uncertain significance were detected
‡Unknown central IHC/ISH test results include patients whose samples were unevaluable (for various technical reasons) and may include patients who did not provide a sample for central testing
§PPA and NPA were calculated excluding not available samples (failed / unprofiled / undetectable ctDNA)
¶CI was calculated using Clopper-Pearson method
‖HER2+: IHC 3+ and IHC 2+/ISH+; HER2−: IHC 2+/ISH− and IHC 1+/0
CI, confidence interval; ctDNA, circulating tumor DNA; HER2, human epidermal growth factor receptor 2; *HER2*, erb-b2 receptor tyrosine kinase 2; ISH, in situ hybridization; NPA, negative percentage agreement; PPA, positive percentage agreement

### ORR subgroups according to IHC, ISH, and ctDNA

- Similar ORRs were observed in patients with plasma *HER2* amplification (60.4%) and patients with HER2 IHC 3+ (61.3%) (**Figure 2**)
- IHC 3+ captured 1.6 times more responders than plasma *HER2* amplification (46 vs 29, respectively)
- IHC 3+ alone captured both the greatest number of responders and the patients with the greatest ORR compared with other assays (**Figure 2**)

### Figure 2. Responders captured by IHC, ISH, and ctDNA

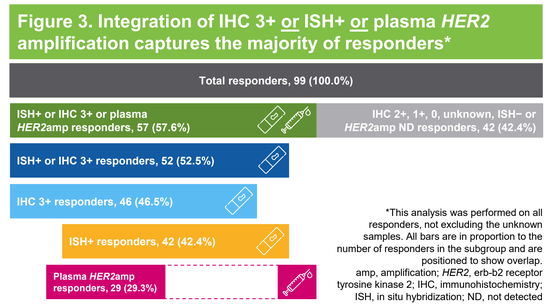



CI, confidence interval; ctDNA, circulating tumor DNA; HER2, human epidermal growth factor receptor 2; *HER2*, erb-b2 receptor tyrosine kinase 2; IHC, immunohistochemistry; ISH, in situ hybridization; ND, not detected; ORR, objective response rate

### Responders captured by IHC 3+ or ISH+ or plasma *HER2* amplification

- Although all testing methods identified responders, IHC 3+ captured the greatest number of responders (**Figure 3**)

### Figure 3. Integration of IHC 3+ or ISH+ or plasma *HER2* amplification captures the majority of responders*




*This analysis was performed on all responders, not excluding the unknown samples. All bars are in proportion to the number of responders in the subgroup and are positioned to show overlap.
amp, amplification; *HER2*, erb-b2 receptor tyrosine kinase 2; IHC, immunohistochemistry; ISH, in situ hybridization; ND, not detected

### Limitations

- Plasma and tissue samples were not collected at the same timepoint
  - Differences in the time and number of treatment(s) between tissue and plasma sample collections may impact the concordance when detecting copy number alterations
- Depending on the indication, low-shedding tumors may represent an issue for plasma next-generation sequencing; low sensitivity of the ctDNA assay can be especially challenging when detecting copy number alterations[9]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DESTINY-PanTumor02