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Exploratory analysis of HER2 status based on central and local testing results from the DESTINY-Gastric04 study

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Objective

- To analyze the human epidermal growth factor receptor 2 (HER2) status of tumor biopsies from patients with gastric cancer (GC) in DESTINY-Gastric04
- To evaluate concordance between local and central HER2 testing by immunohistochemistry (IHC)/in situ hybridization (ISH)

Conclusions

- The HER2 positivity rate by central testing of 67.7% in patients screened for the DESTINY-Gastric04 trial in HER2-positive (HER2+) GC in the second-line (2L) setting whose disease progressed on a prior trastuzumab regimen is consistent with that previously reported in literature[1]
- The concordance rate between local and central laboratories (79.5% positive percentage agreement [PPA]) supports the use of validated, on-market HER2 assays to identify patients with HER2+ GC for 2L treatment
  - The concordance rate of samples scored locally as IHC 3+ was higher than those scored as IHC 2+/ISH+ (91.3% PPA versus 43.3% PPA)
- The similar results between tumors biopsied from primary tissue and tumors biopsied from metastatic tissue (PPA, 79.3% versus 80.0%, respectively) suggests both primary and metastatic tissue may be suitable for HER2 testing. Further analysis of patient matched samples would provide more data for this concordance

Plain Language Summary

Why did we perform this research?
Human epidermal growth factor receptor 2 (HER2), a protein on the surface of some cancer cells, is expressed in approximately 5%-17% of gastric cancer (GC) cases.[1-4] Trastuzumab deruxtecan (T-DXd) is an anticancer therapy that targets HER2 and is approved to treat patients with metastatic GC or gastroesophageal junction adenocarcinoma that is HER2-positive (HER2+).[5-7] In the DESTINY-Gastric04 trial, patients who were given T-DXd had longer overall survival compared with patients given ramucirumab plus paclitaxel, the standard second-line treatment for patients with GC or gastroesophageal junction carcinoma, regardless of the HER2 status of the tumor.[8]
In this study, sections of tumors collected from patients in the DESTINY-Gastric04 trial were tested for their HER2 status in central and local laboratories and the agreement between the laboratory results was analyzed.

How did we perform this research?
The DESTINY-Gastric04 trial enrolled patients with HER2+ GC or gastroesophageal adenocarcinoma who had previously received a treatment containing trastuzumab, but their tumors continued to grow. In this study, sections of tumors were collected from these patients, and central laboratories and local laboratories used immunohistochemistry (IHC) and in situ hybridization (ISH) to determine the HER2 status of the tumors (IHC 3+, IHC 2+/ISH–positive [ISH+], IHC 2+/ISH−, IHC 1+, IHC 0). Later during the trial, the tests performed by local laboratories were assessed by central laboratories, and the results were compared to establish the agreement between the central and local laboratories.

What were the findings of this research?
Local and central laboratories found that almost 70% of tumors were HER2+, and the local and central laboratories agreed on the HER2 status about 80% of the time. The agreement between the laboratories was generally higher when the local laboratory found the HER2 status was IHC 3+ than when the status was IHC 2+/ISH+, and the agreement varied based on which assay was used.

What are the implications of this research?
Patients with GC can have their HER2 status determined with validated assays for identification of those who may benefit from T-DXd treatment.

Where can I access more information?
To learn more about the DESTINY-Gastric04 trial, you can visit https://clinicaltrials.gov/ct2/show/NCT04704934

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Poster

Plain language summary

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Introduction

- Results from the phase 2 DESTINY-Gastric01, DESTINY-Gastric02, and DESTINY-Gastric06 trials[2-4] have led to the approval of trastuzumab deruxtecan (T-DXd) in the 2L or later setting in patients with unresectable or metastatic HER2+ (IHC 3+ or IHC 2+/ISH–positive [ISH+]) GC/gastroesophageal junction adenocarcinoma in several countries
- In the phase 3 DESTINY-Gastric04 trial (NCT04704934), T-DXd as a 2L treatment significantly improved overall survival compared with ramucirumab + paclitaxel in patients with HER2+ (IHC 3+ or IHC 2+/ISH+) metastatic GC[5]
- In DESTINY-Gastric04, tumor biopsies were analyzed to assess HER2 expression; heterogeneous expression of HER2 in GC tumors complicates evaluation of HER2 status[6]
  - Studies have found discordance rates of HER2 status between central and local laboratories of up to 22.3%[7]
- The accurate determination of HER2 status, when feasible, can be important to reliably identify patients who may benefit from HER2-directed therapies

Methods

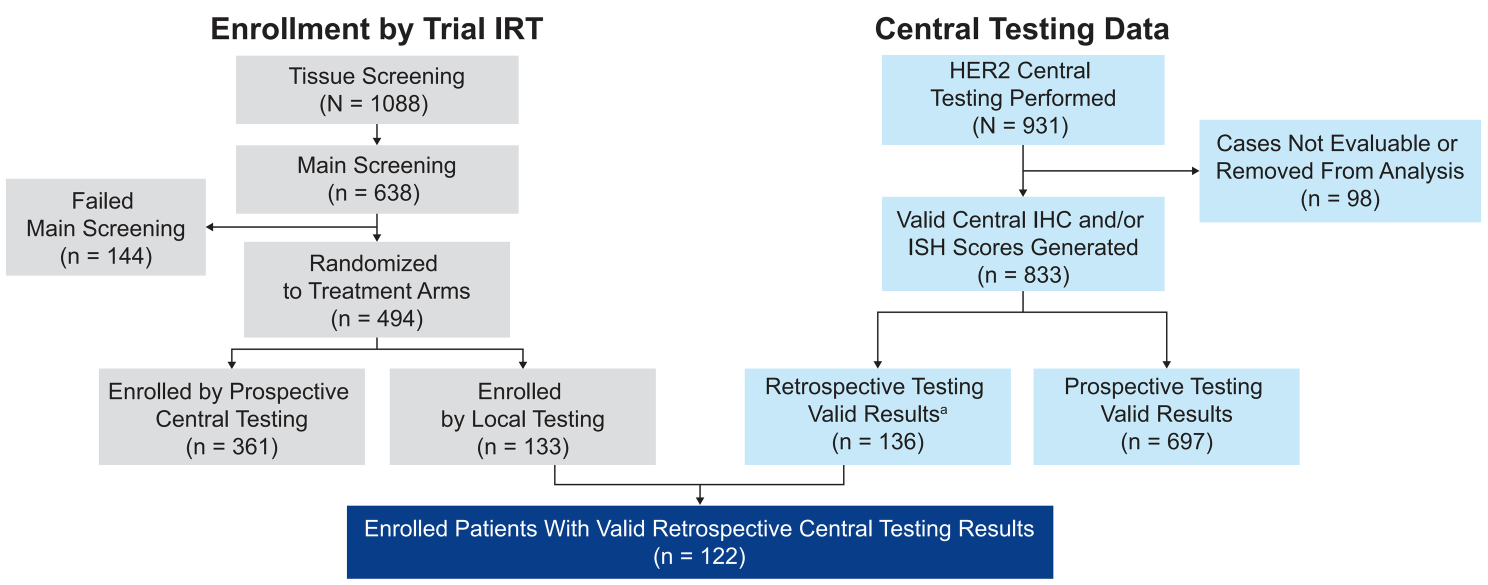
- In DESTINY-Gastric04, fresh biopsies were obtained from patients with HER2+ GC after progression on prior trastuzumab-based therapy
- HER2 status was determined by prospective central testing (performed prior to study enrollment) using IHC (Agilent HercepTest) and ISH (Agilent IQ-FISH) from the first tissue screening in 2021 until a protocol amendment in 2023, and by either central or local testing thereafter
- For central testing, ISH testing was only performed for patients who had IHC 2+ (per ASCO/CAP guidelines for GC)
- For patients enrolled based on HER2 status by local testing, tissue was required to be sent to central laboratory for retrospective testing (performed after study enrollment)
- HER2 positivity was evaluated for both prospective and retrospective central testing
- Concordance of central versus local HER2 status was evaluated for patients enrolled based on local testing

Results

HER2 Status for Patients With Central Testing in DESTINY-Gastric04

- HER2 testing scheme for DESTINY-Gastric04 is shown in **Figure 1**

Figure 1. DESTINY-Gastric04 HER2 Testing Scheme



[a]Local/central concordance analysis only performed for 122 patients who were enrolled/randomized into DESTINY-Gastric04.

- Of the 833 total cases analyzed by either prospective or retrospective central testing, 564 cases (67.7%) were HER2+ (IHC 3+ or IHC 2+/ISH+) (**Table 1**)
- Of 697 cases analyzed by prospective central testing, 457 cases (65.6%) were HER2+. Of these, 395 cases (56.7%) were IHC 3+ and 62 cases (8.9%) were IHC 2+/ISH+ (**Table 1, Table 2**)
- 66% (550/833) of tumors were collected from primary tissue, 34% (283/833) from metastatic tissue
  - HER2 positive rates were similar for primary and metastatic tumors (**Table 1, Table 2**)

Table 1. HER2 Status by Central Screening

	HER2+[a]	HER2–[b]	Total, n
All cases, n (%)	564 (67.7)	269 (32.3)	833
Time of testing, n (%)			
Prospective testing	457 (65.6)	240 (34.4)	697
Retrospective testing[c]	107 (78.7)	29 (21.3)	136
Tissue site, n (%)			
Primary	366 (66.5)	184 (33.5)	550
Metastatic	198 (70.0)	85 (30.0)	283

[a]HER2+ defined as IHC 3+ or IHC 2+/ISH+.
[b]HER2− defined as IHC2+/ISH−, IHC 1+, or IHC 0.
[c]Retrospective central testing results included 122 patients who were enrolled by HER2 local testing.

Table 2. HER2 IHC Score by Central Screening

	IHC 0	IHC 1+	IHC 2+/ISH−	IHC 2+/ISH+	IHC 3+	Total, n
All cases, n (%)	110 (13.2)	56 (6.7)	103 (12.4)	76 (9.1)	488 (58.6)	833
Time of testing, n (%)						
Prospective testing	99 (14.2)	51 (7.3)	90 (12.9)	62 (8.9)	395 (56.7)	697
Retrospective testing[a]	11 (8.1)	5 (3.7)	13 (9.6)	14 (10.3)	93 (68.4)	136
Tissue site, n (%)						
Primary	78 (14.2)	40 (7.3)	66 (12.0)	43 (7.8)	323 (58.7)	550
Metastatic	32 (11.3)	16 (5.7)	37 (13.1)	33 (11.7)	165 (58.3)	283

[a]Retrospective central testing results included 122 patients who were enrolled by HER2 local testing.

Concordance Between Central and Local Testing

- Local HER2 IHC testing results were used to enroll 133 patients for DESTINY-Gastric04
  - Valid HER2 results were generated by retrospective central testing from 91.7% (122/133) of patients enrolled by local testing
- The overall PPA between central and local testing was 79.5% (97/122; 95% CI, 71.3%-86.3%; **Table 3**)
- The PPA of tumors biopsied from primary tissue and tumors biopsied from metastatic tissue was similar (79.3% versus 80.0%; **Table 3**)

Table 3. HER2 Concordance by Tissue Site

	HER2+[a] (central)	HER2–[b] (central)	Total	PPA (95% CI), %
HER2+,[a] all cases (local), n	97	25	122	79.5 (71.3-86.3)
Primary	65	17	82	79.3 (68.9-87.4)
Metastatic	32	8	40	80.0 (64.4-91.0)

[a]HER2+ defined as IHC 3+ or IHC 2+/ISH+.
[b]HER2− defined as IHC2+/ISH−, IHC 1+, or IHC 0.

- Discordance rates were higher in IHC 2+/ISH+ cases compared with IHC 3+ cases (**Table 4, Table 5**)

Table 4. HER2 Concordance by HER2 Status

	HER2+[a] (central)	HER2–[b] (central)	Total	PPA (95% CI), %
IHC 3+ (local), n	84	8	92	91.3 (83.6-96.2)
IHC 2+/ISH+ (local), n	13	17	30	43.3 (25.5-62.6)

[a]HER2+ defined as IHC 3+ or IHC 2+/ISH+.
[b]HER2− defined as IHC2+/ISH−, IHC 1+, or IHC 0.

Table 5. HER2 Concordance by HER2 Score

	IHC 3+ (central)	IHC 2+/ISH+ (central)	IHC 2+/ISH– (central)	IHC 1+ (central)	IHC 0 (central)	Total
IHC 3+ (local), n	78	6	4	1	3	92
IHC 2+/ISH+ (local), n	6	7	9	3	5	30

- Agreement of HER2 IHC scores between local and central laboratories varied depending on the type of assay utilized by local laboratories (**Table 6**)

Table 6. HER2 Concordance by Local Assay Type

	IHC 3+ (central)	IHC 2+ (central)	IHC 1+ (central)	IHC 0 (central)	Total
HercepTest (local), n	7	2	0	0	9
IHC 3+	6	1	0	0	7
IHC 2+	1	1	0	0	2
4B5 (local), n	47	11	2	6	66
IHC 3+	45	5	1	3	54
IHC 2+	2	6	1	3	12
Non-4B5/HercepTest (local) , n	30	13	2	2	47
IHC 3+	27	4	0	0	31
IHC 2+	3	9	2	2	16

Abbreviations

2L, second-line; GC, gastric cancer; HER2 (+/−), human epidermal growth factor receptor 2 (–positive/–negative); IHC, immunohistochemistry; IRT, interactive response technology; ISH (+/−), in situ hybridization (–positive/–negative); PPA, positive percentage agreement; T-DXd, trastuzumab deruxtecan.

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Disclosures

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DESTINY Gastric04