Exploratory Biomarker Analysis of DESTINY-CRC01, a Phase 2, Multicenter, Open-Label Study of Trastuzumab Deruxtecan (T-DXd, DS-8201) in Patients With HER2-Expressing Metastatic Colorectal Cancer

Salvatore Siena, MD, Kanwal Raghav, Toshiki Masuishi, Kensei Yamaguchi, Tomohiro Nishina, Elena Elez, Javier Rodriguez, Ian Chau, Maria Di Bartolomeo, Hisato Kawakami, Fumitaka Suto, Kojiro Kobayashi, Makito Koga, Koichiro Inaki, Yusuke Kuwahara, Issey Takehara, Axel Grothey, Takayuki Yoshino

On behalf of the DESTINY-CRC01 investigators

aDepartment of Oncology and Hemato-Oncology, Università degli Studi di Milano and Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy
Declaration of Interests

Salvatore Siena:

Advisory/Consultancy: Amgen, AstraZeneca, Bayer, BMS, CheckmAb, Daiichi Sankyo, Merck, Seattle Genetics
**DESTINY-CRC01: Study Design**

A multicenter, open-label, phase 2 trial (NCT03384940)\(^1,2\)

**Primary end point**
- ORR\(^b\) (cohort A)

**Secondary end points**
- ORR\(^b\) (cohorts B and C)
- PFS
- OS
- DOR
- DCR
- Safety and tolerability

**Exploratory end point**
- Biomarkers (ctDNA, HER2ECD)

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**Patients**
- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- RAS/BRAF\(^{V600E}\) wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

**Cohort A:**
- HER2 Positive (IHC3+ or IHC2+/ISH+)
  - n = 53
  - 6.4 mg/kg dose of T-DXd administered Q3W (all cohorts)

**Cohort B:**
- HER2 IHC2+/ISH−
  - n = 15

**Cohort C:**
- HER2 IHC1+
  - n = 18

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**Efficacy in Cohort A (Dec 28, 2020 cutoff)**

<table>
<thead>
<tr>
<th>HER2 IHC3+ or IHC2+/ISH+ (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) [95% CI]</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>NE</td>
</tr>
<tr>
<td>PFS, mo, median (95% CI)</td>
</tr>
<tr>
<td>OS, mo, median (95% CI)</td>
</tr>
<tr>
<td>DOR, mo, median (95% CI)</td>
</tr>
<tr>
<td>DCR, % (95% CI)</td>
</tr>
<tr>
<td>Treatment duration, mo, median (95% CI)</td>
</tr>
</tbody>
</table>

CR, complete response; CRC, colorectal cancer; ctDNA, circulating tumor DNA; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HER2ECD, human epidermal growth factor receptor 2 extracellular domain; IHC, immunohistochemistry; ISH, in situ hybridization; mo, month; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q3W, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; T-DXd, trastuzumab deruxtecan.

\(^a\) A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C.

\(^b\) ORR was based on RECIST version 1.1 in all cohorts.

**Exploratory biomarkers analysis in DESTINY-CRC01**

**Cohort A:**
- HER2-positive mCRC (IHC3+ or IHC2+/ISH+)
- n = 53
- 6.4 mg/kg T-DXd Q3W

**Exploratory Biomarkers Analysis**
- Pretreatment
- Cycle 4
- EOT

**Tumor tissue**
- HER2 status
  - IHC\(^b\)
  - ISH\(^c\)

**Liquid biopsy**
- Serum
  - HER2ED\(^d\)
  - HER2-associated liquid biomarker

- Plasma
  - ctDNA (Guardant OMNI panel)
    - ERBB2 focal & aneuploidy amplification
    - ApCN\(^e\)
    - Gene (~500 genes) alterations
    - bTMB

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ApCN, adjusted plasma copy number; bTMB, blood tumor mutation burden; EOT, end of treatment; mCRC, metastatic colorectal cancer.

*Figure adapted from Rockberg J et al. Mol Oncol. 2009;3:238-47 under the terms of the CC BY license (Creative Commons — Attribution 4.0 International — CC BY 4.0).*

\(^a\)VENTANA 4B5. \(^b\)INFORM HER2 Dual ISH DNA Probe Cocktail (Ventana). \(^c\)SIEMENS. \(^d\)To correct for variation in plasma tumor fraction between samples, adjusted plasma ERBB2 copy number (ApCN) was calculated based on the maximum variant allele fraction according to published methods.  

ORR appears to be higher in patients with higher baseline HER2 level in tissue (IHC/ISH) and liquid (plasma ERBB2 copy number and HER2ECD).

- Objective response was observed in patients with or without activating RAS or PIK3CA mutations in ctDNA.
- Response was also observed across bTMB levels.
DESTINY-CRC01

PFS by baseline HER2 status and HER2ECD

PFS by HER2 Status

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>mPFS, mo [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC2+/ISH+ (n = 13)</td>
<td>4.1 [1.3-NE]</td>
</tr>
<tr>
<td>IHC3+ (n = 40)</td>
<td>8.3 [5.4-10.9]</td>
</tr>
</tbody>
</table>

PFS by Serum HER2ECD

<table>
<thead>
<tr>
<th>Serum HER2ECD</th>
<th>mPFS, mo [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below (&lt;23.5 ng/mL; n = 27)</td>
<td>4.1 [2.9-7.3]</td>
</tr>
<tr>
<td>Above (≥23.5 ng/mL; n = 22)</td>
<td>8.3 [5.4-11.3]</td>
</tr>
</tbody>
</table>

mPFS, median progression-free survival.

*Exploratory cutoff values were determined using receiver operating characteristic analysis; serum HER2ECD cutoff = 23.5 ng/mL.
PFS by baseline ERBB2 ApCN and amplification type

### PFS by ERBB2 ApCN

- **ERBB2 ApCN**
  - Below/ND (≤30.9; n = 28): mPFS, mo [95% CI] = 4.1 [2.8-6.9]
  - Above (≥30.9; n = 24): mPFS, mo [95% CI] = 10.9 [8.3-12.7]

### PFS by Plasma ERBB2 Amplification Type

- **ERBB2 amplification**
  - Aneuploidy/ND (n = 16): mPFS, mo [95% CI] = 4.1 [1.6-6.9]
  - Focal Amp (n = 36): mPFS, mo [95% CI] = 8.7 [4.1-11.3]
Antitumor activity of T-DXd was observed in patients with or without activating RAS mutations in ctDNA

PFS by Plasma KRAS/NRAS Mutation Status

RAS mutation status<sup>a</sup> mPFS, mo [95% CI]
- WT/Other Mut (n = 46) 7.6 [4.1-10.8]
- Activating Mut (n = 6) 4.1 [1.3-NE]

### Patient Gene Mutation | HER2 status | CBOR
---|---|---
1<sup>b</sup> | NRAS | G12D | IHC2+/ISH+ | PD
2 | NRAS | Q61R | IHC2+/ISH+ | SD
3 | NRAS | Q61R | IHC3+ | SD
4 | KRAS | G12S | IHC3+ | PR
5 | KRAS | Q61H | IHC3+ | PR
6<sup>c</sup> | KRAS | Q61H<sup>c</sup> | IHC3+ | PD

<sup>a</sup>RAS mutations in codons 12, 13, 59, 61, 117, and 146 in KRAS and NRAS were considered as activating mutations according to a previous report (Serebriiskii IG et al. Nat Commun. 2019;10;3722).

<sup>b</sup>One patient had NRAS mutation identified by tumor biopsy and ctDNA.

<sup>c</sup>Two types of KRAS Q61H mutations (T>G and T>A) were detected in one patient.

CBOR, confirmed best overall response; mPFS.
Antitumor activity of T-DXd was seen in patients with or without activating *PIK3CA* mutations in ctDNA

### PFS by Plasma *PIK3CA* Mutation Status

**Probability of PFS, %**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation</th>
<th>HER2 status</th>
<th>CBOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E545K</td>
<td>IHC3+</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>C420R</td>
<td>IHC2+/ISH+</td>
<td>SD</td>
</tr>
<tr>
<td>3</td>
<td>E545K</td>
<td>IHC3+</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>Q546K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>E542K</td>
<td>IHC3+</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>E545K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>E542K</td>
<td>IHC3+</td>
<td>SD</td>
</tr>
<tr>
<td>6</td>
<td>E542K</td>
<td>IHC2+/ISH+</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>E545A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**mPFS, mo [95% CI]**
- WT/Other Mut (n = 46): 7.3 [4.1-10.9]
- Activating Mut (n = 6): 4.1 [1.3-NE]

Additional acquired mutations in several genes were identified at the time of disease progression

- Additional acquired mutations were identified at the time of disease progression in 12 of 30 patients
- Mutations in \( \text{BRAF} \) (V600mut), \( \text{CASP8} \) (apoptosis-related), and \( \text{KEAP1} \) (reactive oxygen species-related) were identified

### Acquired Gene Mutations in Patients With Disease Progression (n = 30)

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Gene</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>( \text{TP53} )</td>
<td>Y234C, S241C, R273C</td>
</tr>
<tr>
<td>1</td>
<td>( \text{ERBB2} )</td>
<td>D769H</td>
</tr>
<tr>
<td>1</td>
<td>( \text{BRAF} )</td>
<td>V600E, V600M</td>
</tr>
<tr>
<td>1</td>
<td>( \text{CASP8} )</td>
<td>F338fs</td>
</tr>
<tr>
<td>1</td>
<td>( \text{CIC} )</td>
<td>T2002fs</td>
</tr>
<tr>
<td>1</td>
<td>( \text{GRIN2A} )</td>
<td>Q201*</td>
</tr>
<tr>
<td>1</td>
<td>( \text{JAK1} )</td>
<td>L1114fs</td>
</tr>
<tr>
<td>1</td>
<td>( \text{KEAP1} )</td>
<td>F64fs</td>
</tr>
<tr>
<td>1</td>
<td>( \text{KMT2D} )</td>
<td>L671fs</td>
</tr>
<tr>
<td>1</td>
<td>( \text{NOTCH2} )</td>
<td>N396fs</td>
</tr>
<tr>
<td>1</td>
<td>( \text{PIK3CA} )</td>
<td>R88Q</td>
</tr>
</tbody>
</table>

Acquired, patients with acquired mutations detected only at disease progression; lost, patients with lost mutations detected only at cycle 1, day 1; maintained, patients with variants at cycle 1, day 1 and at disease progression.
Conclusions

- This exploratory biomarker analysis suggests an association between baseline HER2 expression level or amplification and the antitumor activity of T-DXd.
- ctDNA analysis suggests there is antitumor activity of T-DXd in patients with HER2+ mCRC who have RAS- or PIK3CA-activating mutations as well as across bTMB levels.
- In paired ctDNA samples collected at baseline and disease progression from 30 patients, acquired alterations were observed in several genes but none was common across patients.
- Interpretation is limited by the small sample size; therefore, further investigation into potential mechanisms of resistance and response to and patient selection for T-DXd in HER2+ mCRC are warranted.
- The efficacy and safety of T-DXd is being evaluated in patients with HER2-overexpressing, RAS mutant or wild-type mCRC in the ongoing DESTINY-CRC02 clinical trial (NCT04744831).
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