A Phase 2, Multicenter, Open-Label Study of Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-Expressing Metastatic Colorectal Cancer: DESTINY-CRC01


On behalf of the DESTINY-CRC01 investigators
T-DXd is a Novel ADC Designed to Deliver an Antitumor Effect

T-DXd is an ADC with 3 components:
- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

Payload mechanism of action:
- Topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio ≈ 8
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.
DESTINY-CRC01 Study Design
An open-label, multicenter, phase 2 study (NCT03384940)

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

Primary endpoint
- Confirmed ORR by independent central review (ICR) in Cohort A

Data cutoff: August 9, 2019
- 38.5% (30/78) remained on treatment
- 61.5% discontinued, primarily for progressive disease (41.0%) and clinical progression (9.0%)

T-DXd 6.4 mg/kg q3w

Cohort A (n = 53)
HER2 Positive (IHC 3+ or IHC 2+/ISH+)

A futility monitoring was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C

Cohort B (n = 7)
HER2 IHC 2+/ISH−

Cohort C (n = 18)
HER2 IHC 1+
## Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HER2+ Cohort A (n = 53)</th>
<th>All Patients (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>57.0 (27-79)</td>
<td>58.5 (27-79)</td>
</tr>
<tr>
<td><strong>Female, %</strong></td>
<td>52.8</td>
<td>47.4</td>
</tr>
<tr>
<td><strong>Region, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe / Asia / North America</td>
<td>52.8 / 28.3 / 18.9</td>
<td>52.6 / 32.1 / 15.4</td>
</tr>
<tr>
<td><strong>ECOG performance status 0 / 1 / 2, %</strong></td>
<td>69.8 / 30.2 / 0</td>
<td>62.8 / 35.9 / 1.3</td>
</tr>
<tr>
<td><strong>Sum of target lesions, median, cm</strong></td>
<td>8.4</td>
<td>8.8</td>
</tr>
<tr>
<td><strong>Primary tumor site, left / right, %</strong></td>
<td>88.7 / 11.3</td>
<td>89.7 / 10.3</td>
</tr>
<tr>
<td><strong>Microsatellite stable / unknown, %</strong></td>
<td>81.1 / 18.9</td>
<td>79.5 / 20.5</td>
</tr>
<tr>
<td><strong>RAS wild type, %</strong></td>
<td>98.1</td>
<td>98.7</td>
</tr>
<tr>
<td><strong>BRAF wild type, %</strong></td>
<td>100</td>
<td>98.7</td>
</tr>
<tr>
<td><strong>HER2 status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 3+ / IHC 2+; ISH+</td>
<td>75.5 / 24.5</td>
<td>51.3 / 16.7</td>
</tr>
<tr>
<td>IHC 2+ / IHC 1+</td>
<td>0 / 0</td>
<td>25.6 / 23.1</td>
</tr>
</tbody>
</table>

*a Left: rectum, sigmoidal, descending; Right: cecum, ascending, transverse. *b By local assessment. *c 1 patient had an NRAS mutation. *d By central assessment. Sums may not total 100% due to rounding.
Prior Treatments

Median prior lines of cancer treatment: 4 (range, 2-11)\(^a\)

<table>
<thead>
<tr>
<th>Prior Treatment</th>
<th>HER2+ Cohort A (n = 53)</th>
<th>All Patients (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Fluorouracil / capecitabine</td>
<td>100 / 54.7</td>
<td>98.7 / 53.8</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cetuximab or panitumumab</td>
<td>100</td>
<td>98.7</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>75.5</td>
<td>79.5</td>
</tr>
<tr>
<td>Prior anti-HER2 agents</td>
<td>30.2</td>
<td>20.5</td>
</tr>
</tbody>
</table>

- Prior anti-HER2 agents in Cohort A included pertuzumab (24.5%), trastuzumab (22.6%), T-DM1 (5.7%), lapatinib (5.7%), and tucatinib (1.9%)

\(^a\) Includes all prior treatments in the adjuvant and metastatic settings.
## DESTINY-CRC01 Cohort A

### Efficacy

#### HER2+ Cohort A (N = 53)

<table>
<thead>
<tr>
<th>Confirmed ORR by ICR</th>
<th>45.3% (n = 24) (95% CI, 31.6%-59.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1.9% (n = 1)</td>
</tr>
<tr>
<td>PR</td>
<td>43.4% (n = 23)</td>
</tr>
<tr>
<td>SD</td>
<td>37.7% (n = 20)</td>
</tr>
<tr>
<td>PD</td>
<td>9.4% (n = 5)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>7.5% (n = 4)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Disease control rate: 83.0% (95% CI, 70.2%-91.9%)

Duration of response, median: Not reached (95% CI, 4.2 months-NE)

<sup>a</sup>Patients were missing postbaseline scans.

Median study duration, 5.0 months (range, 0.6-10.5 months). There were no confirmed responses by ICR in Cohort B or C.
DESTINY-CRC01 Cohort A

Best Change in Tumor Size

HER2+ Cohort A (N = 53)

- IHC3+
- IHC2+/ISH+
- Prior anti-HER2 treatment
- HER2 IHC2+/ISH+ with an NRAS mutation
DESTINY-CRC01 Cohort A

Tumor Shrinkage Over Time

HER2+ Cohort A (N = 53)
## DESTINY-CRC01 Cohort A

### Response by Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ORR, %</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2+ Cohort A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 53</td>
<td>45.3</td>
<td>[31.6-59.6]</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 y (n = 35)</td>
<td>42.9</td>
<td>[26.3-60.6]</td>
</tr>
<tr>
<td>≥ 65 y (n = 18)</td>
<td>50.0</td>
<td>[26.0-74.0]</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 28)</td>
<td>42.9</td>
<td>[24.5-62.8]</td>
</tr>
<tr>
<td>Male (n = 25)</td>
<td>48.0</td>
<td>[27.8-68.7]</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia (n = 15)</td>
<td>33.3</td>
<td>[11.8-61.6]</td>
</tr>
<tr>
<td>North America (n = 10)</td>
<td>60.0</td>
<td>[26.2-87.8]</td>
</tr>
<tr>
<td>Europe (n = 28)</td>
<td>46.4</td>
<td>[27.5-66.1]</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (n = 37)</td>
<td>54.1</td>
<td>[36.9-70.5]</td>
</tr>
<tr>
<td>1 (n = 16)</td>
<td>25.0</td>
<td>[7.3-52.4]</td>
</tr>
<tr>
<td><strong>HER2 status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 3+ (n = 40)</td>
<td>57.5</td>
<td>[40.9-73.0]</td>
</tr>
<tr>
<td>IHC 2+/ISH+ (n = 13)</td>
<td>7.7</td>
<td>[0.2-36.0]</td>
</tr>
<tr>
<td><strong>Prior HER2 treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 16)</td>
<td>43.8</td>
<td>[19.8-70.1]</td>
</tr>
<tr>
<td>No (n = 37)</td>
<td>45.9</td>
<td>[29.5-63.1]</td>
</tr>
</tbody>
</table>
DESTINY-CRC01 Cohort A

Progression-Free and Overall Survival

Progression-Free Survival (N = 53)

Median: 6.9 months
(95% CI, 4.1-NE)

Overall Survival (N = 53)

Median: Not reached
(overall 95% CI, 0.74-NE)

No. at risk
53 50 42 35 33 21 11 7 6 2 0

Months
0 1 2 3 4 5 6 7 8 9 10

Overall Survival (%)
0 20 40 60 80 100

No. at risk
53 49 42 23 14 10 6 5 2 0

Months
0 2 4 6 8 10 12

Progression-Free Survival (%)
0 20 40 60 80 100

Median follow-up for OS was 5.4 month (range, 1.2-11.8 months).
## Overall Safety Summary

### Type of Adverse Event, n (%)\(^a\)

<table>
<thead>
<tr>
<th>Type of Adverse Event</th>
<th>HER2+ Cohort A (n = 53)</th>
<th>All Patients (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>53 (100)</td>
<td>78 (100)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>51 (96.2)</td>
<td>73 (93.6)</td>
</tr>
<tr>
<td>TEAE grade ≥3</td>
<td>32 (60.4)</td>
<td>48 (61.5)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>27 (50.9)</td>
<td>38 (48.7)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>18 (34.0)</td>
<td>26 (33.3)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>12 (22.6)</td>
<td>14 (17.9)</td>
</tr>
</tbody>
</table>

### Dose adjustments

<table>
<thead>
<tr>
<th>Type of Adverse Event</th>
<th>HER2+ Cohort A (n = 53)</th>
<th>All Patients (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE associated with discontinuation</td>
<td>5 (9.4)</td>
<td>7 (9.0)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>2 (3.8)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>TEAE associated with dose reduction</td>
<td>11 (20.8)</td>
<td>15 (19.2)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>10 (18.9)</td>
<td>14 (17.9)</td>
</tr>
<tr>
<td>TEAE associated with dose interruption</td>
<td>20 (37.7)</td>
<td>27 (34.6)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>15 (28.3)</td>
<td>19 (24.4)</td>
</tr>
</tbody>
</table>

### Death

<table>
<thead>
<tr>
<th>Type of Adverse Event</th>
<th>HER2+ Cohort A (n = 53)</th>
<th>All Patients (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE associated with death(^b)</td>
<td>5 (9.4)</td>
<td>7 (9.0)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>2 (3.8)</td>
<td>2 (2.6)</td>
</tr>
</tbody>
</table>

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- **Median treatment duration**
  - HER2+ patients, 4.8 months (range, 1-11)
  - All patients, 3.5 months (range, 1-11)

- **Causes of death related to study drug**
  - According to investigator assessment (n = 2) included pneumonitis (n = 1) andILD (n = 1), both in HER2+ Cohort A

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\(^a\) Relationship to study drug was determined by the treating investigator.  
\(^b\) Each of the following TEAEs was associated with a fatal outcome: sepsis, meningism, disease progression (n = 2), general physical health deterioration (all unrelated to T-DXd), interstitial lung disease, and pneumonitis (both related to T-DXd).
Treatment-Emergent Adverse Events in >15% of Patients

Nausea
Anemia
Neutrophil count decreased\(^{a}\)
Fatigue
Decreased appetite
Platelet count decreased
Vomiting
Diarrhea
Alopecia
Hypokalemia
WBC count decreased

All Patients (N = 78)

- Grade 1 & 2
- Grade ≥3

\(^{a}\) Grade ≥3 neutrophil count decreased, 25.6%; no patients had febrile neutropenia.
AEs of Special Interest: Interstitial Lung Disease

Among the 5 total events:

- Median time to investigator-reported onset was 80 days (range, 22-132)
- 5 of 5 patients with grade ≥ 2 ILD received corticosteroids
- 2 patients recovered, 1 did not recover (later died due to disease progression), and 2 died
- In the 2 fatal cases, onset was from 40-126 days, both received steroids as part of treatment, and death occurred 6-18 days after diagnosis

Protocol recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

Drug related; ILD was determined by an Independent ILD Adjudication Committee based on 44 preferred terms.
One additional grade 5 ILD case in Cohort B was reported after the data cutoff. This case was adjudicated after data cutoff as drug-related ILD.
Conclusions

- T-DXd 6.4 mg/kg q3w demonstrated promising and durable activity in patients with HER2-positive (IHC 3+, IHC 2+/ISH+) metastatic CRC refractory to standard therapies
  - ORR, 45.3%; median DOR not reached
  - Consistent responses were seen across subgroups, including prior anti-HER2 therapy
  - Median PFS, 6.9 months

- No responses were observed in the 2 cohorts of metastatic CRC with low HER2 expression (IHC 2+/1+)

- The safety profile is consistent with what has been previously reported\(^1-5\)
  - Low grade gastrointestinal and hematologic AEs were most common
  - ILD (6.4% of patients; 2.6% grade 5) is an important risk and requires careful monitoring and prompt intervention

- These data demonstrate the potential of T-DXd as a treatment option for patients with advanced HER2-positive CRC

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&

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Collaborator:

AstraZeneca

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DErSTY-CRC01 Cohort A

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