Trastuzumab deruxtecan (T-DXd) for advanced breast cancer patients (ABC), regardless of HER2 status: A phase II study with biomarkers analysis (DAISY)

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Background

The HER2-targeted antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) demonstrated efficacy in heavily pretreated HER2+ and HER2-low expressing ABC (1, 2).

T-DXd also showed a highly significant improvement in progression-free survival (PFS) over trastuzumab emtansine (T-DM1) in patients with HER2-positive unresectable or metastatic breast cancer (MBC) previously treated by taxane and trastuzumab, according to the phase III DESTINY-Breast3 (3).

The aims of this trial were to assess the activity of T-DXd in 3 cohorts HER2-over, HER2-low and HER2-null expressing ABC, to describe the drug mechanisms of action and to identify biomarkers associated with drug resistance or response.

Results as of October 19th, 2021

185 women and 1 man were enrolled between November 2019 and March 2021. Among the patients enrolled in the safety population (see Table 2), median (range) age was 55 (24-82) years, all received at least one prior line of chemotherapy and 12 patients had triple Negative breast cancer.

Patients' characteristics

Table 1: Study population

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>N</th>
<th>Cohort 1 (HER2 over-expressing)</th>
<th>Cohort 2 (HER2 low-expressing)</th>
<th>Cohort 3 (HER2 non-detected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>38</td>
<td>2 (1.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HER2-</td>
<td>31 (29.9%)</td>
<td>1</td>
<td>0</td>
<td>4 (13.6%)</td>
</tr>
<tr>
<td>HER2 unknown</td>
<td>23 (21.9%)</td>
<td>0</td>
<td>0</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR+</td>
<td>2 (2.6%)</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>HR-</td>
<td>1 (1.3%)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HR status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC0+</td>
<td>1 (1.3%)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IHC2+/ISH</td>
<td>25 (25.5%)</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>27</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Study Scheme

Figure 1: Study Scheme

Biopsy of metastatic sites was performed: at baseline, on treatment (mandatory for cohort 1, optional for cohort 2 and 3) and at tumor progression. Blood samples for constitutional DNA analysis were collected at baseline.

Toxicities

A total of 175 patients (96.6%) had at least one treatment-related adverse event (TRAE).

13 patients discontinued treatment due to treatment-related adverse events (5 patients for interstitial Lung Disease). No drug-related deaths occurred.

Table 3: Patients & characteristics

Conclusions

T-DXd showed clinically meaningful activity in patients with heavily pretreated HER2-overexpressing ABC. It is noteworthy to underline that T-DXd also showed efficacy in patients with heavily pretreated HER2-low and HER2-null ABC. The safety profile was consistent with previous reports. Biomarkers analyses are ongoing.

Acknowledgements

Patients & families
All DAISY investigators teams

References


Bibliography

Figure 2: Number of patients in each cohort with TRAE (Govitron (Sp) treated by PF at ADx).

Figure 3: waterfall plot of ORR by cohort according to HR status

Figure 4: PFS by cohort according to HER status

Figure 5: OS by cohort according to HER status

Table 4 shows investigator-reported T-DXd activity in the 3 cohorts at a median follow-up of 15.6 months (95%CI: 12.6-16.7).

Table 3: Statistical design

Sample size estimation: 147 evaluable / 162 pts included

Centers: Ounice: 21 - Caen: 21 - Open: 17 - Recruiting: 15

Table 4: T-DXd activity in the three cohorts according to investigator assessment