Multicenter retrospective cohort study of the sequential use of the antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC)

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Background

• Antibody drug conjugates (ADCs) have demonstrated substantial improvements in progression-free survival (PFS) and overall survival (OS) in patients with metastatic HR+/HER2-negative breast cancer (MBC) in phase III clinical trials, prompting the FDA-approval of two ADCs to date in this setting:
  - Sacituzumab govitecan (SG) for HR+HER2− and TNBC
  - Trastuzumab deruxtecan (T-DXd) for HER2 low BC

• A single-center retrospective study evaluating ADC-after-ADC demonstrated longer PFS for ADC #1 than ADC #2, however additional data are needed

• There are several outstanding questions about the use of ADCs in clinical practice:
  - What is the safety and efficacy of ADCs in a real-world clinical setting?
  - Given that patients with HR+ and TNBC MBC may be eligible for multiple ADCs, what is the safety and efficacy of ADCs used in sequence?

Study Design

• Retrospective multi-institutional cohort study at 5 academic centers. We identified patients with HER2-low MBC who had received both T-DXd and SG, in either order, per SOC or on a clinical trial with ADC monotherapy.
• Chart extraction was performed to collect demographic data, treatment history, ADC response, key safety parameters, and survival
• Real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) calculations were performed using the Kaplan-Meier estimator.

Demographic Data and Treatment History

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>T-DXd MBC (n=56)</th>
<th>SG MBC (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at time ofADC #1, yrs</td>
<td>59.6 (52.7-71.7)</td>
<td>60.0 (59.4-69.5)</td>
</tr>
<tr>
<td>Sex, %</td>
<td>Male 54 (96.4%)</td>
<td>Female 26 (92.9%)</td>
</tr>
<tr>
<td>Race, %</td>
<td>Hispanic 12 (21.4%)</td>
<td>Other 8 (28.6%)</td>
</tr>
<tr>
<td>Histology, %</td>
<td>Mucinous 8 (14.3%)</td>
<td>Adenocarcinoma 14 (50.0%)</td>
</tr>
<tr>
<td>Pathology, %</td>
<td>Nonlymphomatous 21 (37.5%)</td>
<td>Nonlymphomatous 7 (25.0%)</td>
</tr>
<tr>
<td>Prior disease, %</td>
<td>Brain 44 (78.6%)</td>
<td>Liver 30 (106.4%)</td>
</tr>
<tr>
<td>Prior chemotherapy, %</td>
<td>11 (19.1%)</td>
<td>11 (19.1%)</td>
</tr>
<tr>
<td>Prior radiation, %</td>
<td>11 (19.1%)</td>
<td>11 (19.1%)</td>
</tr>
<tr>
<td>Prior hormonal therapy, %</td>
<td>11 (19.1%)</td>
<td>11 (19.1%)</td>
</tr>
<tr>
<td>Prior metastatic breast disease, %</td>
<td>11 (19.1%)</td>
<td>11 (19.1%)</td>
</tr>
<tr>
<td>Prior systemic therapy</td>
<td>27 (48.2%)</td>
<td>12 (43.1%)</td>
</tr>
</tbody>
</table>

Conclusions

• This study represents the largest multicenter series to date of patients treated with sequential ADCs for HR+/HER2-low or HER2-HER2-low MBC.
• ORR was higher and rwPFS was longer for ADC #1 than ADC #2 in all subgroups, regardless of HR+ status and ADC sequence order. However, there was a subset of patients with more durable responses to ADC2 compared to ADC1.
• Rates of ADC discontinuation and dose reduction in this real-world cohort show relatively low rates of discontinuation but higher rates of dose reduction. Most patients on SG needed growth factor support.
• Optimal sequencing of ADCs is an unmet clinical need that is becoming increasingly important with the introduction of novel ADCs. Future prospective studies are needed to further clarify the safety and efficacy of sequential ADC use and to identify biomarkers of response and mechanisms of resistance.

Key Safety Parameters

During treatment with SG (#n=44)

- Discontinued SG due to toxicity, %: 7 (15.9%)
- Required a SG dose reduction, %: 39 (88.6%)
- Due to lab abnormalities: 11 (25.6%)
- Due to symptoms, %: 11 (25.6%)
- Due to other reasons: 11 (25.6%)
- Received growth factor support: 1 (2.3%)

During treatment with T-DXd (#n=56)

- Discontinued T-DXd due to toxicity, %: 10 (18.7%)
- Required a T-DXd dose reduction, %: 53 (95.0%)
- Due to lab abnormalities: 11 (20.0%)
- Due to symptoms, %: 11 (20.0%)
- Due to other reasons: 11 (20.0%)
- Diagnosed with interstitial lung disease (ILD) or pneumonitis of any grade, %: 14 (25.0%)

References & Acknowledgements

• References:
• Acknowledgments:
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