Impact of HER2 kinase domain mutations on trastuzumab deruxtecan efficacy in HER2 low metastatic breast cancer

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Abstract

PURPOSE: HER2 expression is a key determinant for trastuzumab deruxtecan (T-DXd) use in metastatic breast cancer (MBC). Although HER2 kinase domain mutations have emerged as biomarkers in solid tumors, their clinical significance in breast cancer remains unclear. We investigated the association between specific HER2 mutations and T-DXd efficacy in HER2-low MBC.

METHODS: We retrospectively analyzed 25 Japanese women with HER2-low MBC treated with T-DXd. Tumor samples from primary or metastatic sites were assessed for four HER2 kinase domain mutations (L755S, D769Y, V777L, V842I) using droplet digital PCR. Time to treatment discontinuation (TTD) was examined by mutation status, and its association with TTD was evaluated.

RESULTS: Mutation frequencies were L755S 64%, D769Y 32%, V777L 8%, and V842I 92%. D769Y was associated with higher Ki67 (P = 0.027). L755S-positive tumors showed a shorter median TTD than L755S-negative tumors (32 vs 41 weeks). No clear TTD differences were observed for D769Y, V777L, or V842I. Patients with ≥2 mutations had significantly shorter TTD compared with those with a single mutation (30 vs 52 weeks).

CONCLUSION: Specific HER2 kinase domain mutations may affect the therapeutic response to T-DXd in HER2-low MBC. In particular, L755S and multiple concurrent mutations were associated with shorter treatment duration, suggesting reduced benefit from T-DXd in these subgroups.

Introduction

HER2-targeted antibody–drug conjugates have transformed therapy for HER2-positive breast cancer[1]. T-DXd demonstrated substantial efficacy in previously treated HER2-positive MBC[2] and subsequently showed benefit in HER2-low disease, expanding HER2-directed therapy beyond traditional indications[3].

Gain-of-function HER2 mutations have been identified in breast cancer and may influence tumor biology and therapeutic response[4,5]. T-DXd has demonstrated activity in HER2-mutant tumors, including breast cancer in the DESTINY-PanTumor01 study (ORR 29.4%)[6,7]. These findings suggest that specific HER2 mutations may confer sensitivity to T-DXd regardless of HER2 expression level.

However, the relevance of HER2 mutations in HER2-low breast cancer remains insufficiently defined. We therefore evaluated mutation-specific outcomes in HER2-low MBC treated with T-DXd.

Methods

Patients and treatments

Women with HER2-low MBC (IHC 1+ or 2+ and FISH–) who received T-DXd between January 2022 and October 2024 at three institutions were screened. As shown in Fig 1A, 25 patients met eligibility criteria. The study received ethics approval (E23-0337) with opt-out consent. T-DXd was administered at 5.4 mg/kg once every 3 weeks. TTD served as the efficacy endpoint.

Mutation analysis

Metastatic samples were prioritized (48%; 12/25), otherwise primary tumors were used, and DNA was extracted from macrodissected FFPE tissue. Based on DESTINY-PanTumor01[6], four HER2 kinase domain mutations (L755S, D769Y, V777L, V842I) were selected (Fig 1B). Digital droplet PCR used PrimePCR assays (Bio-Rad), and droplets were analyzed with the QX200 system and QuantaSoft.

Statistical analysis

Analyses used JMP 14.2. Fisher's exact and t-tests compared clinicopathological factors by mutation status. TTD was estimated by the Kaplan-Meier method and compared by log-rank testing. Given the small sample size, analyses were exploratory.

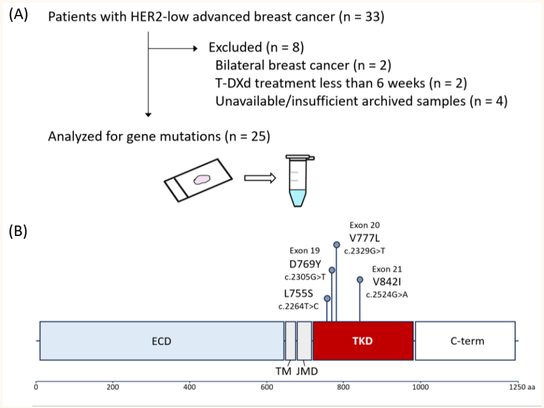


Figure 1. Overview of patient selection and HER2 mutation analysis.

Results

The median TTD was 36.0 weeks (range, 6-78) and a clinical benefit (partial response/stable disease) was obtained in 76% of patients. HER2 mutation positivity rates were 64% for L755S, 32% for D769Y, 8% for V777L, and 92% for V842I. Associations between mutation status and clinicopathological characteristics are summarized in Fig 2.

Median TTD was shorter in patients with the L755S mutation (32 weeks; range, 6-76) than in those without (41 weeks; range, 9-78). For D769Y, median TTD was similar between mutation-positive (38 weeks; range, 9-76) and negative (36 weeks; range, 6-78) groups. Focusing on the number of mutations, the median TTD was 52 weeks (range, 36-66) in patients with a single mutation (n = 5), and 30 weeks (range, 6-76) in those with multiple (≥ 2) mutations (n = 18).

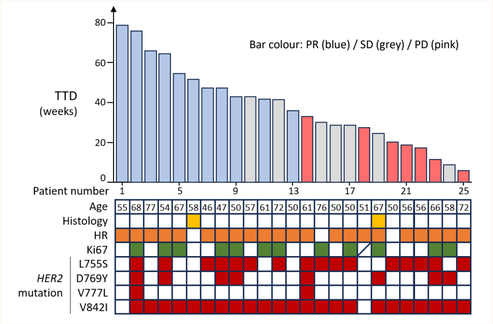


Figure 2. Association of HER2 mutations with clinical features and TTD. Details of individual HER2 mutation status, clinicopathological parameters, including HR status, and TTD are illustrated. Bar length represents TTD with light blue bars indicating clinical PR, light grey indicating SD, and pink indicating PD. In the histology row, white squares represent invasive ductal carcinoma, and yellow squares indicate invasive lobular carcinoma. In the HR row, orange squares denote HR-positive tumors, while white squares denote HR-negative tumors. For the Ki67 labeling index, green squares indicate tumors with Ki67 > 20%, and white squares indicate Ki67 ≤ 20%. For each mutation status, red squares represent the presence of the mutation, while white squares indicate wild-type. TTD: time to treatment discontinuation; HR: hormone receptor; PR: partial response; SD: stable disease; PD: progressive disease.

Kaplan-Meier curves of TTD by mutation status were generated (Fig 3). Although no statistical comparison was conducted due to the small sample size, patients with the L755S mutation showed a tendency toward shorter TTD compared to those without the mutation.

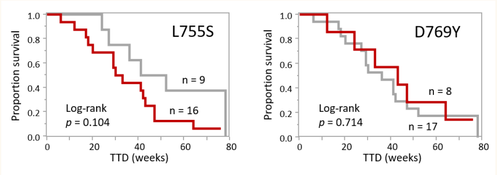


Figure 3. Kaplan-Meier curves of TTD according to mutation status. Red lines indicate patients with the mutation, while grey lines indicate those without the mutation.

Discussion

Based on our findings, HER2 mutations appeared to be associated with resistance to T-DXd. In contrast, in lung cancer, certain HER2 mutations are known to enhance receptor internalization and increase sensitivity to antibody–drug conjugates[7], suggesting that the biological impact of HER2 mutations may vary across tumor types.

The L755 mutation, located within the tyrosine kinase domain, is known to affect the binding of tyrosine kinase inhibitors such as lapatinib and contribute to treatment resistance[8]. Furthermore, this mutation has been reported to shift HER2 into an active conformation[4], and this change may also influence sensitivity to T-DXd, which binds to the extracellular domain.

Limitations

- Retrospective real-world design; small sample size
- Heterogeneous treatment lines; TTD used as a surrogate endpoint
- Japanese-only cohort; external validation needed

Conclusions

In conclusion, specific HER2 kinase domain mutations may influence treatment duration in patients with HER2-low MBC receiving T-DXd therapy. These findings may support future stratified treatment strategies.

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