Advances in HER2-Positive Gastric and Gastroesophageal Cancer: Insights from KEYNOTE-811

Since 2009, trastuzumab combined with chemotherapy has been the standard of care for HER2-positive metastatic gastric (mGC) and gastroesophageal junction cancer (GEJ), based on findings from the phase 3 ToGA trial (1). However, despite this initial success, the following decade brought a series of negative phase 3 trials, leaving first-line treatment options for HER2-positive gastric and gastroesophageal cancers without significant advancements (2–5).

As a result, clinicians have faced limited options in improving outcomes, despite a significant clinical demand given that most patients with HER2-positive gastric and gastroesophageal cancers are diagnosed at an advanced stage and commonly develop resistance to therapy over the course of their treatment (6,7). One proposed mechanism underlying this resistance is the downregulation of the HER2 receptor during therapy with trastuzumab. Supporting this hypothesis, prior research in a transgenic mouse model immune-tolerant to human HER2 has shown that trastuzumab can upregulate programmed death-ligand 1 (PD-L1), a critical modulator of T-cell response inhibition (8). This upregulation was observed in HER2-overexpressing breast cancer cells when co-cultured with human peripheral blood mononuclear cells and could be blocked by an IFN?-neutralizing antibody. These findings suggest that trastuzumab-mediated PD-L1 upregulation through immune effector cell engagement may contribute to resistance, supporting further exploration of combining anti-PD-1 therapies with trastuzumab-based treatment. In recent years, PD-1 inhibitors have also emerged as a promising approach, demonstrating enhanced immune infiltration and T-cell response in preclinical models (8). Clinical translations of this strategy combining pembrolizumab, trastuzumab, and chemotherapy, have shown encouraging results for patients with HER2-positive mGC/GEJ. These findings led to the design of the phase 3 KEYNOTE-811 trial.

KEYNOTE-811 is a randomized, double-blind, placebo-controlled phase 3 trial conducted internationally. The study enrolled 698 treatment-naïve patients with unresectable HER2-positive (IHC 3+ or IHC 2+ and ISH-positive) mGC or GEJ adenocarcinoma, stratified by PD-L1 expression (CPS ≥1 or CPS <1). Participants were randomized 1:1 to receive either pembrolizumab (200 mg IV every 3 weeks) or placebo in addition to standard chemotherapy (platinum-fluoropyrimidine doublet) and trastuzumab. Randomization was further stratified by geographic region and chemotherapy regimen. Treatment continued for a maximum of two years or until disease progression or intolerable toxicity. The dual primary endpoints were progression-free survival (PFS) and overall survival (OS).

Following the IA3 interim analysis with a 38.5-month follow-up, the final survival and PFS outcomes were presented at ESMO 2024 (Abstract 1400O). Consistent with prior interim data the final results demonstrated prolonged overall survival (OS) with a median of 20.0 months in the pembrolizumab group versus 16.8 months in the placebo group (HR, 0.80; 95% CI, 0.67-0.94; p=0.004), based on a median follow-up of 50.2 months. Subgroup analysis showed that patients with a CPS ≥1 had an even greater benefit with a median OS of 20.1 months compared to 15.7 months in the control group (HR, 0.79; 95% CI, 0.66-0.95). Additionally, the median PFS favored pembrolizumab in both the overall population (10.0 vs. 8.1 months; HR, 0.73; 95% CI, 0.61-0.87) and in the CPS ≥1 subgroup (10.9 vs. 7.3 months; HR, 0.72; 95% CI, 0.60-0.87). However, the benefit of adding immunotherapy was only observed in patients with CPS ≥1. Patients with CPS <1 showed no benefit from additional pembrolizumab, reflected in regulatory approval from both EMA and FDA, limited to patients with CPS ≥1. The final results of the KEYNOTE-811 underscore the clinical benefit of combining pembrolizumab with trastuzumab and chemotherapy for patients with advanced HER2-positive disease and CPS ≥1. These findings represent a significant step forward in the treatment paradigm for this patient population (9).

Despite these advances and the near two-year median OS landmark a subset of patients continues to develop resistance to therapy. This clinical challenge is an area of active research with limited understanding of the underlying biology. A recent pre-published study by Taotao Sheng using spatial profiling showed trastuzumab resistance associated with CLDN18 upregulation and increased TIL and immunity-high signatures. CLDN18.2 is a clinically relevant therapeutic target, and a targeted therapy combining zolbetuximab with chemotherapy for CLDN18.2-positive locally advanced, unresectable, or metastatic GC/GEJ has demonstrated efficacy in the GLOW and SPOTLIGHT studies (10,11). Thus, a dual targeting approach of HER2 and CLDN18.2 may offer a promising strategy to overcome trastuzumab resistance in the future (12). To conclude these new discoveries may guide future strategies for HER2-positive gastric and gastroesophageal cancers in the coming years. □

Author: M. D. Louisa Hempel, Universitätsspital Zürich
Mentor: Prof. Dr. med. Viviane Hess, Universitätsspital Basel

References:
1. Bang YJ et al.: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
2. Stulnig TM et al.: Polyunsaturated fatty acids inhibit T cell signal transduction by modification of detergent-insoluble membrane domains. J Cell Biol. 1998;143(3):637–44.
3. Thuss-Patience PC et al.: Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): An international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017;18(5):640–53.
4. Kahn E et al.: Clinical ecology: Environmental medicine or unsubstantiated theory? Ann Intern Med. 1989;111(2):104–6.
5. Satoh T et al.: Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. J Clin Oncol. 2014;32(19):2039–49.

6. Roviello G et al.: Current status and future perspectives in HER2-positive advanced gastric cancer. Clin Transl Oncol. 2022;24(6):981–96.
7. Mindell J.: Deprivation and emergency admissions for cancers. Other possible explanations for findings need to be explored. BMJ. 1999;318(7179):326.
8. Chaganty BKR et al.: Trastuzumab upregulates PD-L1 as a potential mechanism of trastuzumab resistance through engagement of immune effector cells and stimulation of IFN? secretion. Cancer Lett. 2018;430:47–56.
9. Janjigian YY et al.: Final overall survival for the phase III, KEYNOTE-811 study of pembrolizumab plus trastuzumab and chemotherapy for HER2+ advanced, unresectable or metastatic G/GEJ adenocarcinoma. Ann Oncol. 2024;35:S877–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753424029855
10. Shah MA et al.: Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: The randomized, phase 3 GLOW trial. Nat Med. 2023;29(8):2133–41.
11. Shitara K et al.: Final overall survival results from phase 3 SPOTLIGHT study evaluating zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients with claudin 18 isoform 2 (CLDN18.2)+, HER2?, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol. 2024;42(16_suppl):4036–4036.
12. Sheng T et al.: Spatial profiling of patient-matched HER2-positive gastric ancer reveals resistance mechanisms to trastuzumab and trastuzumab deruxtecan. 2024.