Cancer Cell

CellPress

Spotlight

Breaking Barriers in HER2+ Cancers

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https://doi.org/10.1016/j.ccell.2020.07.012

Treatment with the immunoconjugate trastuzumab deruxtecan leads to unprecedented improvements in response and overall survival in patients with HER2-positive (HER2+) metastatic gastroesophageal carcinoma (GEA), according to a study published in the *New England Journal of Medicine*. Until now, no HER2-targeted drugs other than trastuzumab have shown significant benefit in patients with HER2+ GEA.

Despite a 50-year decline in its incidence, gastroesophageal carcinoma (GEA) is a major global health burden. GEA is the third leading cause of cancer death, affecting more than 1 million people newly diagnosed worldwide each year, mostly already metastatic, and with no foreseeable effective screening program in sight (Bray et al., 2018). The proto-oncogene HER-2/neu (*erbb2*) is overexpressed and amplified in the tumors of approximately 1 in 5 GEA patients (Bang et al., 2010). A well-known oncogenic driver, HER2 has been validated as an effective target in breast cancer as well as in GEA by ToGA trial, showing a clear survival benefit in HER2-positive (HER2+) patients treated with chemotherapy and the anti-HER2 monoclonal antibody trastuzumab over those treated with chemotherapy alone (Bang et al., 2010). However, in contrast to breast cancer, other HER2-targeted strategies to date have not improved outcomes in this molecular subtype of GEA. These include the addition to trastuzumab of either a second anti-HER2/3 monoclonal antibody (pertuzumab, JACOB trial) or a cytotoxic cargo (trastuzumab emantansine, T-DM1, GATSBY trial) or the alternative use of a dual HER1/HER2 tyrosine kinase inhibitor to shut down HER2 signaling instead of trastuzumab (TYTAN and LOGiC trials) (Figure 1A). Intrinsic and acquired resistance to trastuzumab occurs frequently in GEA and is due to intralesional heterogeneity of *ERBB2* amplification, deletion of *ERBB2* exon 16, and co-mutations and/or -amplification of *KRAS*, *EGFR*, *MET*, *HER3*, *PI3K*, or *PTEN* genes (Janjigian et al., 2018; Sanchez-Vega et al., 2019; Volpi et al., 2019).

Trastuzumab deruxtecan (T-DXd), previously known as DS2801, is an antibody-drug conjugate "cargoing" a topoisomerase I inhibitor attached to trastuzumab via a cleavable, tetrapeptide-based linker as a cytotoxic payload to HER2-expressing cells (Shitara et al., 2019). With a drug-to-antibody ratio of approximately 8 and the ability of the released payload to diffuse across membranes and enter neighboring tumor cells, T-DXd does not necessarily require high-level HER2 expression. This might be advantageous in the treatment of gastric cancer, which, unlike breast cancer, often has heterogeneous HER2 expression.

Shitara et al. recently reported on DESTINY-Gastric01 (DESTINY), an industry-supported, randomized phase 2 trial (Shitara et al., 2020). They show that T-DXd treatment leads to significant improvements in objective response (OR) and overall survival (OS) in patients with pretreated, advanced HER2+ gastric cancer compared with standard therapies. DESTINY builds on a previous phase 1 study that already documents a response rate higher than 40% in HER2+ GEA patients pretreated with trastuzumab (Shitara et al., 2019). In the DESTINY trial, 187 patients with centrally confirmed HER2+ tumor, progressing after at least 2 previous therapies including trastuzumab, are randomly assigned in a 2:1 ratio to receive either T-DXd (6.4 mg/kg every 3 weeks) or a mono chemotherapy regimen at standard doses (N 55 irinotecan, N 7 paclitaxel). Centrally assessed OR is the primary end point. Secondary end points are response duration, progression-free survival, OS, and safety. The RECIST OR rates (ORR) are 43% and 12% in the T-DXd and chemotherapy arms, respectively. Importantly, a significant gain in median OS (mOS) is also achieved with T-DXd (12.5 versus 8.4 months).

The results of this well-conducted and positive trial are expected to have profound repercussions for patient care and the development of HER2-targeted drugs in metastatic GEA. DESTINY clearly shows for the first time that continuation of HER2 blockade through T-DXd in second line can provide a clinically important benefit in patients that have failed a previous treatment with trastuzumab (Figure 1A). The biological readout of this clinical fact is that T-DXd acts as a "pharmacological sniper" that can deliver an active cytotoxic cargo to a HER2-expressing cancer cell, thus potentially bypassing molecular-driven mechanisms of HER2 resistance.

On the other hand, several clinical and translational issues remain to be elucidated. First, it is paramount to understand the mechanisms of resistance to this novel immunoconjugate, a task that implies dissecting resistance to the trastuzumab and deruxtecan components. Circulating tumor DNA analysis by liquid biopsy, already used for detecting HER2-resistance in colon cancer (Siravegna et al., 2018), could be helpful with the former. Focusing on primary resistance is pivotal for the development of T-DXd, since such an active compound should be compared without delay in first line against the current standard ToGA regime of cisplatin and fluoropyrimidines plus trastuzumab (Bang et al., 2010). Second, DESTINY has accrued only Japanese and Korean patients. As it is known that

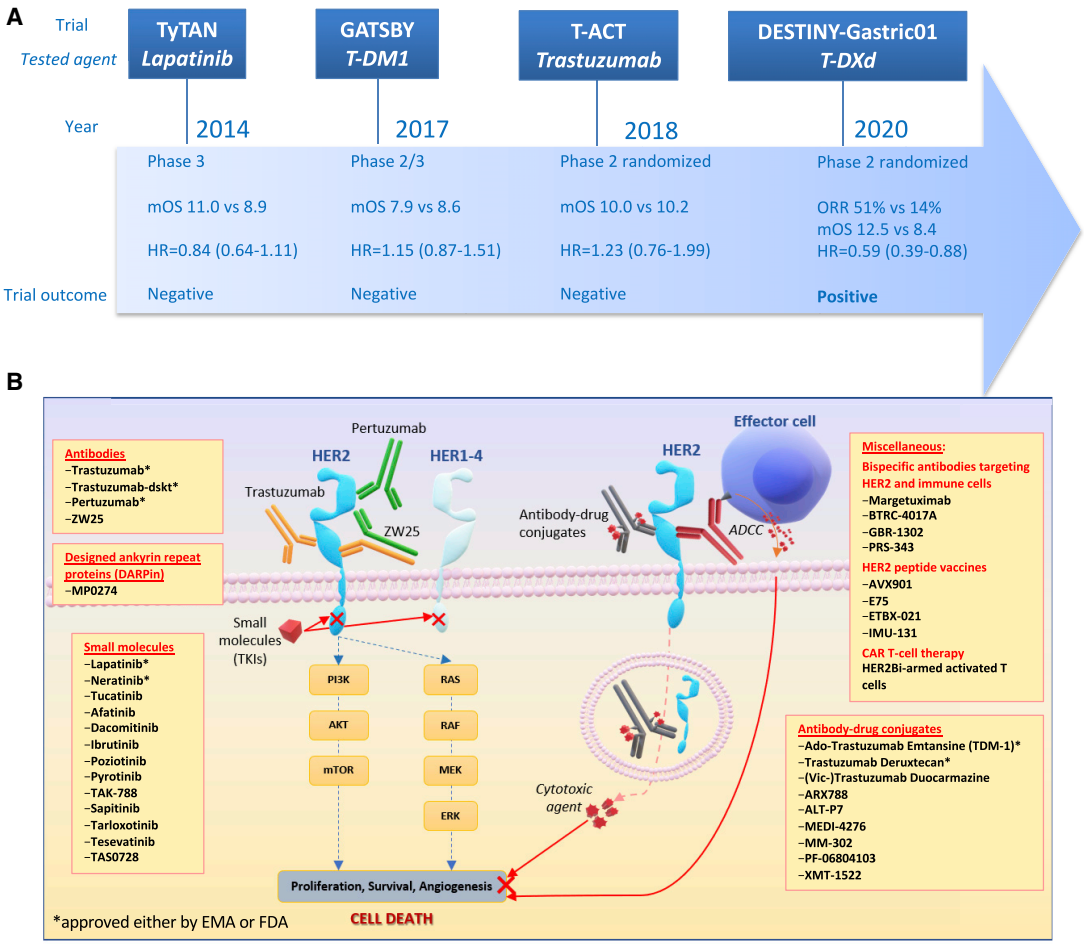

Figure 1. The Landscape of HER2-Targeted Therapies

(A) HER2-targeted clinical trials in pretreated metastatic gastric cancer. In the last years, several studies address the use of HER2-targeted agents in pretreated patients, providing negative results until DESTINY-Gastric01.

(B) Approved and emerging HER2-targeted therapies on the horizon for cancer treatment.

there are ethnic differences associated with the treatment of metastatic GEA in Asian individuals (Bray et al., 2018), the results should be confirmed in other ethnicities. Finally, interstitial lung disease (ILD) is an element of attention that has been associated with the use of T-DXd across tumor types, requiring early detection and proactive bedside management. ILD, mostly G1-2, has been reported in 10% of the relatively small cohort (N = 125) of DESTINY patients treated with a dose of 6.4 mg/Kg. However, in a larger cohort of breast cancer patients treated with a lower dose (5.4 mg/Kg) of T-DXd, the incidence of ILD is 13.6%, most worriedly with 2.2% ILD-related deaths. ILD as a collateral effect has been reported for both irinotecan and other HER2-targeted therapies, including trastuzumab and the immunoconjugate trastuzumab emtansine (TDM-1), and is thus a compelling clinical challenge to be researched at a mechanistic level to prevent and ameliorate the therapeutic index of these compounds, specifically T-DXd that combines trastuzumab to an irinotecan analog.

Looking at the developmental horizon of T-DXd in GEA, the present results certainly support the investigation of combination therapies either concurrently blocking HER2 and other components of the HER receptors family or engaging immune mediators together with HER2 blockers (Figure 1B). The latter strategy has been strikingly successful (70% of patients remaining progression-free at 6 months) in a recent phase 2 study, which is morphing into a full-fledged phase 3 randomized trial, combining chemotherapy, trastuzumab, and the anti-PD-1 pembrolizumab in untreated patients (Janjigian et al., 2020). Moreover, the appealing strength of a HER-targeted cytotoxic such as T-DXd could potentially be leveraged in the context of molecularly identified subsets of GEA with specific vulnerabilities to "HER2 tampering," as suggested in preclinical *in vivo* models (Corso et al., 2019) and in HER2-amplified colorectal cancer (Siena et al., 2020).

ACKNOWLEDGMENTS

Authors are supported by an Associazione Italiana Ricerca Cancro (AIRC) 5 x mille grant (Project ID 51000), Special Program Molecular Clinical Oncology, an AIRC Investigator Grant (Project ID 20685), and an AIRC Special Program 5 per mille Metastases (Project ID 21091); a CORDIS Community Research and Development Information Service, Horizon 2020 (Project ID 635342) grant; Molecularly Guided Trials with Specific Treatment Strategies in Patients with Advanced Newly

Molecular Defined Subtypes of Colorectal Cancer (MoTriColor); Fondazione Oncologia Niguarda Onlus; Terapia Molecolare dei Tumori and grant Studies to Develop Therapies Against Colorectal Cancer in Young Adults (12018); and a Fondazione Regionale Ricerca Biomedica (FRRB) Grant (IANG-CRC CP_12/2018).

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