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Emerging molecular drugs for the treatment of gastroesophageal tumors

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Despite being a "treatment desert" for decades, new drugs and particularly immunotherapy compounds have significantly changed the treatment algorithm of gastroesophageal (GE) tumors in recent years. This positive trend appears to be continuing as more new molecular drugs are in the pipeline.

The antibody–drug conjugate trastuzumab deruxtecan is well established in Her2-positive breast cancer and also shows promising activity in GE tumors [1]. The single arm phase II study DESTINY-GASTRIC-02 demonstrated a notable benefit in confirmed overall response rate (cORR), overall survival (OS), and progression-free survival (PFS) in Her2-positive GE tumor patients who were previously treated with trastuzumab [2]. Based on these results, treatment of trastuzumab deruxtecan is already approved by the European Medicines Agency as a second-line treatment option in this setting. A confirmatory phase III trial, DESTINY-GASTRIC-04 is ongoing [3]. This trend seems to go far beyond second line as additional studies are investigating trastuzumab deruxtecan as a first-line treatment option in Her2-positive GE tumors with or without immunotherapy [2]. There is also an ongoing small phase II trial evaluating the efficacy of this agent in resectable Her2-positive tumors [4]. Therefore, it is very likely that this drug will become an important part of treatment for Her2-positive GE tumor patients in the near future.

Another drug that seems to set a new standard for treating GE tumor patients is zolbetuximab. Claudin 18.2 is a tight junction protein and is highly expressed on the mucosa of GE cancer tissue [5]. In a phase II study, inhibition of Claudin 18.2 via the chimeric monoclonal antibody zolbetuximab induced a remarkable prolongation of OS in advanced GE tumors, particularly in patients with high Claudin 18.2 expression [6]. The subsequent phase III trial SPOTLIGHT aimed to demonstrate this benefit in a larger cohort. First results of this study, as presented in the last ASCO-GI 2023 meeting [7], suggest that the study met its primary endpoint (PFS) and increased OS in patients with Claudin-18.2-positive tumors by an additional 2.8 months when treated with zolbetuximab concomitantly with mFOLFOX6. This is the first study investigating a targeted therapy with positive outcomes after the success of the ToGA trial in 2010 as establishing trastuzumab as first-line treatment in the first-line setting [8]. Now, Claudin 18.2 testing could become an important part of the initial pathological work-up of advanced GE tumors and the inhibition of this molecule in Claudin-18.2-positive patients with zolbetuximab seems to represent a new standard.

Fibroblast growth factor receptor 2 (FGFR2b) is a growth factor signaling molecule and thus represents a promising target for GE tumors [9]. Overexpression of the splice variant FGFR2b is highly present in GE tumors and its activation can be suppressed by the recombinant humanized monoclonal antibody bemarituzumab [10]. A phase II study investigated this drug in advanced GE tumors and randomized the treatment naïve patients to either bemarituzumab + mFOLFOX6 or to placebo + mFOLFOX6 [11]. Although no improvement in PFS was demonstrated as the primary endpoint of the study, the initial analysis shows a promising prolongation of OS in the bemarituzumab arm vs placebo arm (median OS NR [95% CI NR–13.8] vs 12.9 months [95% CI 9.1–15.0], hazard ratio = 0.58 [95% CI 0.35–0.95], $p = 0.027$, with a median follow-up time of 10.9 months [interquartile range 6.3–14.2]; respectively). This led to designation of two large clinical phase III trials, FORTITUDE 101

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and FORTITUDE 102, where bemarituzumab will be tested together with mFOLFOX6 or nivolumab plus mFOLFOX6 in patients with FGFR2b-positive advanced GE tumors, respectively [12, 13]. Based on the significant and promising findings of the phase II trial of the same question, there is immense expectation for the results of these two prospective phase III studies.

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Conflict of interest A. Ilhan-Mutlu declares following competing interests: Participation in advisory boards organized by MSD, Servier, Daiichi Sankyo, BMS and Astellas; Lecture honoraria from Eli Lilly, Servier, BMS, Daiichi Sankyo, Astellas and MSD; Consulting for Astellas, MSD, Amgen and Astra Zeneca; Travel support from BMS, Roche, Eli Lilly and Daiichi Sankyo.

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