Worldwide, gastric cancer is the fifth common cancer type and causes the third most cancer-associated deaths (1), mostly due to its commonly fatal outcome especially in locally advanced or metastatic disease. For over a decade, standard of care in metastatic disease was based on chemotherapy doublets or triplets containing platinum agents plus fluoropyrimidine in combination with either taxanes or anthracyclines (2). Molecular subtyping of gastric adenocarcinoma has identified promising protooncogenes as novel therapeutic targets (3). One of them is the human epidermal growth factor receptor 2 (HER2/ERBB2), detected in a subset of roughly 9% to 18% of gastric adenocarcinomas (4).

HER2-overexpression in gastric cancer was mostly reported to be associated with reduced overall survival (OS), yet few studies show no effect on prognosis or even rebut this finding. In contrast to breast cancer, HER2-positivity in gastric cancer might still have other prognostic implications (4).

Following the 2010 published data of the ToGA trial, HER2-targeting monoclonal antibody trastuzumab was granted first line approval for advanced, HER2 overexpressing gastric adenocarcinoma. A combination chemotherapy of cisplatinum plus capecitabine or 5-fluorouracil was complemented by trastuzumab in the verum test cohort (5). Herein an OS benefit of 2.7 months prolonged survival for the trastuzumab treated patients (5).

Recently data from the phase II/III GATSBY trial in second line treatment of HER2-positive gastric adenocarcinoma were published (6). Next to evaluation of an adequate trastuzumab emtansine dosage, the antibody-drug conjugate was tested against physicians choice docetaxel or paclitaxel, primarily measured in OS rates. Though trastuzumab emtansine was previously reported to show benefit in HER2-positive pretreated breast cancer (7), in gastric adenocarcinoma beneficial survival for the antibody-drug conjugate could not be reported (median OS 7.9 months for trastuzumab vs. 8.6 months for taxane, P=0.86). Yet, in case of tolerability, the more specific treatment showed fewer and less intense side effects (6).

First line combination therapy of trastuzumab emtansine plus capecitabine (NCT01702558) is still being evaluated. Lately, data from the TRIO-013/LOGiC placebo controlled phase III trial in advanced gastric adenocarcinoma were published (8). This study conducted capecitabine plus oxaliplatin (CapeOx) regimen randomly added by lapatinib or placebo in n=545, thereof n=487 centrally confirmed HER2 FISH-positive, patients. While its primary endpoint OS in the latter cohort was not met (12.2 months OS in the lapatinib cohort vs. 10.5 months OS in the placebo cohort, P=0.3492), progression free survival (PFS) was significantly prolonged by 0.6 months adding lapatinib to CapeOx (P=0.0381). Furthermore overall response rate to therapy...
was higher with than without lapatinib (53% vs. 39%, P=0.0031) (8). In post hoc descriptive analyses, interestingly OS improvement for lapatinib treated patients was found for Asians (P=0.0261) and those under 60 years of age (P=0.0141) (8), suggesting possible detrimental effects of age and diverging tumor’s biological behavior regarding the patients origin. Upon a closer look at lapatinib plus CapeOx safety profile serious adverse events (AE) were only slightly higher, yet fatal AE’s were 6% in the lapatinib arm and 3% in the placebo arm. Most relevant AE in the CapeOx plus lapatinib arm were diarrhea (any grade 58% vs. 29%) and vomiting (any grade 44% vs. 36%). Among others, fatigue, peripheral neuropathy, asthenia, neutropenia, anemia or ascites were of comparable incidence (8). Lapatinib is a small molecule drug and acts as an intracellular disruptor of HER2 downstream signaling. Therefore it seems legitimate to test patient’s HER2 status preferably by FISH analysis. Especially with the awareness of the Asian TyTAN trial (9), it must be questioned why regular IHC evaluations, as proposed by the FDA before starting extracellular monoclonal antibody therapy with trastuzumab (IHC 3+ plus FISH positivity and IHC 2+ plus FISH positivity) (4) were not relevantly evaluated in this study.

The phase II GastroLab trial in second line treatment of gastric adenocarcinoma with lapatinib vs. lapatinib plus capecitabine was performed by German AIO society (10). This study also failed to show beneficial effects on survival. Yet, response rates to therapy were significantly higher in combination therapy of capecitabine plus lapatinib compared to lapatinib alone. Due to these findings, lapatinib seems to improve response to anti-neoplastic therapy but does not promise a durating treatment approach for gastric adenocarcinoma solely.

A series of molecular resistance mechanisms against lapatinib (and trastuzumab) have been identified and are depicted in simplified downstream model of HER2-activation in Figure 1.

(I) Heregulin is an activator of HER3-activation. Lapatinib use consecutively leads to heregulin liberation and HER3-dependent AKT activation (12). (II) AKT-driven downregulation of FOXO1 indirectly induces a MET-emphasized pro-tumor signaling under continuously applied HER2-inhibition (13). (III) PTEN deficiency results in imbalanced phosphoinositol-3-kinase (PI3K) activity towards AKT signaling (14).
antibody (16) was built to contact tumor cells with CD3+ T-cells (phase I trial, NCT02829372).

In conclusion, HER2-targeted therapy is a relevant option in IHC- and FISH-positive gastric adenocarcinoma. In contrast to trastuzumab, lapatinib was not able to improve outcome of HER2-positive gastric cancer patients but emphasizes response rates in cytotoxic combination therapy. Lapatinib seems to be suitable especially for a subset of patients (i.e., <60 years of age and Asian origin). Resistance mechanisms against lapatinib have been reported and might be overcome by adding further targeted therapies to HER2-antagonizing combination therapies. In contrast to breast cancer, HER2-targeting in gastric adenocarcinoma seems to be more challenging. Therefore treatment strategies such as the enhancement of T-cellular activity in the tumor's microenvironment are focus of recruiting studies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References
