Targeted therapy in esophageal cancer

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Abstract: Esophageal cancer consists of two distinct histological types, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Esophageal carcinoma is a grave malignancy with regards to prognosis and mortality. ESCC remains the dominant histological type of esophageal cancer worldwide, with about 90 percent of all cases worldwide. However, EAC is now much more common in the United States and the Western World, and represents one of the fastest growing cancers there. Despite significant progress in multimodality treatment options, the overall prognosis remains poor, and 5-year survival rates for all-comers are still below 20 percent. Although esophageal cancer initially responds well to systemic therapy, most patients recur and eventually die from their disease. Therefore, new treatment options are urgently needed. The combination of traditional systemic therapy with new biologicals and/or targeted agents is one of these new treatment options. Some of these agents are already approved, while others are currently undergoing clinical trials. These targeted therapies have emerged as an important tool for the treatment of many different cancer types, including esophageal cancer. Herein, we review the recent literature and ongoing clinical trials in esophageal cancer targeted therapies, and discuss the different targeted pathways. Currently, most esophageal cancer patients are still treated with a combination of chemotherapies like taxanes (paclitaxel, docetaxel), platinum (carboplatin, cisplatin), anthracyclines (doxorubicin, epirubicin) or pyrimidine analogs (5-fluorouracil). Future treatment strategies should be based on the molecular features of each patient's individual tumor, and should include biologicals/targeted agents tailored to these specific findings.

Keywords: Esophageal cancer; esophageal squamous cell carcinoma; esophageal adenocarcinoma (EAC); targeted therapy

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Introduction

Esophageal cancer consists of two distinct histological types, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). While squamous cell carcinoma is mostly found in the upper and middle parts of the esophagus, adenocarcinoma starts with the glandular cells and occurs usually in the lower part of the esophagus (1). Esophageal cancer remains the eighth most common cancer worldwide (2). The variation in incidence of esophageal cancer is geographical with ESCC continuing to be the major type in Asia (2), and EAC the dominant type in the United States and the western world (1,3-5). EAC is one of the most aggressive human cancers, and the only major cancer in the United States with increasing incidence (1,6,7). In addition, EAC can occur at the gastric junction, known as esophagogastric junction adenocarcinoma (GEJAC) (8). Gastroesophageal reflux disease (GERD) and obesity are the main known risk factors for EAC and obesity can cause or worsen GERD (2,9,10). In addition, GERD can...
cause Barrett’s esophagus (BE), the recognized precursor lesion consisting of columnar metaplasia of the lower esophagus. BE remains the strongest known risk factor for the development of EAC (11-13). It is believed that Barrett’s metaplasia progresses through low to high grade dysplasia before developing into adenocarcinoma (14-16). The main risk factors of ESCC are tobacco smoking, alcohol consumption, hot beverage drinking, and poor nutrition. Unfortunately, overall 5-year survival rates for all stages of esophageal cancer are still below 20 percent. Despite significant progress in multimodality treatment options, the overall prognosis remains poor due to high resistance to chemotherapy (17,18). In addition, most esophageal cancers are already unresectable by the time of diagnosis (19). Although esophageal cancer initially responds well to systemic therapy, most patients recur and eventually die from their disease (20). Therefore, new treatment options are needed. With the identification of new biomarkers for esophageal cancers (21), targeted therapies are gaining interest (22). In esophageal cancer, several potentially targetable pathways have been identified (23). These targets include the human epidermal growth factor receptor 2 (HER2, Neu, ErbB2) (23), the epidermal growth factor receptor (EGFR, Her1, ErbB1) (24), the vascular endothelial growth factor (VEGF) (25), the mesenchymal-epithelial transition (MET) factor (26), and the programmed death ligand 1 (PD-L1) (27). Drugs targeting these proteins have been developed, brought into preclinical studies and clinical trials, and have shown clinical benefits (Table 1).

### HER2

The human epidermal growth factor receptor 2 (HER2, Neu, ErbB2) emerged as a major target (41). Abnormal frequencies of HER2/neu have been identified in cancers other than breast cancer, making it a good target for therapies (42). HER is associated with cancer progression and a subset (0-83%) of esophageal cancer has been shown to overexpress HER2 (43-45). Thus blocking HER2 with a drug could increase esophageal cancer tumor regression and therapeutic efficacy in HER2 expressing esophageal cancer (46).

#### Trastuzumab

Trastuzumab (Herceptin), is a monoclonal antibody to HER2, and was the first FDA approved HER2 targeted agent for gastroesophageal (GE) cancer (47). Trastuzumab was initially used to treat HER-2 positive breast cancer (48). Trastuzumab was shown to inhibit the growth of esophageal cancers with HER2 expression (49). When added to chemotherapy for HER2-positive advanced gastric and gastro-esophageal junction cancers, there was a significant increase in median overall survival (OS) with a hazard ratio (HR) of 0.74; and a 95% confidence interval (CI) of 0.60–0.91; P=0.0046 (28).

#### Pertuzumab

Pertuzumab, a humanized monoclonal antibody that also targets the HER2 receptor, similar to trastuzumab. However, it binds to a different epitope of the HER2 receptor. Pertuzumab, in combination with trastuzumab and docetaxel demonstrated improved survival in patients with HER2-positive breast cancer (50). However, in the phase 3 JACOB trial, the addition of pertuzumab to trastuzumab plus chemotherapy showed no significant improvement in survival of patients with HER-2 positive gastro-esophageal cancer (29). The median overall survival (OS) was 17.5 months (95% CI: 16.2–19.3) in the treatment group with pertuzumab, and 14.2 months (95% CI: 12.9–15.5) in the control group. While a statistically significant difference

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**Table 1 Main targeted agents used in esophageal carcinoma**

<table>
<thead>
<tr>
<th>Protein targets</th>
<th>Therapies</th>
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<tbody>
<tr>
<td>HER2/neu</td>
<td>Trastuzumab (28)</td>
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<tr>
<td></td>
<td>Pertuzumab (29)</td>
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<td>Lapatinib (30)</td>
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<td></td>
<td>Zanidatamab (31)</td>
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<td></td>
<td>Fam-trastuzumab deruxtecan-nxki (32)</td>
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<td>EGFR</td>
<td>Nimotuzumab (33)</td>
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<td></td>
<td>Panitumumab (34)</td>
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<td></td>
<td>Cetuximab (35)</td>
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<td>VEGF</td>
<td>Ramucirumab (36)</td>
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<td>MET</td>
<td>AMG 337 (37)</td>
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<td></td>
<td>Onartuzumab (38)</td>
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<tr>
<td>PD-1 and PD-L1</td>
<td>Pembrolizumab (39)</td>
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<td>Nivolumab (40)</td>
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EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; MET, mesenchymal-epithelial transition; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.
in overall survival was not reached between the two groups with an HR of 0.84 (95% CI: 0.71–1.00); P=0.057, there was a clinical survival benefit of more than 3 months. Furthermore, in a Chinese subpopulation analysis of the JACOB trial, the median overall survival was 18.7 months in the treatment group as opposed to 16.1 months in the control group (HR 0.75; 95% CI: 0.49–1.14). The authors concluded that overall survival was numerically improved by addition pertuzumab to trastuzumab and chemotherapy (51). The results from the Japanese subgroup analysis of the JACOB trial suggested a similar effect of pertuzumab in Japanese patients (22 months in the pertuzumab group, versus 15.6 months in the placebo group) (52).

**Zanidatamab (ZW25)**

Zanidatamab is a Her-2 targeted biparatopic antibody that binds to two different domains of Her-2 at the same time (ECD4 and ECD2). In a recently reported phase 1 study, this agent showed antitumor activity with good tolerability in patients with HER2-expressing GE adenocarcinoma who had progression of disease after standard-of-care therapy, with an overall response rate (ORR) of 33% and a disease control rate of 61% as monotherapy, and an ORR of 54% and a disease control rate of 79% in combination with chemotherapy (31).

**Fam-trastuzumab deruxtecan-nxki**

Fam-trastuzumab deruxtecan-nxki is a HER2-directed antibody and a topoisomerase inhibitor drug conjugate. It was approved by the FDA in January 2012 for the treatment of patients with progressing locally advanced or metastatic Her-2 positive gastric or Ge adenocarcinoma, who were treated with at least two prior regimens. In the DESTINY-Gastric01 trial (32), a response rate of 51% was observed in the trastuzumab deruxtecan group, compared to 14% in the control group. The median overall survival was 12.5 months in the trastuzumab deruxtecan group, and 8.4 months in the control chemotherapy group (HR for death 0.59; 95% CI: 0.39–0.88; P=0.01).

**EGFR**

EGFR (Her1, ErbB1) is a receptor tyrosine kinase that belongs to the ErbB family that includes three other members (ErbB2/HER2/Neu, ErbB3/HER3 and ErbB4/HER4). Activation of EGFR leads to phosphorylation of the receptor which then activates several downstream effectors, such as the RAS-RAF-MEK-ERK-MAPK and the PI3K-AKT-mTOR pathways (53). EGFR overexpression has been reported in esophageal cancer, and anti-EGFR agents are used in clinical targeting of this receptor (54,55). To date addition of an anti-EGFR agent to chemotherapy seems to convey no additional benefit for patients with esophageal cancer (55,56), but the data remains inconclusive.

**Nimotuzumab**

Nimotuzumab is a fully recombinant, humanized monoclonal antibody against EGFR. A phase 1 study is looking at the use of nimotuzumab together with neoadjuvant chemotherapy before surgery for advanced esophageal cancer (33). The addition of nimotuzumab in combination with chemotherapy showed a significant anticancer effect with tolerable toxicities in advanced esophageal cancer. A phase 2 long-term follow-up study looked at the use of nimotuzumab in combination with paclitaxel and cisplatin as first line treatment for esophageal cancer (57). This study concluded that patients with limited local lymph node metastasis survived longer (the median OS was 26.2±10.0 months, with a 95% CI: of 6.6–45.8) than patients with distant metastasis (the median OS was 11.5±3.7 months, with a 95% CI: of 4.2–18.8) with the nimotuzumab, paclitaxel, and cisplatin combination therapy.

**Panitumumab**

Panitumumab is a fully human monoclonal IgG antibody targeting the EGFR. A phase 3 trial of panitumumab together with cisplatin and 5-fluorouracil failed to show an improvement in patient survival (34). Another phase 3 trial with panitumumab showed that adding it to chemotherapy as a first line treatment was found to be ineffective in advanced GE cancer (58).

**Cetuximab**

Cetuximab is an FDA approved chimeric (mouse/human) monoclonal antibody that is used to treat patients with advanced metastatic colorectal cancer. It targets EGFR and inhibits its activation, preventing cancer progression. Several studies have demonstrated that cetuximab can be used to treat esophageal cancer, especially in combination with chemotherapies (59). In a phase Ib/II trial, the addition of cetuximab to preoperative chemoradiotherapy showed
its feasibility and higher 5 years survival rates in patients with squamous histology than that of adenocarcinoma (58% versus 25%, P=0.011) (35). Another phase II trial however showed that although still promising, the drug was correlated with high toxicity (60). The Swiss Group of Clinical Cancer Research phase III trial (SAKK 75/08) showed that the addition of cetuximab to multimodal therapy significantly improved the loco-regional control, leading to a clinically, but not statistically significant improvement of overall survival [5.1 years (95% CI: 3.7 to not reached) versus 3.0 years (95% CI, 2.2–4.2), HR, 0.73; 95% CI: 0.52–1.01; P=0.055] (61).

**Lapatinib—a dual EGFR and HER2 inhibitor**

Lapatinib is a potent ATP-competitive inhibitor which is available in oral preparation that simultaneously inhibits both EGFR and HER2, and is used in a phase 2 clinical trial (30). This randomized phase 2 study investigated the addition of lapatinib to standard perioperative chemotherapy (30). Administration of lapatinib in combination with chemotherapy was feasible, and did not affect the operative management, but the toxic effects of the drug were higher (30).

**VEGF**

The VEGF is a signaling protein that is involved in tumor angiogenesis, involving several complex processes (62). VEGF (VEGF-A, VEGF-B, VEGF-C, VEGF-D and PIGF) is produced by multiple cell types including tumor cells, and binds with VEGF receptor (VEGFR1, VEGFR2, VEGFR3) to activate various signaling pathways related to tumor growth, among them the extracellular regulated protein kinases 1/2 (ERK1/2) and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways (62). Thus the VEGF/VEGFR signaling pathway seems to be a potential target for esophageal cancer therapy.

**Ramucirumab**

Ramucirumab is a VEGFR-2 antagonist fully humanized monoclonal antibody. When added to cisplatin and fluoropyrimidine in the first-line therapy for patients with metastatic gastric or junctional adenocarcinoma (RAINFALL Trial), it failed to demonstrate improvement in patient outcome (36). However, in the RAINBOW trial (63), a significant increase in overall survival was present when patients were given ramucirumab plus paclitaxel alone, median OS of 9.6 months [95% CI: 8.5–10.8] vs. 7.4 months [95% CI: 6.3–8.4], HR 0.807 [95% CI: 0.678–0.962]; P=0.017. Ramucirumab (CYRAMZA) is now approved for the treatment of patients with advanced or metastatic gastric or GE junction cancer.

**MET**

The tyrosine protein kinase MET is a receptor for the hepatocyte growth factor (HGF). HGF-MET ligand-receptor interaction leads to tumor cell growth, invasion and metastasis (64). Several studies have demonstrated that MET is overexpressed in a subset of esophageal cancer, and that this overexpression is related to poor prognosis (65). In addition, MET-HER2 co-overexpression is also frequent in esophageal cancer patients (66), and they may be resistant to lapatinib, a dual EGFR and HER2 inhibitor therapy (26,67,68). Thus MET-HER2 targeting could be a new treatment approach for esophageal cancer that have overexpression or activation of MET and HER2 (26).

**AMG337**

AMG337 is a small molecule selective inhibitor of the MET receptor that has been shown to inhibit c-MET/HGF binding (69). Phase I and phase II clinical trials have shown that AMG337 is associated with antitumor activity in MET-amplified gastric, GE junction, and esophageal cancer patients (37).

**Onartuzumab**

Onartuzumab is a recombinant, fully humanized anti-MET monoclonal antibody that can inhibit the binding of MET to HGF, thereby restricting cellular signaling via the MET pathway. The results of phase II and phase III clinical trials of onartuzumab, in combination with FOLFOX chemotherapy in GE adenocarcinoma could not show improved progressive-free-survival in MET-positive patients (38,70). Furthermore, phase III trials have failed to show a survival benefit (68/69) and did not improve outcome in patients (38).

Although clinical trials of other inhibitory anti-MET antibodies like rilotumumab (AMG-102) (71) failed to demonstrate any survival benefits in esophageal cancer patients, further research is required to better elucidate which patient populations may potentially benefit from these therapies.
PD-1 and PD-L1

The PD-1 (programmed cell death-1) receptor is expressed on the surface of activated T cells, and its ligand, PD-L1 (is expressed on the surface of dendritic cells or macrophages. Cancer cells exhibit immune escape by the expression of PD-L1 when PD-L1 on cancer cells bind to PD-1 on immune cells. Therefore, PD-1 and PD-L1 targeted therapy blocking this interaction is considered an effective therapy for a multitude of different tumors (72). PD-L1 protein expression in gastric or GEJ adenocarcinoma is determined by using the combined positive score (CPS). This score is calculated by the number of PD-L1 stained cells (tumor cells, lymphocytes, and macrophages), divided by the number of viable tumor cells, and multiplied by 100 (73).

Pembrolizumab

Pembrolizumab is a humanized monoclonal IgG4 kappa antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thus preventing PD-L1 on cancer cells from binding to the PD-1 receptor on T cells, and therefore enabling these T cells to kill cancer cells. Pembrolizumab is approved by the FDA for the treatment of PD-L1 positive tumors in patients with advanced GE junction adenocarcinoma, who received at least two prior lines of chemotherapy (39). The approval was granted based on the demonstration of a durable ORR in the multi-centerKEYNOTE-059 trial (74). The FDA also granted approval for pembrolizumab as a second line option for PD-L1 positive ESCC, based on the KEYNOTE-180 phase II and KEYNOTE-181 phase III trials (75,76). The KEYNOTE-590 trial demonstrated that pembrolizumab and chemotherapy significantly improved overall survival, progression-free survival, and objective response rates as compared to chemotherapy alone in patients with locally advanced, unresectable or metastatic esophageal cancer, with a median overall survival of 12.4 months (95% CI: 10.5–14.0) vs. 9.8 months (77).

Nivolumab

Nivolumab is a PD-1 blocking antibody that has been approved for a variety of metastatic or locally advanced tumors, including esophageal squamous cell carcinoma. In the phase III CheckMate 649 trial, nivolumab, in combination with chemotherapy, showed superior overall survival and progression-free survival as first-line treatment in patients with unresectable advanced, or metastatic GC/GEJC/EAC with a median overall survival of 14.4 months in the nivolumab plus chemotherapy arm, vs. 11.1 months for the chemotherapy arm in the PD-L1 CPS ≥5 population (HR =0.71; P<0.0001). In addition, there was also a statistically significant OS benefit in patients with PD-L1 CPS ≥1, as well as the all-randomized population (40). Moreover, Nivolumab, administered as adjuvant treatment following neoadjuvant chemoradiation and complete surgical resection in patients with esophageal or GE junction cancer, demonstrated statistically significant improvement in disease-free survival (DFS) in the phase 3 CheckMate-577 trial (78) with a doubling of DFS (22.4 vs. 11.0 months).

Combination therapies and new emerging targets

Several clinical trials with combinations of the above described targets are ongoing, such as the combination of PD-L1 or PD-1 directed therapy with Her-2 based therapy, as in the MAHAGONY trial with margetuximab plus checkpoint inhibitors (79), or the combination of check point inhibition with trastuzumab and chemotherapy (80,81).

One of the new emerging targets is claudin 18.2. This is a tight junction protein that is expressed in the gastric epithelia, and is retained in malignancy (82). Zolbetuximab, a chimeric IgG1 monoclonal antibody against claudin 18.2, showed promising results in a phase II trial (83). The phase III GLOW trial will investigate Zolbetuximab in combination with CAPOX chemotherapy in gastric and GE junction cancer (84). The Spothlight trial will use the same antibody in combination with mFOLFOX chemotherapy (85).

Another emerging target is the Fibroblast growth factor receptor 2 (FGFR2). FGFR2 overexpression has been shown to be associated with tumor cell proliferation, cell cycle progression, and anti-apoptosis in adenocarcinoma of the GE junction (86). The FiGhT eR trial is a phase II study investigating the FGFR inhibitor pemigatinib as second-line therapy in metastatic gastroesophageal adenocarcinoma or gastric cancer patients who were progressing under trastuzumab-containing therapies (87).

Conclusions

EAC which resembles gastric/GEJ adenocarcinoma evolved into leading type of esophageal cancer in the US, and is
one of the fastest growing cancers in the Western World. In contrary, in Asia, esophageal squamous cells carcinoma (ESCC) is far more common than EAC. Despite significant progress in multimodality treatment options, the overall prognosis remains poor, and most patients survive less than one year on average. Therefore, new therapeutic approaches using targeted drugs with good efficacy and limited side effect are urgently needed. HER-2 (trastuzumab), VEGFR (ramucirumab) and PD-L1 (pembrolizumab) targeted therapies have demonstrated improved survival and prognosis in advanced EAC and ESCC. Clinical trials are currently underway to explore the benefits of combination treatments, including cytotoxic and targeted agents with different mechanisms of actions to improve the survival of patients with esophageal cancer.

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Footnote

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