Evolving Management Strategies for Metastatic Esophageal and Gastroesophageal Junction Adenocarcinoma

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Metastatic or unresectable esophageal and gastroesophageal junction adenocarcinoma represent a devastating disease with 5-year survival rate of <5%. Although cytotoxic chemotherapy with platinum doublet based regimens is initially effective, patients inevitably progress. Patients often decline rapidly after this initial progression, making later lines of therapy a challenge to successfully administer. There have been multiple efforts to incorporate biologic agents, targeting pathways known to be dysregulated in esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma, into existing chemotherapy backbones. Other than therapeutics targeting human epidermal growth factor receptor-2 (HER2) and vascular endothelial growth factor receptor (VEGFR), other strategies have failed. Given the mixed success of biologic agents, along with the promise of immunotherapy to generate durable and sometimes complete responses, immune-agent based trials are a major area of interest for patients with this disease. Checkpoint inhibitors blocking programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) have demonstrated modest single-agent efficacy in patients with progressive esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma. However, other approaches such as novel checkpoint combinations, vaccine-based approaches and autologous T cells hold more promise to change the trajectory of disease.

Keywords

Metastatic esophageal adenocarcinoma, gastroesophageal adenocarcinoma, immunotherapy, chemotherapy

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Esophageal cancer remains a devastating malignancy with an anticipated 15,850 deaths out of 17,290 new cases in the US in 2018.[1] Forty percent of patients with esophageal cancer are diagnosed with metastatic disease and carry an even more dismal prognosis, with 5-year survival rates of <5%.[1] The two predominant esophageal cancer histologic subtypes, comprising over 90% of all cases, are adenocarcinoma and squamous cell carcinoma. Esophageal adenocarcinoma is now more common than squamous cell carcinoma in the US in roughly a 6:4 distribution.[2] While the overall incidence of esophageal cancer has declined, rates of esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma are rising. Defined by primary tumor location 5 cm above and below the gastric cardia, gastroesophageal junction adenocarcinoma represents a unique tumor subtype whose rising incidence has been attributed to higher rates of obesity, gastroesophageal reflux disease, and sequelae of acid reflux associated mucosal dysplasia. This review will focus on systemic treatment options for metastatic esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma.

For several decades, treatment of metastatic esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma was limited to cytotoxic chemotherapy alone.[3] However, targeted therapies eventually emerged. In the 2010 ToGA trial, patients with human epidermal growth factor receptor 2 (HER2)-positive gastric or gastroesophageal junction adenocarcinoma were randomly assigned to chemotherapy alone or trastuzumab (an anti-HER2 monoclonal antibody) plus chemotherapy.[4] Those who received trastuzumab plus chemotherapy saw a greater overall survival (OS) benefit than those who were assigned to chemotherapy alone.[4] In 2014, the anti-vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody, ramucirumab, demonstrated activity alone or in combination with single agent paclitaxel in patients who previously received a platinum- plus fluoropyrimidine-based regimen.[5,6] Despite the success of some these targeted agents, many others have failed.[7–9] In addition to targeted therapy, immunotherapy is now gaining traction. Over the last year, immunotherapy with anti-programmed cell death protein-1 (PD-1) and its ligand (PD-L1) checkpoint inhibitors was approved in the third-line setting and in subsets of second-line treatment for patients with metastatic esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma.[10] Given this mixed record of success with biologic agents, along with the emergence of immunotherapy, immune agent focused trials have become an area of great interest.

Ongoing studies are exploring the utility of targeting alternative checkpoints (both stimulatory and inhibitory), the potency of different immune-combinations, and combining immunotherapy with chemotherapy (for example, ClinicalTrials.gov Identifiers: NCT03143153, NCT02494583, NCT003189719, and NCT02625610.) In this review, we will highlight some of the major studies which established standard of care therapy for metastatic esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma patients, as well as some of the trials seeking to redefine these standards.

Treatment approaches

Chemotherapy

Platinum doublet chemotherapy with cisplatin and fluorouracil (CF) was first established as the standard of care for patients with esophageal cancer based on trial results from Bleiberg et al., where the combination was compared to fluorouracil alone.[11] Although all patients in this study had squamous cell carcinoma, its results were extrapolated to esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma. Given the success of platinum doublet chemotherapy, multiple efforts have been made to add a third agent to increase efficacy of the combination in patients with esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, or gastric adenocarcinoma. Ajani et al. randomized 158 patients with metastatic gastroesophageal junction adenocarcinoma and gastric adenocarcinoma (gastroesophageal junction adenocarcinoma: n=49 [32%]) to docetaxel, cisplatin, fluorouracil (DCF) chemotherapy or docetaxel and cisplatin (DC) chemotherapy every 3 weeks in the phase II portion of the V-325 study, with a primary endpoint of overall response rate (ORR).[12] ORR was 43% with DCF chemotherapy versus 26% with DC chemotherapy. The DCF regimen was then compared to CF chemotherapy in the phase III portion of the study.[13] In this study, 445 patients with gastroesophageal junction adenocarcinoma or gastric adenocarcinoma (gastroesophageal junction adenocarcinoma: n=98 [22%]) were randomized to DCF chemotherapy every 3 weeks versus CF every 3 weeks, with a primary endpoint of time to progression (TTP). Median TTP was 5.6 months in the DCF arm versus 3.7 months in the CF arm (hazard ratio [HR]: 0.68; p<0.001). OS was also improved in the DCF arm compared to the CF arm (HR: 0.77; p=0.02) at the cost of increased toxicity (69% versus 59% grade 3 and 4 toxicities, respectively).[13] The REAL-2 study assessed another triplet platinum combination (epirubicin, cisplatin, fluorouracil [ECF]).[14] In REAL-2, 1,002 patients with metastatic or unresectable esophageal cancer, gastroesophageal junction adenocarcinoma or gastric adenocarcinoma (esophageal adenocarcinoma: n=333 [33%]; gastroesophageal junction adenocarcinoma: n=248 [25%]) were randomized to ECF or variations of it including epirubicin, cisplatin, capecitabine; epirubicin, oxaliplatin, fluorouracil; and epirubicin, oxaliplatin, capecitabine, with a primary endpoint of OS. Switching oxaliplatin for cisplatin and capecitabine for fluorouracil in the ECF backbone was non-inferior (HR: 0.86; p=0.06, and HR: 0.92; p=0.16, respectively).[14]

Despite initial suggestions of greater efficacy from triplet platinum chemotherapy, standard of care for first-line patients with metastatic esophageal adenocarcinoma or gastroesophageal junction adenocarcinoma remains platinum doublet therapy due to its similar effectiveness with reduced toxicity. Given the difficulty administering cisplatin to patients, oxaliplatin has been assessed as a potential alternative. Al-Batran et al. compared fluorouracil, leucovorin and oxaliplatin (FLO) with fluorouracil, leucovorin and cisplatin (FLP) in a randomized trial in 220 treatment-naive patients with metastatic gastric or gastroesophageal junction adenocarcinoma (gastroesophageal junction adenocarcinoma: n=44 [20%]), with a primary endpoint of median progression-free survival (PFS).[15] Median PFS in the FLO group was 5.8 months and in the FLP group was 3.9 months; however, this difference did not meet statistical significance (p=0.07). Six-month PFS was 44% and 31% with FLO and FLP, respectively (p=0.02). The FOLFOX regimen has also been assessed: 35 patients with metastatic esophageal cancer (esophageal adenocarcinoma: n=29 [82%]; squamous cell carcinoma: n=3 [9%]; previously treated with one line of chemotherapy: n=4 [11%]) received the FOLFOX regimen every 2 weeks with a primary endpoint of ORR. ORR was 40%, median duration of response was 4.6 months and median OS was 7.1 months.[16] Given the efficacy signal suggested by this regimen, Jotoi et al. sought to make it even easier to administer by switching infusional fluorouracil for capecitabine in their trial of 43 patients with esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma or gastric adenocarcinoma.[17] Patients received first-line capecitabine and oxaliplatin every 21 days with a primary endpoint of ORR. ORR was 35% in treated patients with a median TTP and OS of 4 months and 6.1 months, respectively.

Targeted therapy

Commonly activated oncogenes in esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma include *HER2*, epidermal growth factor receptor (*EGFR*), VEGFR and tyrosine-protein kinase MET (*MET*). Each of these tyrosine kinase receptors promotes oncogenesis through heterogeneous mechanisms, and the molecules described in the following paragraphs block activation of these receptors through extra-cellular or intra-cellular disruption.

HER family

HER2 is a member of the EGFR receptor family and is amplified aberrantly in 6–30% of gastric and gastroesophageal junction adenocarcinomas; gastroesophageal junction tumors and proximal cardia tumors tend to have the highest rates of amplification.[18] The ToGA trial examined trastuzumab in combination with chemotherapy in 584 patients with gastric or gastroesophageal junction adenocarcinoma (gastroesophageal junction adenocarcinoma: n=105 [18%]) and overexpression of HER2.[4] Patients were randomized to CF chemotherapy every 3 weeks for six cycles with or without trastuzumab (8 mg/kg with cycle 1 then 6 mg/kg on subsequent cycles), followed by trastuzumab until progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint for the study was OS. Median OS in the trastuzumab arm was 13.8 months versus 11.1 months in the chemotherapy alone arm (HR: 0.74; p=0.005). In a pre-specified exploratory analysis, patients with stronger HER2 expression (2+ by immunohistochemistry [IHC] with fluorescence *in situ* hybridization positivity or 3+ by IHC) garnered an even larger benefit from the addition of trastuzumab with a median OS of 16.8 months.

To extend HER family inhibition and extrapolate the experience from breast cancer, the JACOB trial randomized 780 patients with metastatic gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (unspecified numbers of each) to trastuzumab and CF chemotherapy with or without the additional HER2/HER3 dimerization inhibitor pertuzumab (840 mg every 3 weeks), with a primary endpoint of OS.[19] After a median follow up of just over 2 years, OS was not significantly different between the two arms. Median OS was 17.5 months in the dual HER2 blockade arm and 14.2 months in the control arm (HR: 0.84; p=0.056). Additional trials have investigated HER2-directed therapy in the second-line setting; however,

this strategy has not been advantageous. In the TyTAN trial, reported by Satoh et al., 261 patients with progressive HER2-positive gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (unspecified number of patients with gastroesophageal junction adenocarcinoma) were randomized to lapatinib and paclitaxel, or paclitaxel alone.[20] Median OS was 11 months with the combination and 8.9 months with paclitaxel; this difference did not meet statistical significance (p=0.104). The GATSBY study randomized patients with second-line HER2-positive gastric adenocarcinoma or gastroesophageal junction adenocarcinoma to ado-trastuzumab emtansine (T-DM1) or a taxane (either docetaxel 75 mg every 3 weeks or paclitaxel 80 mg weekly).[21] Median OS was 7.9 months with T-DM1 and was 8.6 months with either taxane (p=0.86). Preliminary findings from the phase I study of the agent trastuzumab deruxtecan (DS-8201), a HER2 antibody conjugated to a camptothecin-analog (topoisomerase I inhibitor), were presented at the American Society of Clinical Oncology (ASCO) 2018 meeting.[22] In this study, patients with second-line HER2-positive gastric adenocarcinoma or gastroesophageal junction adenocarcinoma represented one of four expansion cohorts. ORR was 44% in patients with gastric adenocarcinoma with a disease control rate of 79%; median duration of response was 7.1 months and median OS was not reached. Common grade 3 or 4 adverse events included decreased appetite (4.5%), nausea (3.5%), and vomiting (1.5%).[22]

EGFR overexpression occurs in nearly 27–55% of gastroesophageal junction adenocarcinomas.[16] HER1 (EGFR) inhibition with cetuximab was studied in the EXPAND trial.[23] Built upon efficacy demonstrated in earlier phase II studies,[24] 904 patients (gastroesophageal junction adenocarcinoma: n=73 [16%]) with previously untreated, advanced disease were randomized to capecitabine and cisplatin every 3 weeks with or without weekly cetuximab (400 mg/m^2 with first infusion, 250 mg/m^2 thereafter). The primary endpoint was PFS while HER2 tumor status, EGFR IHC score, and presence of rash in cycle 1 (an on-target effect of cetuximab) were correlated with outcomes. Median PFS in the cetuximab arm was 4.4 months compared to 5.6 months in the non-cetuximab arm (HR: 1.09; p=0.32). There were no significant differences with regards to OS (9.4 months with cetuximab versus 10.7 months without) or ORR (30% with cetuximab versus 29% without). In patients with HER2-positive tumors, the ORR was 51% with cetuximab versus 38% in the control arm.[23] EGFR inhibition with the fully human immunoglobulin G2 antibody, panitumumab, was studied in the REAL3 study where 533 patients with untreated metastatic or unresectable esophageal, gastric, or gastroesophageal junction adenocarcinoma were randomized to epirubicin, oxaliplatin and capecitabine (EOC) with or without panitumumab (9 mg/kg) every 21 days (EOC alone arm: n=111 [40%] with esophageal adenocarcinoma, n=75 [27%] with gastroesophageal junction adenocarcinoma; EOC + panitumumab arm: n=106 [38%] with esophageal adenocarcinoma, n=94 [34%] with gastroesophageal junction adenocarcinoma).[7] The primary endpoint of the study was OS. Median OS was 8.8 months in the panitumumab arm compared to 11.3 months in the chemotherapy alone arm (HR: 1.37; p=0.013). Based on these results, anti-EGFR therapy has not been utilized in the first-line setting for patients with metastatic esophageal adenocarcinoma or gastroesophageal junction adenocarcinoma.

Angiogenesis inhibition

Gastric adenocarcinoma and gastroesophageal junction adenocarcinoma expressing high levels of VEGF have been associated with poor prognosis and increased biological aggression.[25] VEGF inhibitors have been trialed in different lines of therapy in these patients with varying degrees of success. Activity of bevacizumab, a monoclonal antibody against the VEGF-A ligand, has been investigated in patients with first-line metastatic or unresectable gastric adenocarcinoma or gastroesophageal junction adenocarcinoma.[26] Forty-seven patients (gastroesophageal junction adenocarcinoma: n=23 [49%]; gastric adenocarcinoma: n=24 [51%]) were treated with irinotecan, cisplatin and bevacizumab on 21-day cycles; the primary endpoint of the study was TTP. Median TTP was 8.3 months in all patients with no difference in TTP based on primary tumor location. Median OS was 12.3 months.[26] Unfortunately, the suggestion for first-line bevacizumab benefit was not confirmed by the phase III AVAGAST study.[8] In this study, 774 (gastroesophageal junction adenocarcinoma: n=103 [13%]) patients with metastatic or locally unresectable gastric or gastroesophageal junction adenocarcinoma were randomized to capecitabine and cisplatin with or without bevacizumab every 21 days with a primary endpoint of OS. Median OS in the bevacizumab arm was 12.1 months versus 10.1 months in the chemotherapy alone arm (HR: 0.87; p=0.1002). The RAINFALL study explored the utility of adding of the VEGFR-2 receptor antagonist ramucirumab (8 mg/kg day 1 and day 8 every 3 weeks) to first-line CF or cisplatin and capecitabine in metastatic gastric adenocarcinoma and gastroesophageal junction adenocarcinoma (645 total patients; the number of patients with gastroesophageal junction adenocarcinoma has not yet been listed) patients.[27] Median PFS (the primary endpoint) in the experimental arm was 5.85 months compared to 5.5 months in the chemotherapy alone arm (HR: 0.75; p=0.011). Although statistical significance was met, clinical significance was not. Median OS was not statistically different between the two arms. Based on these results, VEGF pathway inhibitors have not been added to chemotherapy in the first-line setting for patients with gastric adenocarcinoma or gastroesophageal junction adenocarcinoma.

Targeting the VEGF pathway has been a more successful endeavor for second-line treatment and beyond in these metastatic patients. In the REGARD study, 355 patients with advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (gastroesophageal junction adenocarcinoma: n=90 [25%]) were randomly assigned 2:1 to receive ramucirumab monotherapy every 2 weeks or placebo plus best supportive care.[5] The primary endpoint of median OS was met (5.2 months in the ramucirumab group compared to 3.8 with placebo; HR 0.77; p=0.047). The follow-up RAINBOW trial randomized a similar population of 665 patients with gastric or gastroesophageal junction adenocarcinoma (gastroesophageal junction adenocarcinoma: n=137 [21%]) to ramucirumab plus paclitaxel or paclitaxel alone. Median OS in the combination arm was 9.6 months compared to 7.4 months in the paclitaxel alone arm (HR: 0.807, p=0.017).[6]

MET inhibition

MET amplification is also a poor prognostic marker in gastric adenocarcinoma and gastroesophageal junction adenocarcinoma, and is expressed in 2–4% of these patients.[28] The YO28252 MetGastric study investigated the addition of the extra-cellular MET binding monoclonal antibody, onartuzumab, in combination with FOLFOX.[29] A total of 123 patients with HER2-negative gastric or gastroesophageal junction adenocarcinoma (gastroesophageal junction adenocarcinoma: n=29 [24%]) were randomized to onartuzumab plus FOLFOX, or FOLFOX alone with a pre-planned analysis in patients with MET amplified (>50% by IHC) tumors. The primary endpoint was median OS in all patients and MET amplified (IHC 2+ or 3+) patients. Median OS was not

significantly different in the experimental arm versus FOLFOX alone arm (HR: 0.82; p=0.24) nor in the MET amplified population (HR: 0.64; p=0.06).[29] Hepatocyte-growth factor (HGF) is a ligand which promotes cancer growth through the MET receptor.[30,31] The anti-HGF monoclonal antibody rilotumumab was evaluated in the RILOMET-1 study.[32] Patients with MET-amplified (at least 25% of the tumor with ≥1+ MET expression by IHC) esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, or gastric adenocarcinoma (esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma: n=187 [31%]) were randomized to epirubicin, cisplatin and capecitabine with or without rilotumumab (15 mg/kg) every 3 weeks with a primary endpoint was OS. However, the study was stopped early after an independent data monitoring committee found significantly more deaths in the experimental arm compared to the control arm. At the time of final analysis, median OS in experimental arm was 8.8 months versus 10.7 months in the control arm (HR: 1.34; p=0.003).[32]

Dickkopf-related protein 1

Dickkopf-related protein 1 (DKK1) is a secreted protein which inhibits the Wnt pathway, a pathway which has been implicated in esophageal cancer carcinogenesis. High levels of DKK1 *in vitro* are associated with a more invasive phenotype, and in patients are correlated with poorer OS.[33] DKN-01 is a monoclonal antibody to this protein which is under study in combination with paclitaxel in progressive DKK1-positive (by IHC) metastatic or unresectable esophageal cancer and gastroesophageal junction adenocarcinoma.[34] In this study >90% of screened patients had DKK1-positive tumors. Dose escalation has been completed and the maximum tolerated dose of the drug has been determined to be 300 mg in combination with paclitaxel weekly for 3 out of 4 weeks. The dose expansion phase is ongoing.

Claudin

Claudin represents a gastric mucosa tight-junction protein which is over-expressed in 49% of patients with gastric adenocarcinoma, gastroesophageal junction adenocarcinoma, or esophageal adenocarcinoma.[35] The FAST2 study randomized 352 patients with CLDN18.2-positive gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (20% gastroesophageal junction adenocarcinoma and esophageal adenocarcinoma) to an epirubicin-oxaliplatin-capecitabine chemotherapy regimen with or without IMAB362 (800 mg/m^2 loading dose, then 600 mg/m^2 every 21 days), a novel anti-CLDN18.2 antibody.[36] The primary endpoint of the study of PFS was met. Patients who received IMAB362 plus epirubicin-oxaliplatin-capecitabine chemotherapy demonstrated a median PFS of 7.9 months compared to 5.2 months in the control arm (HR: 0.5; p=0.001). Patients who received the monoclonal antibody combination also demonstrated a median OS of 12.5 months versus 8.7 months (HR: 0.5; p-value significant but not reported). In patients who expressed very high levels of CLDN18.2 (>2+ intensity by IHC in 70% of tumor cells), efficacy was even more pronounced (HR: 0.46 for PFS, HR: 0.44 for OS).[36]

Immunotherapy

Treatments with single-agent or combinations of checkpoint inhibitors have revolutionized the care of patients with advanced cancer across multiple tumor types, some of which include melanoma, renal cell carcinoma, non-small cell lung cancer and subsets of colorectal carcinoma.[37–39] Given their general tolerability and potential to elicit durable and sometimes complete responses, efforts to incorporate these agents into the care of patients with esophageal adenocarcinoma or gastroesophageal junction adenocarcinoma are underway. Unfortunately, most patients do not benefit from immunotherapy and searches for suitable predictive markers outside of microsatellite instability (MSI-H) remain a work in progress. Potential candidate biomarkers of immune responsiveness include PD-L1 and PD-L2 expression and tumor mutational burden.

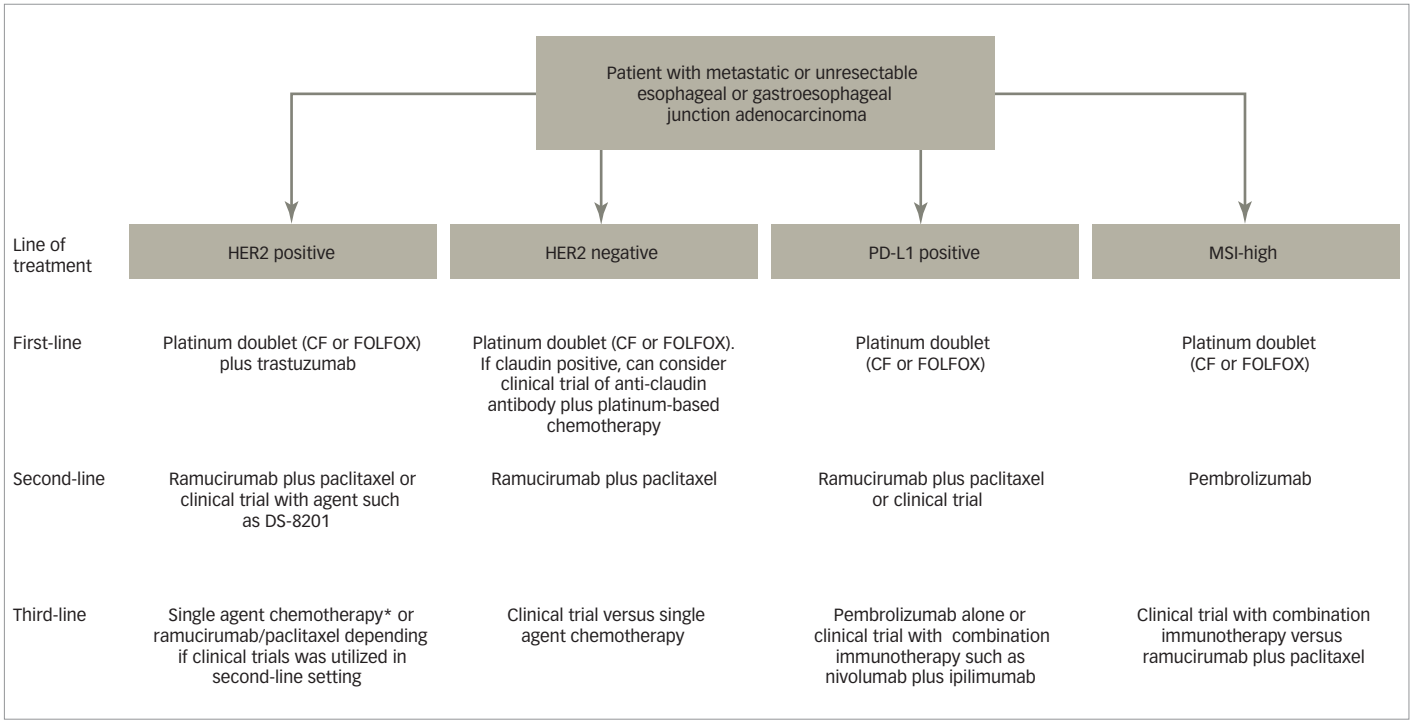
Completed single-agent checkpoint inhibitor trials

The Keynote-012 trial was a large phase Ib study looking at the effectiveness of pembrolizumab (10 mg/kg every 2 weeks) across disease sites.[40] All but one cohort in this study, including the gastric adenocarcinoma and gastroesophageal junction adenocarcinoma cohort, required PD-L1 positivity (>1% by IHC). Findings from the gastric adenocarcinoma and gastroesophageal junction adenocarcinoma cohort were reported by Muro et al.[40] Thirty-nine patients with metastatic or unresectable gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (85% in the second-line or beyond setting) received pembrolizumab. ORR was demonstrated in 22% of patients and only 13% of patients had grade 3 adverse events.

The efficacy demonstrated in the Keynote-012 trial led to the phase II Keynote-059 trial. This trial explored the role for pembrolizumab (200 mg every 3 weeks) in patients with metastatic gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (ClinicalTrials.gov Identifier: NCT02335411). The three parallel cohorts in the single study arm included pembrolizumab monotherapy in previously treated patients, pembrolizumab monotherapy in treatment-naive patients, and pembrolizumab plus CF chemotherapy in treatment-naive patients. Data from cohort 1 was reported by Fuchs et al., and included 259 patients with gastric adenocarcinoma or gastroesophageal junction adenocarcinoma who had received at least two prior lines of chemotherapy; 57% of patients were PD-L1 positive.[41] Patients received pembrolizumab for up to 2 years or until disease progression; 52% of patients received the drug in the third-line while 48% received it in the fourth-line setting. ORR was the primary endpoint and was 11.6% in all patients; ORR was 14.9% in patients who received the drug in the third-line setting and was 7.2% in patients who received it in the fourth-line setting. In patients who were PD-L1 positive, ORR was 21.4%. Data from cohort 2 was reported by Bang et al.[42] In this portion of the study, 25 patients were treated with pembrolizumab every 3 weeks. ORR was 60% in all patients, 68.8% in PD-L1-positive patients, and 37.5% in PD-L1-negative patients. Disease control rate was 92%. Median PFS was 6.6 months and median OS was 13.8 months. Treatment discontinuation occurred in only three patients due to adverse events.[42] Safety data, but not efficacy data, has been reported from cohort 3 of the study; patients treated thus far with pembrolizumab plus CF chemotherapy have not had any treatment-related discontinuations.[43] Based on this trial pembrolizumab is approved in the third-line or beyond for patients with gastric or gastroesophageal junction adenocarcinoma with PD-L1 of >1%.

The US Food and Drug Administration (FDA) recently granted approval for pembrolizumab in MSI-H tumors of any origin after standard chemotherapy (at least two prior lines). MSI-H status is found in 10–39% of esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma, albeit in lower numbers in the metastatic setting.[44] In a proof-of-principle study in 86 patients (five with gastroesophageal junction adenocarcinoma) with refractory metastatic cancer of various origins treated with pembrolizumab, 21% of patients demonstrated complete

Figure 1: Treatment algorithm for patients with metastatic gastroesophageal junction adenocarcinoma or esophageal adenocarcinoma



A general treatment algorithm we utilize when approaching patients with metastatic gastroesophageal junction adenocarcinoma or esophageal adenocarcinoma. Although by no means exhaustive, it does highlight the importance of considering clinical trials at all lines of therapy.
**TAS-102 also recently demonstrated third-line activity in the TAGS study and is a chemotherapy option for patients with gastroesophageal junction adenocarcinoma.*
CF = cisplatin and fluorouracil; HER2 = human epidermal growth factor receptor 2; MSI = microsatellite instability; PD-L1 = programmed death-ligand 1.

response, 54% demonstrated ORR, and disease control was achieved in 77% of patients.[10] Three out of five patients with gastroesophageal junction adenocarcinoma had complete response.

The ONO-4538-12 trial is an Asia-limited study that randomized unselected (by PD-L1 expression status) patients with metastatic progressive gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (unspecified percentage of patients with gastroesophageal junction adenocarcinoma), who had received a minimum of two prior therapies in a 2:1 fashion to nivolumab 3 mg/kg every 2 weeks, or placebo.[45] Median OS in the nivolumab treated arm was 5.26 months compared to 4.14 months in the placebo arm (HR: 0.63; p<0.0001). Twelve-month OS in the nivolumab arm was 26.2% while in the placebo arm was 10.9%.

Ongoing single and dual-agent checkpoint inhibitor trials

The Javelin Gastric 300 study explored whether the PD-L1 inhibitor avelumab (10 mg/kg every 2 weeks) improved OS compared to physician's choice of chemotherapy (paclitaxel or irinotecan) in the third-line setting in metastatic gastric adenocarcinoma or gastroesophageal junction adenocarcinoma patients regardless of PD-L1 expression.[46] A total of 371 patients were randomized with a primary endpoint of OS. The primary endpoint was not met; however, formal results from the study remain pending.

The Javelin Gastric 100 study seeks to answer a different question about whether avelumab may play a role in the maintenance setting in first-line metastatic gastric adenocarcinoma and gastroesophageal junction adenocarcinoma patients.[47] In this ongoing study, an anticipated 466 patients who have not progressed after 3 months of first-line FOLFOX, will be randomized 1:1 to continue FOLFOX or to initiate avelumab. The primary study endpoints are OS and PFS.

Single-agent checkpoint inhibitors targeting PD-1 and PD-L1 have only modest activity in patients with metastatic esophageal adenocarcinoma or gastroesophageal junction adenocarcinoma, as seen from the data above. Thus, there is an interest in trying combinations of checkpoint inhibitors to increase responses.

The CheckMate-032 trial is a phase I/II study in Western patients looking at the efficacy (primary endpoint ORR) of nivolumab monotherapy or nivolumab plus the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor ipilimumab (at various doses) in refractory metastatic tumors of diverse histologies. Results from the gastric adenocarcinoma, esophageal adenocarcinoma, and gastroesophageal junction adenocarcinoma cohorts have been reported by Jangigian et al.[48] A total 160 patients with metastatic disease, 80% in the third-line setting, received nivolumab 3 mg/kg every 2 weeks, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1+I3) every 3 weeks, or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3+I1) every 3 weeks. ORR was 12%, 24%, and 8% in the nivolumab alone, N1+I3 and N3+I1 arms, respectively. In patients with PD-L1 expression of ≥1% ORR was 19%, 40%, and 23%, in the nivolumab alone, N1+I3 and N3+I1 arms, respectively. Eighteen-month OS was 25%, 28%, and 13% in the nivolumab alone, N1+I3 and N3+I1 arms, respectively.

In patents with PD-L1 expression of ≥1%, 18-month OS was 13%, 50%, and 15%, respectively. It appears from the preliminary data that the N1+I3 arm is the most active of the three approaches with regards to improving ORR and OS in this subset of patients.

The Durvalumab and Tremelimumab in Combination With First-Line Chemotherapy in Advanced Solid Tumors study (ClinicalTrials.gov Identifier: NCT02658214) is looking at the combination of the PD-L1 inhibitor durvalumab and the CTLA-4 inhibitor tremelimumab in the first-line setting in a cohort of solid tumor patients including those with gastroesophageal junction adenocarcinoma. Pembrolizumab and the HER2-directed monoclonal antibody margetuximab are being explored in patients with HER2-positive gastric adenocarcinoma and gastroesophageal junction adenocarcinoma who have progressed on trastuzumab plus chemotherapy.[49] There are many more checkpoint inhibitor combinations beyond CTLA-4, PD-1, and PD-L1 being trialed in esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma patients which are not being discussed in this review.[50]

Other immunotherapy

The NY-ESO-1 antigen is a cancer testis antigen which is over-expressed in 31–33% of patients with esophageal cancer.[51] Given the prevalence of its expression, there was an interest in generating a vaccine toward the antigen. An early phase dose-finding study looked at the safety of administering a NY-ESO-1 complex vaccine to 25 patients with metastatic refractory esophageal adenocarcinoma with NY-ESO-1 expression.[52] Patients received either 100 µg or 200 µg every 2 weeks for a total of 6 administrations. No dose limiting toxicities were noted. Seven of 13 patients demonstrated an immune response with the development of antibodies toward the antigen. Mean PFS was 11 weeks and mean OS was 33 weeks in both cohorts. Patients who received the higher dose per administration seemed to demonstrate improved OS compared to patients who received the lower dose.[52] Although anti-NY-ESO-1 vaccines have not been pursued further in esophageal adenocarcinoma patients, there is an ongoing phase I study assessing whether autologous T-cells engineered to express an NY-ESO-1 targeting the T-cell receptor can play a role in progressive NY-ESO-1 overexpressing malignancies (ClinicalTrials.gov Identifier: NCT02457650).

Gastrin, beyond serving as a peptide hormone responsible for HCl secretion, has a trophic effect on gastric adenocarcinoma and gastroesophageal junction adenocarcinoma (among other cancers) through promoting angiogenesis and anti-apoptotic effects.[53] G17DT is a vaccine directed toward its most prevalent circulating form, gastrin-17, and was trialed in a phase II study in metastatic or unresectable gastric adenocarcinoma and gastroesophageal junction adenocarcinoma.[54] In this study 79 patients received CF chemotherapy plus G17DT (500 µg every 4 weeks for four treatments) and were assessed for treatment response with a primary endpoint of ORR. ORR was 30%, median TTP was 5.4 months and median OS was 9 months. Patients who demonstrated an immune response (measured by anti-gastrin titers), demonstrated statistically significant improved TTP (5.5 versus 2.1 months; p=0.0005) and OS (10.3 versus 3.8 months; p<0.0001) compared to those who did not.[54] Phase III trials in gastric adenocarcinoma and gastroesophageal junction adenocarcinoma with the compound have not been reported.

Summary

Metastatic esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma are challenging diseases for which there are limited effective options. Despite much study, the only advance for treatment in the first-line setting is the addition of trastuzumab to platinum doublet chemotherapy in patients whose tumors overexpress HER2. A major push to exploit the disease biology of patients with esophageal adenocarcinoma or gastroesophageal junction adenocarcinoma by categorizing patients with specific oncogenic signatures through wide genomic profiling efforts such as the TCGA, and matching them with targeted therapies such as HER2, EGFR, MET, DKK1, and claudin, is underway. These approaches have demonstrated mixed results, suggesting resistance from mechanisms such as cross-talk between the pathways. While inhibition of a broad spectrum of targets is ongoing, immunotherapy is moving to the forefront. Single agent checkpoint inhibition with pembrolizumab is already approved in the third-line (the exception to this being the MSI-H sub-group) and beyond setting (*Figure 1*). Other immune modulating approaches include checkpoint inhibitor combinations, vaccines, engineered autologous T-cell transfer and addition of cytokines. The search for specific predictive biomarkers for immunotherapy is also underway. Although the challenge is great, the potential for return on the investment of ongoing and future trials is immense. ❑

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