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REVIEW

Targeting Esophageal Cancer: Promising Drugs for the Clinical Landscape and Key Knowledge Gaps

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Abstract: Esophageal cancer remains a major global health burden, ranking seventh in cancer-related mortality. The prognosis is poor with five-year survival rates below 5% for metastatic disease. Tumor heterogeneity and the development of treatment resistance have limited durable responses to conventional chemotherapy. The emergence of biomarker-driven therapies has begun to transform management and enable more personalized treatment approaches. This narrative review summarizes current clinical strategies for esophageal cancer, emphasizing clinically validated biomarkers —HER2, PD-L1, CLDN18.2, and MMR/MSI status—that inform therapeutic selection for advanced metastatic disease. Both esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) are addressed; however, this review centers on biomarker-directed therapies for EAC, reflecting its predominance in Western populations and recent therapeutic progress. We highlight pivotal phase II and III clinical trials that have established the current landscape of esophageal cancer treatment. In addition, we review key early phase clinical data for promising new modalities such as antibody-drug conjugates, novel monoclonal antibodies, and cellular therapies—highlighting their biomarker associations and mechanisms of action. Finally, we discuss the ongoing challenges—including elucidating tumor heterogeneity, improving biomarkers, targeting novel tumor intrinsic vulnerabilities, overcoming treatment resistance, and preventing esophageal cancer development—and identify key research directions that present unique opportunities for the development of new biomarker-driven treatments for esophageal cancer.

Keywords: Gastroesophageal, targeted therapy, immunotherapy, tumor microenvironment

Introduction

Esophageal cancer is a common, aggressive malignancy with high global incidence and mortality. According to GLOBOCAN estimates, over 510,000 new cases and more than 450,000 deaths occurred in 2022, making it the seventh leading cause of cancer deaths worldwide.[1] In the US, over 22,000 new cases and 16,000 deaths are projected for 2025.[2] Survival remains dismal with only 5% of patients with metastatic disease surviving five years.[2] Clinical presentation often includes symptoms of esophageal luminal narrowing such as dysphagia, weight loss, odynophagia, and regurgitation.[3] Physical findings of advanced disease may include lymphadenopathy, hoarseness from laryngeal nerve involvement, pleural effusions, ascites, hepatomegaly, bony tenderness, or upper gastrointestinal (GI) bleeding.[4] Esophageal cancer includes two main histologic subtypes: esophageal adenocarcinoma (EAC), more common in Western countries and linked to Barrett's esophagus (BE);[5] and esophageal squamous cell carcinoma (ESCC), more common in Asia and associated with tobacco and alcohol use.[6] Anatomically, esophageal cancers are classified as upper, middle, or lower.[7] Distal tumors near the gastroesophageal junction (GEJ) are further categorized by Siewert classification.[8] Type I and II Siewert tumors, located within 5 cm proximal or 2 cm distal to the GEJ, are treated as esophageal cancers based on American Joint Committee on Cancer[9] and National Comprehensive Cancer Network[10] guidelines. The anatomic and histologic variability of esophageal cancers contributes to the complexity of the disease.

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Tumor heterogeneity drives treatment resistance and contributes to variable long-term therapeutic responses.[11–14] Molecular studies[14,15] have shown that ESCC and EAC are distinct at the genomic and transcriptomic levels.[16] ESCCs display *CCND1, TP63, SOX2* amplifications, and *KDM6A* deletions. Mid and distal EACs are often enriched for *TP53* mutations, *ERBB2* and *VEGFA* amplifications, and can be classified as the chromosomal instability (CIN) subtype. Further, distally into the stomach, additional molecular subtypes appear, including Epstein-Barr virus (EBV), microsatellite instability (MSI), and genomic stability (GS).[16–18] These findings underscore the genomic diversity of esophageal cancers while also highlighting the molecular similarities between esophageal, GEJ, and gastric adenocarcinomas. Such overlap is reflected in clinical practice, where data from gastric cancer trials are often extrapolated to guide treatment of EAC and GEJ adenocarcinomas.

The emergence of predictive and prognostic biomarkers has enabled practical subclassification of esophageal cancers and personalized treatment. All newly diagnosed patients should be tested for programmed death-ligand 1 (PD-L1) and microsatellite instability (MSI) or mismatch repair (MMR) status, while patients with advanced disease should also be tested for HER2/neu and claudin-18.2 (CLDN18.2).[19] This review focuses on biomarker-driven systemic therapies for esophageal cancers, with emphasis on EAC given its rising incidence in Western populations. We include phase II–III clinical trials evaluating biomarker-guided systemic therapies, primarily in advanced metastatic disease, detailing key efficacy and safety outcomes, Table 1. Here, we also highlight emerging biomarker-driven treatments supported by clinical efficacy data such as antibody-drug conjugates, novel monoclonal antibodies, and cellular therapies, Table 2. Finally, we examine key knowledge gaps that must be addressed to improve future esophageal cancer treatment, Figure 1. Our work is timely given the changing epidemiology,[20,21] emergence of new targeted therapies,[22] and improved molecular understanding of these diseases at unprecedented resolution[12,23,24] that will continue to herald treatment advances.

Current Therapeutic Landscape for Esophageal Cancers

HER2-Overexpressing Esophageal Adenocarcinomas

HER2/neu, a member of the human epidermal growth factor receptor family associated with tumor proliferation, apoptosis, adhesion, migration, and differentiation, is overexpressed in 10% to 30% of gastroesophageal adenocarcinomas.[75,76] HER2-positivity is defined as immunohistochemistry (IHC) 3+ or fluorescence in situ hybridization (FISH) positive (HER2:CEP17 ratio ≥2).[25] The ToGA trial established the efficacy of adding trastuzumab, a monoclonal antibody against HER2, to chemotherapy in HER2-expressing advanced gastric or GEJ adenocarcinomas.[77] Trastuzumab plus chemotherapy improved median overall survival (OS) from 11.1 to 13.8 months and progression-free survival (PFS) from 5.5 to 6.7 months. The KEYNOTE-811 trial showed that adding pembrolizumab, a programmed cell death-1 (PD-1) inhibitor, to trastuzumab and chemotherapy further improved OS in advanced gastric or GEJ adenocarcinoma patients with PD-L1 combined positive score (CPS) ≥1 (20.1 vs 15.7 months).[28,29] For second-line and beyond treatment, trastuzumab deruxtecan, a HER2 antibody–drug conjugate (ADC), improved survival in gastroesophageal adenocarcinomas.[27,78,79] Specifically, the DESTINY-Gastric04 trial showed a median OS benefit over ramucirumab plus paclitaxel (14.7 vs 11.4 months).[27] Notably, interstitial lung disease and pneumonitis occurred in 15% of patients treated with trastuzumab deruxtecan.[80]

PD-L1-Positive Esophageal Cancers

Immune checkpoint inhibitors targeting the immune inhibitory PD-1 receptor[81] have become frontline treatment for gastroesophageal cancers. Efficacy depends on PD-L1 expression, assessed by IHC-based tumor proportion score (TPS) or CPS.[82–84] For advanced ESCCs, the utility of immunotherapy has been shown in the CheckMate 648 trial.[30] This phase III trial compared nivolumab (an anti–PD-1 antibody) plus chemotherapy, nivolumab plus ipilimumab (an inhibitor of another immunologic synapse termed cytotoxic T lymphocyte antigen 4 [CTLA-4]), and chemotherapy alone. In patients with PD-L1 ≥1, OS improved in both immunotherapy arms. Nivolumab plus chemotherapy extended OS to 15.4 months versus 9.1 months with chemotherapy alone; dual immunotherapy yielded 13.7 months. For EACs (and gastric/GEJ cancers), the CheckMate 649 trial[31,85,86] evaluated nivolumab plus chemotherapy versus chemotherapy alone, demonstrating improved OS (14.4 vs 11.1 months) and PFS (7.7 vs 6.0 months) among patients with PD-L1 CPS ≥5.

Table 1 Current Treatments for Esophageal Cancers

Molecular Target	Biomarker	Targeted Agent	Trial	Treatment	Clinical Efficacy
HER2	HER2-positivity defined as a score of 3+ on IHC or 2+ on IHC and FISH positive (HER2:CEP17 ratio ≥ 2)	Trastuzumab (Herceptin)	ToGA (Phase III)[25]	Untreated advanced metastatic HER2-positive gastric and GEJ adenocarcinoma patients treated with trastuzumab and chemotherapy (capecitabine plus cisplatin or 5-FU plus cisplatin, n=298) compared with chemotherapy alone (n=296).	Median overall survival was 13.8 months in those assigned to trastuzumab pluschemotherapy compared with 11.1 months in those assigned to chemotherapy alone (HR 0.74; 95% CI 0.60–0.91; P=0.0046).
		Trastuzumab deruxtecan (Enhertu)	DESTINY-Gastric01 (Phase II)[26]	Advanced metastatic HER2-positive gastric and GEJ adenocarcinoma patients were treated with trastuzumab deruxtecan (n=125) compared to physician's choice chemotherapy (irinotecan or paclitaxel, n=62) after progression on at least two previous therapies.	Objective response rate was 51% in patients treated with trastuzumab deruxtecan as compared with 14% of those in the physician's choice treatment group (P<0.001).
			DESTINY-Gastric04 (Phase III)[27]	Advanced metastatic HER2-positive gastric and GEJ adenocarcinoma patients with progression after trastuzumab-based therapy received trastuzumab deruxtecan (n=246) compared to ramucirumab plus paclitaxel (n=248).	Median overall survival improved to 14.7 months in trastuzumab deruxtecan compared to 11.4 months with ramucirumab plus paclitaxel (HR 0.70; 95% CI 0.55–0.90; P=0.004).
HER2 and PD-1/PD-L1	HER2-positivity defined as a score of 3+ on IHC or 2+ on IHC and FISH positive PD-L1-positive defined as CPS (number of PD-L1–expressing tumor cells, lymphocytes, and macrophages with staining divided by the total number of viable tumor cells and multiplied by 100) ≥ 1 by IHC	Trastuzumab (Herceptin) and Pembrolizumab (Keytruda)	KEYNOTE-811 (Phase III)[28,29]	Untreated advanced metastatic HER2-positive gastric and GEJ adenocarcinoma patients treated with trastuzumab, pembrolizumab and chemotherapy (capecitabine plus oxaliplatin or 5-FU plus cisplatin, n=350) compared with trastuzumab and chemotherapy (n=348).	Median overall survival was 20.0 months with pembrolizumab, as compared with 16.8 months with placebo (HR 0.80; 95% CI 0.67–0.94; P=0.004). PD-L1-positive (CPS ≥1), the median overall survival was 20.1 months with pembrolizumab, as compared with 15.7 months with placebo (HR 0.79; 95% CI 0.66–0.95; P=0.006).

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Table 1 (Continued).

Molecular Target	Biomarker	Targeted Agent	Trial	Treatment	Clinical Efficacy
PD-1/PD-L1	PD-L1-positive defined as TPS (% of viable tumor cells with partial or complete membrane staining in at least 100 viable tumor cells) ≥ 1 by IHC or CPS ≥ 1 by IHC	Nivolumab (Opdivo)	CheckMate 648 (Phase III)[30]	Untreated advanced metastatic ESCC patients treated with nivolumab plus chemotherapy (5-FU plus cisplatin, n=321), nivolumab plus ipilimumab (n=325), or chemotherapy alone (n=324).	PD-L1-positive (TPS ≥1), the median overall survival was 15.4 months in nivolumab plus chemotherapy vs 9.1 months with chemotherapy alone (HR 0.54; 99.5% CI 0.37–0.8; P<0.001); 13.7 months in nivolumab plus ipilimumab and 9.1 months with chemotherapy alone (HR 0.64; 98.6% CI, 0.46 to 0.90; P=0.001).
	PD-L1-positive defined as CPS ≥ 5		CheckMate 649 (Phase III)[31]	Untreated advanced metastatic gastric, esophageal, and GEJ adenocarcinoma patients treated with nivolumab and chemotherapy (capecitabine or 5-FU plus oxaliplatin, n=789) compared to chemotherapy only (n=792). A third treatment arm of nivolumab and ipilimumab (n=409) also included.	PD-L1-positive (CPS ≥ 5), the median overall survival was 14.4 months with nivolumab plus chemotherapy compared to 11.1 months with chemotherapy alone (HR 0.71; 98.4% CI 0.59–0.86; P<0.0001).
	PD-L1-positive defined as CPS ≥ 10	Pembrolizumab (Keytruda)	KEYNOTE-590 (Phase III)[32]	Untreated advanced metastatic esophageal cancer patients were treated with pembrolizumab plus chemotherapy (5-FU plus cisplatin, n=373) or placebo plus chemotherapy (n=376).	PD-L1-positive (CPS ≥ 10), the median overall survival was 13.5 months with pembrolizumab plus chemotherapy compared to 9.4 months with chemotherapy (HR 0.62; 95% CI 0.49–0.78; p<0.0001). Improved OS seen in ESCC compared to EACs.
			KEYNOTE-859 (Phase III)[33]	Untreated advanced metastatic gastric and GEJ patients were treated with pembrolizumab plus chemotherapy (5-FU plus cisplatin or capecitabine plus oxaliplatin, n=790) or placebo plus chemotherapy (n=789).	PD-L1-positive (CPS ≥ 10), the median overall survival was 15.7 months with pembrolizumab plus chemotherapy compared to 11.8 months with chemotherapy alone (HR 0.65; 95% CI 0.53–0.79; P<0.0001).

	PD-L1-positive defined as CPS ≥ 1 or TAP (% tumor area covered by tumor cells and tumor-associated immune cells with PD-L1 staining at any intensity) ≥ 1	Tislelizumab (Tevimbra)	RATIONALE-306 (Phase III)[34]	Untreated advanced metastatic ESCC patients were teated with tislelizumab plus chemotherapy (cisplatin or oxaliplatin plus 5-FU or capecitabine or placlitaxel, n=326) or placebo plus chemotherapy (n=323)	PD-L1-positive (CPS ≥ 1 or TAP ≥ 1), the median overall survival was 16.8 months when treated with tislelizumab plus chemotherapy compared 9.6 months with placebo plus chemotherapy alone (HR 0.66; 95% CI 0.54–0.81).
	PD-L1-positive defined as TAP ≥ 5		RATIONALE-305 (Phase III)[35]	Untreated advanced metastatic gastric and GEJ adenocarcinoma patients were treated with tislelizumab plus chemotherapy (capecitabine plus oxaliplatin or 5-FU plus cisplatin=501) or chemotherapy alone (n=496)	PD-L1-positive (TAP ≥ 5), the median overall survival of patients was 17.2 months compared to 12.6 months with chemotherapy alone (HR 0.74; 95% CI 0.59–0.94; P=0.006). PD-L1-positive (CPS ≥ 5), the median overall survival of patients was 17.8 months compared to 13.2 months with chemotherapy alone (HR 0.73; 95% CI 0.6–0.89).
	N/A	Durvalumab (Imfinzi)	MATTERHORN (Phase III)[36]	Resectable gastric and GEJ adenocarcinoma patients were treated with FLOT (5-FU, leucovorin, oxaliplatin, and docetaxel) and durvalumab (n=474) or placebo (n=474).	Two-year event-free survival was 67.4% in the durvalumab group compared to 58.5% in the placebo group (HR 0.71; 95% CI 0.58-0.86; P<0.001). Pathological complete response was 19.2% in the durvalumab group and 7.2% in the placebo group (RR 2.69; 95% CI 1.86–3.90).
	N/A	Atezolizumab (Tecentriq)	DANTE (Phase II/III)[37]	Resectable gastric and GEJ adenocarcinoma patients were treated with FLOT (5-FU, leucovorin, oxaliplatin, and docetaxel) and atezolizumab (n=146) or placebo (n=149).	Pathological complete response was 24% in the atezolizumab group and 15% in the chemotherapy only group (P=0.032). For PD-L1 CPS ≥ 10, pathologic complete response was 33% in the atezolizumab group and 12% in the chemotherapy only group.
CLDN18.2	CLDN18.2-positive (defined as ≥75% of tumor cells showing moderate-to-strong membranous CLDN18.2 staining)	Zolbetuximab (Vyloy)	SPOTLIGHT (Phase III)[38]	Untreated advanced metastatic CLDN18.2-positive gastric and GEJ adenocarcinoma patients were treated with zolbetuximab plus FOLFOX (n=283) or placebo plus FOLFOX (n=282).	Median progression free survival was 10.6 months in the zolbetuximab group compared to 8.67 months in the placebo group (HR 0.75; 95% CI 0.60–0.94; P=0.0066). Median overall survival was 18.2 months in the zolbetuximab group compared to 15.5 months in the placebo group (HR 0.75; 95% CI 0.60–0.94; P=0.0053).
			GLOW (Phase III)[39]	Untreated advanced metastatic CLDN18.2-positive gastric and GEJ adenocarcinoma patients were treated with zolbetuximab plus CAPOX (n=254) or placebo plus CAPOX (n=253).	Median progression free survival was 8.21 months in zolbetuximab plus CAPOX compared to 6.80 months in placebo plus CAPOX (HR 0.69; 95% CI 0.54–0.87; P=0.0007). Median overall survival was 14.4 months in the zolbetuximab group compared to 12.2 months in the placebo group (HR 0.77; 95% CI 0.62–0.97; P=0.0118).

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Table 1 (Continued).

Molecular Target	Biomarker	Targeted Agent	Trial	Treatment	Clinical Efficacy
Deficient MMR/MSI-high	Deficient MMR/MSI-high defined as absence of MMR proteins (MLH1, MSH2, MSH6, and PMS2) by IHC or analyses by PCR or NGS for tumor DNA instability at specific DNA microsatellite sequences.	Nivolumab (Opdivo)	CheckMate 649 (Phase III)[31]	Untreated advanced metastatic gastric, esophageal, and GEJ adenocarcinoma patients treated with nivolumab and chemotherapy (capecitabine or 5-FU plus oxaliplatin, n=789) compared to chemotherapy only (n=792). A third treatment arm of nivolumab and ipilimumab (n=409) also included.	Subgroup analysis of 44 patients with dMMR/MSI-H cancers showed median overall survival of 38.7 months in the nivolumab plus chemotherapy compared to 12.3 months with chemotherapy alone (HR 0.34; 95% CI 0.16–0.74). Subgroup analysis of 21 dMMR/MSI-H patients showed median overall survival not reached in the third treatment arm of nivolumab and ipilimumab compared to 10 months in the chemotherapy only group (HR 0.28; 95% CI 0.08–0.92).
		Pembrolizumab (Keytruda)	KEYNOTE-859 (Phase III)[33]	Untreated advanced metastatic gastric and GEJ patients were treated with pembrolizumab plus chemotherapy (5-FU plus cisplatin or capecitabine plus oxaliplatin, n=790) or placebo plus chemotherapy (n=789).	Subgroup analysis of 39 patients with dMMR/MSI-H cancers showed improved OS in the pembrolizumab plus chemotherapy compared to chemotherapy alone (HR 0.34; 95% CI 0.18–0.66).
			KEYNOTE-059 (Phase II)[40]	Advanced metastatic gastric and GEJ adenocarcinoma patients treated with pembrolizumab monotherapy (n=259) after progression on at least two previous therapies.	Post hoc analysis showed median OS for pembrolizumab monotherapy was NR in KEYNOTE-059 or KEYNOTE-061 compared with a median OS of 8.1 months for chemotherapy alone. The median OS was not reached for both pembrolizumab monotherapy and pembrolizumab plus chemotherapy compared with a median OS of 8.5 months for chemotherapy alone in KEYNOTE-062.
			KEYNOTE-061 (Phase III)[40]	Advanced metastatic gastric and GEJ adenocarcinoma patients treated with pembrolizumab (n=196) compared to paclitaxel (n=199) after progression on firstline chemotherapy.	
			KEYNOTE-062 (Phase III)[40]	Advanced metastatic gastric and GEJ adenocarcinoma patients treated with firstline pembrolizumab (n=256), pembrolizumab plus chemotherapy (cisplatin plus 5-FU or capecitabine, n=257), or chemotherapy (n=250).	
		Ipilimumab (Yervoy) and Nivolumab (Opdivo)	NEONIPIGA (Phase II)[41]	Resectable gastric and GEJ adenocarcinoma patients were treated with ipilimumab and nivolumab (n=32)	Pathological complete response rate was 58.6%. Patients with no residual tumor had a 65% overall survival and those with no nodal involvement had a 79% overall survival.
		Tremelimumab (Imjudo) and Durvalumab (Imfinzi)	INFINITY (Phase II)[42]	Resectable gastric and GEJ adenocarcinoma patients were treated with tremelimumab and durvalumab (n=15)	Pathological complete response was 60% and the major complete response (<10% viable cells) was 80%.
VEGFR-2	N/A	Ramucirumab (Cyrmaza)	REGARD (Phase III)[43]	Advanced metastatic gastric and GEJ adenocarcinoma patients treated with ramucirumab (n=238) compared to placebo (n=117) after progression on first-line chemotherapy.	Median overall survival was 5.2 months in patients in the ramucirumab group and 3.8 months in those in the placebo group (HR 0.776; 95% CI 0.603–0.998; P=0.047).
			RAINBOW (Phase III)[44]	Advanced metastatic gastric and GEJ adenocarcinoma patients treated with ramucirumab and paclitaxel (n=330) compared to paclitaxel (n=335) after progression on first-line chemotherapy.	Median overall survival was 9.9 months in patients treated with ramucirumab pluspaclitaxel group compared to 7.4 months in the placebo plus paclitaxel group (HR 0.807; 95% CI 0.678–0.962; P=0.017).

Table 2 Future Treatments for Esophageal Cancers

Molecular Target	Biomarker	Targeted Agent	Trial	Treatment	Clinical Efficacy
HER2	HER2-positivity defined as a score of 3+ on IHC or 2+ on IHC and FISH positive	Zandidatamab (anti-HER2 bispecific antibody)	Zanidatamab plus standard chemotherapy for first-line treatment of patients with select HER2-expressing gastrointestinal cancer, including gastro-oesophageal adenocarcinoma (Phase II)[45]	Untreated advanced metastatic HER2-positive gastric, GEJ, and esophageal adenocarcinoma patients (n=46) were treated with zandidatamab plus chemotherapy (5-FU/capecitabine plus oxaliplatin or 5-FU plus cisplatin).	Objective response rate was 76.2%, median progression free survival was 12.5 months, and overall survival was 36.5 months. The most common ≥ grade 3 adverse events were diarrhea and hypokalemia.
	High HER2 (3+ by IHC or 2+ by IHC and FISH positive) and low HER2 (1+ by IHC or 2+ by IHC and FISH negative)	KN026 (anti-HER2 bispecific antibody)	KN026 in patients with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancer (Phase II)[46]	Advanced metastatic HER2-expressing gastric and GEJ adenocarcinoma patients who have failed at least one prior line of standard treatment were treated with 10 mg/kg, 20 mg/kg, or 30 mg/kg of KNO26.	For the high HER2 patients, objective response rate was 56%. For the low HER2 patients, objective response rate was 14%. The most common ≥ grade 3 adverse events were GI disorders.
	HER2-positivity defined as a score of 3+ on IHC or 2+ on IHC and FISH positive	HLX22 (anti-HER2 antibody targeting a different epitope than trastuzumab)	A randomized study of HLX22 plus trastuzumab biosimilar HLX02 and XELOX as first-line therapy for HER2-positive advanced gastric cancer (Phase II)[47]	Untreated advanced metastatic HER2-positive gastric and GEJ adenocarcinoma patients were treated with 25 mg/kg HLX22 plus HLX02 plus XELOX (n=18) or 15 mg/kg HLX22 plus HLX02 plus XELOX (n=17) or placebo plus HLX02 plus XELOX (n=18).	Objective response rate was 77.8% in 25mg/kg HLX22 plus HLX02 and XELOX, 82.4% in 15mg/kg HLX22 plus HLX02 and XELOX and 88.9% in placebo plus HLX02 and XELOX. Median progression free survival was 15.1 months with 25mg/kg HLX22 plus HLX02 and XELOX compared to 8.2 months with placebo plus HLX02 and XELOX.
	HER2-low positivity defined as a score of 2+ on IHC and FISH negative or 1+ on IHC	Trastuzumab deruxtecan (Enhertu)	DESTINY-Gastric01 (Phase II)[48]	Advanced metastatic HER2-positive gastric and GEJ adenocarcinoma patients were treated with trastuzumab deruxtecan (n=125) compared to physician's choice chemotherapy (irinotecan or paclitaxel, n=62) after progression on at least two previous therapies.	Exploratory cohort analysis showed objective response rate was 26.3% in cohort 1 (HER2 2+ by IHC and FISH negative) and 9.5% in cohort 2 (HER2 1+ by IHC). The median overall survival was 7.8 months in cohort 1 and 8.5 months in cohort 2.
	HER2-positivity defined as a score of 3+ on IHC or 2+ on IHC and FISH positive	ARX788 (HER2-targeting ADC)	Multicenter, dose-expansion study of ARX788 as monotherapy in HER2-positive advanced gastric and gastroesophageal junction adenocarcinoma (Phase I)[49]	Advanced metastatic HER2-positive gastric and GEJ adenocarcinoma patients that progressed on prior trastuzumab-based treatment were treated with 1.3 mg/kg ARX788 (n=9), 1.5 mg/kg ARX788 (n=14) or 1.7 mg/kg ARX788 (n=7).	Objective response rate was 37.9%, median progression free survival was 4.1 months, and overall survival was 10.7 months. The most common ≥ grade 3 adverse events were anemia, blurred vision, increased γ-glutamyltransferase, and interstitial lung disease.
	HER2-positivity defined as a score of 3+ on IHC or 2+ on IHC and FISH positive	HER-Vaxx (IMU-131, HER2 vaccine)	HERIZON (Phase II)[50]	Untreated advanced HER2-positive gastric and GEJ adenocarcinoma patients were treated with chemotherapy (cisplatin plus 5FU or capecitabine, or oxaliplatin plus capecitabine n=17) or HER-Vaxx plus chemotherapy (n=19).	Median overall survival was 13.9 months in patients treated with HER-Vaxx plus chemotherapy compared to 8.31 months with chemotherapy alone (HR 0.60; 80% CI 0.380–0.957; P=0.08). No additional toxicity due to HER-Vaxx was observed; the most common adverse events were headache, decreased appetite, diarrhea, and nausea. HER-Vaxx induced strong HER2-specific antibodies.

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Table 2 (Continued).

Molecular Target	Biomarker	Targeted Agent	Trial	Treatment	Clinical Efficacy
HER2 and PD-1	HER2 IHC ≥ 1 or FISH positive	Disitamab vedotin (RC48, HER2-targeting ADC) and Toripalimab (anti-PD-1 antibody)	Disitamab vedotin plus toripalimab for HER2-expressing advanced gastric or gastroesophageal junction and other solid tumours (Phase I)[51]	Patients with advanced metastatic gastric or GEJ or other solid tumors refractory to at least one line of treatment were treated with 2.0 mg/kg disitamab vedotin plus toripalimab (n=7) or 2.5 mg/kg disitamab vedotin plus toripalimab (n=49).	Objective response rate was 43%, median progression free survival was 6.2 months, and median overall survival was 16.8 months. The most common ≥ grade 3 adverse events were decreased neutrophil count and white blood cell count.
			Disitamab vedotin plus toripalimab and chemotherapy/trastuzumab as first-line treatment of patients with HER2-expressing locally advanced or metastatic gastric cancer (Phase II)[52]	Untreated advanced metastatic HER2-positive gastric cancer patients were treated with 2.5 mg/kg disitamab vedotin plus toripalimab plus CAPOX or disitamab vedotin plus toripalimab plus trastuzumab or toripalimab plus trastuzumab plus CAPOX.	Objective response rate was 82.4% in HER2-positive (3+ by IHC or 2+ by IHC and FISH positive) patients treated with disitamab vedotin plus toripalimab plus trastuzumab. The objective response rate in HER2-low (1+ by IHC or 2 + by IHC and FISH negative) patients treated with disitamab vedotin plus toripalimab plus CAPOX was 70.8% (76.9% with dose reduced CAPOX).
CLDN18.2 and PD-1	CLDN18.2 and PD-L1 expression agnostic	Osemitamab (TST001, anti-CLDN18.2 antibody)	TransStar102 (Phase I/II)[53]	Untreated advanced metastatic gastric and GEJ adenocarcinoma patients were treated with 3 mg/kg osemitamab plus nivolumab and CAPOX (n=40) or 6 mg/kg osemitamab plus nivolumab and CAPOX (n=42).	Objective response rate was 55.7%. CPS known and CLDN18.2 high/medium expression (CLDN18.2 membranous staining ≥ 2+ in ≥ 40% of tumor cells), objective response rate was 68%, median progression free survival was 16.6 months, and median overall survival was 20.4 months. The most common ≥ grade 3 adverse events were neutrophil decreased, platelet count decreased, nausea and vomiting.
	CLDN18.2-positivity defined as ≥2 + membrane staining intensity in ≥40% of tumor cells and PD-L1 expression agnostic	ASKB589 (anti-CLDN18.2 antibody)	ASKB589 combined with CAPOX and PD-1 inhibitor as first-line treatment for metastatic gastric/gastro-esophageal junction adenocarcinoma (Phase I/II)[54]	Untreated advanced metastatic CLDN18.2-positive gastric and GEJ adenocarcinoma patients were treated with 6 mg/kg ASKB589 plus CAPOX and sintilimab (PD-1 inhibitor) or 10 mg/kg ASKB589 plus CAPOX and sintilimab.	Objective response rate was 73.5% (76.2% for CPS<1 and 74.1% for CPS<5). 9 month progression free survival was 58.1%, and 12 month overall survival was 77.1%. The most common adverse events were hypoalbuminemia, nausea, and vomiting.

CLDN18.2	CLDN18.2-positivity defined as ≥2 + membrane staining intensity in ≥5% of tumor cells	CMG901 (CLDN18.2-targeting ADC)	KYM901 (Phase I)[55]	Treatment refractory advanced CLDN18.2-positive metastatic gastric and GEJ adenocarcinoma patients were treated with 2.2 mg/kg CMG901 (n=41), 2.6 mg/kg CMG901 (n=49) or 3.0 mg/kg CMG901 (n=17).	Objective response rate was 29%, median progression free survival was 3.7 months and median overall survival was 10.1 months.The most common ≥ 3 grade adverse events were neutrophil count decreased, anemia, and vomiting.
	CLDN18.2-positivity defined as membranous staining of any intestinty in ≥1% of tumor cells	IBI343 (CLDN18.2-tageting ADC)	CLDN18.2–targeting antibody–drug conjugate IBI343 in advanced gastric or gastroesophageal junction adenocarcinoma (Phase I)[56]	Treatment refractory advanced CLDN18.2-positive metastatic gastric and GEJ adenocarcinoma patients were treated in dose escalation (n=19) and dose expansion (n=108) phases.	Objective response rate was 29% and median progression free survival was 5.5 months at the recommended phase 2 dose of 6 mg/kg for CLDN18.2-high expressing tumors (≥2+ membrane staining intensity in ≥75% of tumor cells). The most common ≥ 3 grade adverse events were white blood cell count decreased, neutrophil count decreased, and anemia.
	CLDN18.2-positivity defined as ≥2 + membrane staining intensity in ≥40% of tumor cells	Satricabtagene autoleucel (satri-cel or CT041, CAR-T cell therapy targeting CLDN18.2)	CT041-ST-01 (Phase II)[57]	Advanced metastatic CLDN18.2-positive gastric and GEJ cancer patients refractory to at least 2 previous lines of treatment were treated with satri-cel (n=104) or treatment of physician's choice (n=52).	Median progression free survival was 3.25 months for the satri-cel group compared to 1.77 months for treatment of physician's choice group (HR 0.37; 95% CI 0.24–0.56; P<0.0001). Median overall survival was 7.92 months for the satri-cel group compared to 5.49 months for treatment of physician's choice group (HR 0.69; 95% CI 0.46–1.05; P<0.0416). The most common ≥ grade 3 adverse events were decreased lymphocyte count, decreased white blood cell count, and decreased neutrophil count. Cytokine release syndrome occured in 95% of the patients in the satri-cel group.
FGFR2b	FGFR2b-positivity defined as 2+/3+ membranous staining in more than 0% of tumor cells or *FGFR2* gene amplification by circulating tumor DNA assay	Bemarituzumab (anti-FGFR2b antibody)	FIGHT (Phase II)[58,59]	Untreated advanced metastatic FGFR2b-positive gastric and GEJ adenocarcinoma patients were treated with bemarituzumab plus FOLFOX (n=77) or FOLFOX alone (n=78).	Median progression free survival was 9.5 months in patients treated with bemarituzumab plus FOLFOX compared to 7.4 months with FOLFOX alone (HR 0.72; 95% CI 0.49–1.08). Median overall survival was 19.2 months in patients treated with bemarituzumab plus FOLFOX compared to 13.5 months with FOLFOX alone (HR 0.77; 95% CI 0.52–1.14). The most common ≥ grade 3 adverse events were decreased neutrophil count, cornea disorder (only reported in the bemurituzumab group), neutropenia, stomatitis, and anemia.
	FGFR2b-positivity defined as 2+/3+ membranous staining in more than 10% of tumor cells		FORTITUDE-101 (Phase III)[60]	Untreated advanced metastatic FGFR2b-positive gastric and GEJ adenocarcinoma patients were treated with bemarituzumab plus FOLFOX or FOLFOX alone.	Met primary endpoint of overall survival at pre-specified interim analysis. The most common treatment-emergent adverse events in patients treated with bemarituzumab plus chemotherapy were reduced visual acuity, punctate keratitis, anaemia, neutropenia, nausea, corneal epithelium defect and dry eye.

(*Continued*)

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Table 2 (Continued).

Molecular Target	Biomarker	Targeted Agent	Trial	Treatment	Clinical Efficacy
TROP2	TROP2 expression agnostic	Sacituzumab tirumotecan (SKB264/MK2870, TROP2-targeting ADC)	KL264-01 (Phase II)[61]	Advanced metastatic gastric and GEJ cancer adenocarcinoma patients refractory to at least one prior line of treatment were treated with 5 mg/kg SKB264 (n=48) monotherapy until disease progression.	Objective response rate was 22%, median progression free survival was 3.7 months, and median overall survival was 7.6 months. Patients with high and low TROP2 expression showed an objective response rates of 25% and 21.7%, respectively. The most common ≥ grade 3 adverse events were anemia, neutrophil count decreased, white blood cell count decreased, and neutropenia.
PD-1	PD-L1 expression agnostic	Camrelizumab (anti-PD-1 antibody)	ESCORT-1st (Phase III)[62]	Untreated advanced metastatic ESCC patients were treated with camrelizumab plus chemotherapy (paclitaxel plus cisplatin, n=298) or chemotherapy alone (n=298).	Median overall survivals for camrelizumab plus chemotherapy was 15.3 months compared to 12.0 months for the chemotherapy alone (HR 0.70; 95% CI 0.56–0.88; P=0.001). Subgroup analysis showed for patients with PD-L1 expression TPS ≥ 1, HR 0.59 (95% CI 0.43–0.80).
	PD-L1 expression agnostic	Toripalimab (anti-PD-1 antibody)	JUPITER-06 (Phase III)[63]	Untreated advanced metastatic ESCC patients were treated with toripalimab plus chemotherapy (paclitaxel plus cisplatin, n=257) or placebo plus chemotherapy (n=257).	Median overall survival was 17.0 months in patients treated with toripalimab plus chemotherapy compared to 11.0 months with those treated with chemotherapy alone (HR 0.58; 95% CI 0.43–0.78; P=0.0004). Subgroup analysis showed for patients with PD-L1 expression CPS ≥ 1, median overall survival was 15.2 months (HR 0.61; 95% CI 0.44–0.93; P=0.0056).
	PD-L1 expression agnostic	Sintilimab (anti-PD-1 antibody)	ORIENT-15 (Phase III)[64]	Untreated advanced metastatic ESCC patients were treated with sintilimab plus chemotherapy (5-FU or paclitaxel plus cisplatin, n=327) or placebo plus chemotherapy (n=332).	Median overall survival was 16.7 months in patients treated with sintilimab plus chemotherapy compared to 12.5 months in patients treated with chemotherapy alone (HR 0.63; 95% CI 0.51–0.78; P<0.001). In patients with CPS ≥10, median overall survival was 17.2 months with sintilimab plus chemotherapy compared to 13.6 months with chemotherapy alone (HR 0.64; 95% CI 0.48–0.68; P=0.002). Subgroup analysis showed for patients with PD-L1 expression CPS ≥ 1, HR 0.59 (95% CI 0.47–0.74).
	PD-L1 expression agnostic	Sugemalimab (anti-PD-1 antibody)	GEMSTONE-304 (Phase III)[65]	Untreated advanced metastatic ESCC patients were treated with sugemalimab plus chemotherapy (5-FU plus cisplatin, n=358) or placebo plus chemotherapy (n=182).	Median overall survival was 15.3 months with sugemalimab plus chemotherapy compared to 11.5 months with chemotherapy alone (HR 0.70; 95% CI 0.55–0.90; P=0.0076). Subgroup analysis showed for patients with PD-L1 expression CPS ≥ 10, HR 0.50 (95% CI 0.36–0.69).

B7H3	B7H3 expression agnostic	YL201 (B7H3-targeting ADC)	Efficacy of YL201 in patients with advanced solid tumors refractory to standard therapies (Phase I)[66]	312 patients with treatment refractory advanced metastatic solid tumors were enrolled with the most common cancer types being extensive-stage small cell lung cancer (n = 79), nasopharyngeal carcinoma (n = 75), non-small cell lung cancer (n = 68) and esophageal squamous cell carcinoma n = 37), and were treated with 2.4 mg/kg or 2.0 mg/kg YL201.	The objective response rate for ESCC patients was 25% and median progression free survival was 4.8 months. The most common ≥ grade 3 adverse events were neutropenia, leukopenia, and anemia. No significant correlation was observed between B7H3 expression and the clinical response across different tumor types
CTLA-4 and PD-1	PD-L1 expression agnostic	Cadonilimab (CTLA-4/PD-1 bispecific antibody)	COMPASSION-15 (Phase III)[67]	Untreated advanced metastatic gastric and GEJ adenocarcinoma patients were treated with cadonilimab plus chemotherapy (XELOX, n=305) or chemotherapy alone (n=305).	The median overall survival was 14.1 months in patients treated with cadonilimab and chemotherapy compared to 11.1 months in patients treated with chemotherapy alone (HR 0.66; 95% CI 0.54–0.81; P<0.001). For patients with a PD-L1 CPS ≥ 5, the median overall survival was 15.3 months in the cadonilimab and chemotherapy group and 10.9 months in the chemotherapy only group (HR 0.58; 95% CI 0.41–0.82). The most common ≥ grade 3 adverse events were decreased platelet count, decreased neutrophil counts, and anemia.
LAG-3 and PD-1	LAG-3 and PD-L1 expression agnostic	Relatlimab (anti-LAG-3 antibody)	RELATIVITY-60 (Phase II)[68]	Untreated advanced metastatic gastric and GEJ adenocarcinoma patients were treated with relatilimab plus nivolumab and chemotherapy (XELOX, FOLFOX, or SOX; n=138) or nivolumab and chemotherapy (n=136).	In patients with LAG-3 expression ≥ 1%, the objective response rate was 48% in the relatlimab plus nivolumab and chemotherapy arm and 61% in the nivolumab plus chemotherapy arm. Median overall survival was 13.5 months in the relatlimab plus nivolumab and chemotherapy arm and 16.0 in the nivolumab plus chemotherapy arm (HR 1.04; 95% CI 0.70–1.54). The most common ≥ grade 3 adverse events were neutropenia, fatigue, diarrhea, peripheral neuropathy, and anemia. Subgroup analysis showed potential efficacy signal for LAG-3 expression ≥ 5% and LAG-3 expression ≥ 1% combined with PD-L1 CPS ≥ 1 to <5.
			Neoadjuvant nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable esophageal/gastroesophageal junction cancer (Phase I)[69]	Resectable esophageal and GEJ adenocarcinoma patients were treated with relatilimab plus nivolumab plus chemoradiation (carboplatin and paclitaxel with 50.4 Gy, n=16) or nivolumab plus chemoradiation (n=16).	Pathologic complete response rate was 21.4% for relatlimab plus nivolumab and chemoradiation compared to 40% in patients treated with nivolumab plus chemoradiation. The most common adverse events were dermatitis, elevated AST/ALT, and hypothyroidism. Patients who attained a pCR had a trend toward higher baseline LAG-3 and PD-L1 expression.
		Favezelimab (anti-LAG-3 antibody)	Phase 1 trial of the anti-LAG3 antibody favezelimab plus pembrolizumab in advanced gastric cancer[70]	Advanced metastatic treatment refractory gastric cancer patients were treated with 200 mg (n=40) or 700 mg (n=40) favezelimab plus pembrolizumab.	Objective response rate was 11.3% for patients treated with favezelimab plus pembrolizumab. Subgroup analysis showed for PD-L1 expression CPS ≥ 1 and treated with 700 mg of favezelimab, objective response rate was 22.7%.

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Table 2 (Continued).

Molecular Target	Biomarker	Targeted Agent	Trial	Treatment	Clinical Efficacy
TIGIT and PD-1	PD-L1 expression agnostic	Rilvegostomig (TIGIT/PD-1 bispecific antibody)	GEMINI-Gastric (Phase II)[71]	Untreated advanced metastatic gastric cancer patients were treated with rilvegostomig plus chemotherapy (XELOX or FOLFOX, n=40).	Objective response rate in all patients was 67.5%. For patients with PD-L1 expression CPS ≥ 5, the objective response rate was 81.3%. The most common adverse events were nausea, neutrophil count decreased, and decreased appetite.
		Domvanalimab (anti-TIGIT antibody) and zimberelimab (anti-PD-1 antibody)	EDGE-Gastric (Phase II)[72]	Untreated advanced metastatic gastric, GEJ, and esophageal adenocarcinoma patients were treated with domvanalimab plus zimberelimab and chemotherapy (FOLFOX, n=41)	Objective response rate was 59% and median progression free survival was 12.9 months. For patients with PD-L1 expression TAP ≥ 5, the objective response rate was 69% and median progression free survival was 13.8 months. The most common adverse events were neutropenia, nausea, and anemia.
DKK1 and PD-1	DKK1 and PD-L1 expression agnostic	DKN-01 (anti-DKK1 antibody)	DisTinGuish (Phase II)[73]	Untreated advanced metastatic gastric and GEJ adenocarcinoma patients were treated with DKN-01 plus tislelizumab and chemotherapy (CAPOX, n=25).	Objective response rate was 73%, median progression free survival was 11.3 months, and median overall survival was 19.5 months. Subgroup analysis showed the objective response rate was 90% in patients whose tumors were DKK1-high (*DKK1* RNA expression by RNAscope chromogenic in situ hybridization assay and an H-score with ≥ 35 defined has high). The most common ≥ grade 3 adverse events were diarrhea, decreased potassium, and decreased hemoglobin.
IRAK4 and PD-1	PD-L1 expression agnostic	Emavusertib (CA-4948, IRAK4 inhibitor)	Phase I trial of CA-4948, an IRAK4 inhibitor, in combination with FOLFOX/PD-1 inhibitor ± trastuzumab for untreated unresectable gastric and esophageal cancer[74]	Untreated advanced metastatic gastric, GEJ, and esophageal adenocarcinoma patients were treated with emavusertib plus nivolumab and FOLFOX chemotherapy (for HER2-negative) or pembrolizumab and trastuzumab and FOLFOX chemotherapy (for HER2-positive).	Efficacy and safety results have not been reported.

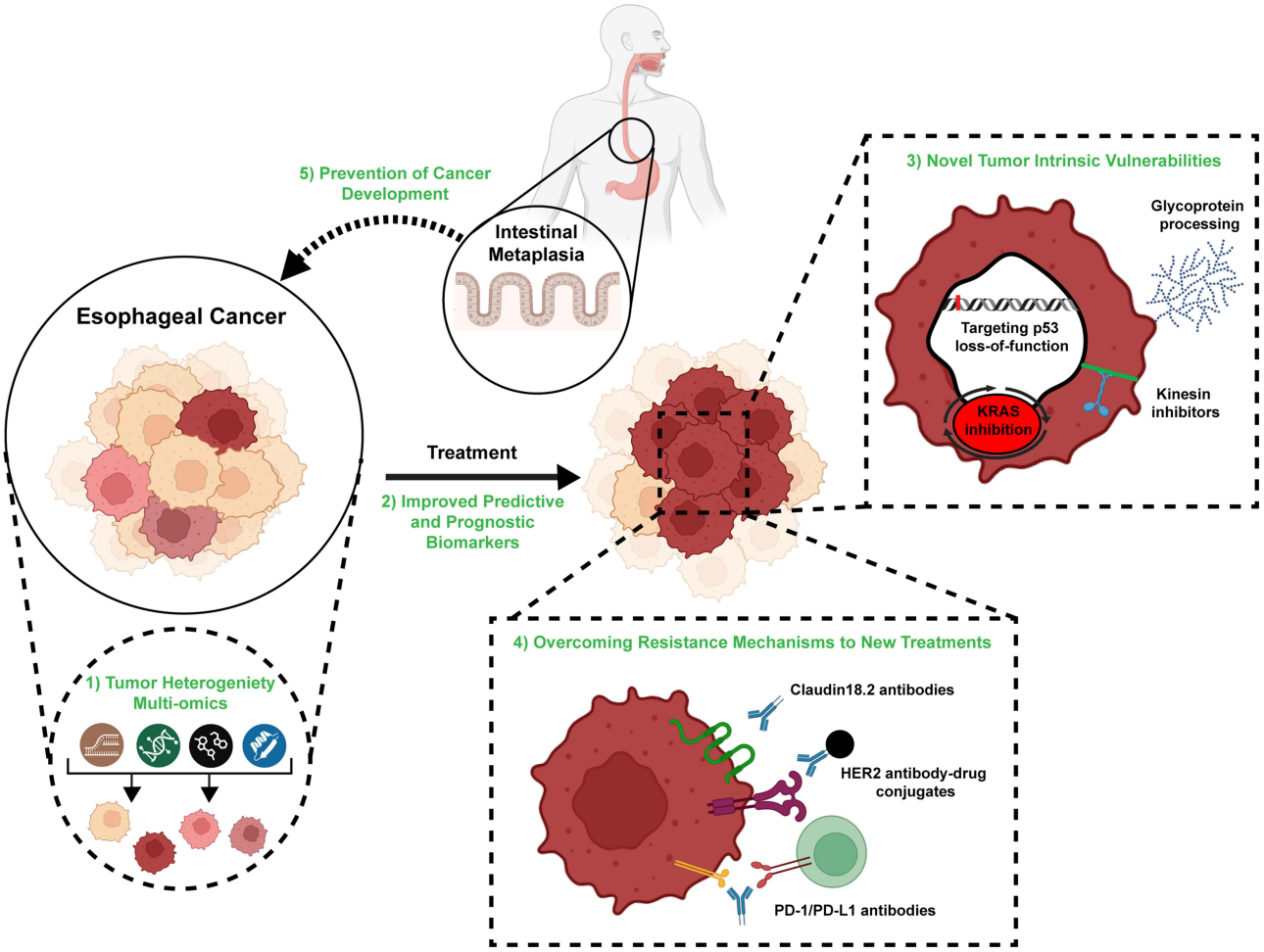

Figure 1 Gaps in knowledge and future directions. Schematic reflecting key gaps in knowledge and areas of research for esophageal cancer. Highlighting: 1) elucidation of tumor heterogeneity with multi-omic analyses at bulk and single-cell spatially-resolved resolutions, 2) improving biomarkers of treatment efficacy, 3) targeting novel tumor intrinsic vulnerabilities, 4) overcoming emerging resistance mechanisms to new treatments, and 5) developing novel cancer prevention strategies. Created with https://BioRender.com.

Additional PD-1 inhibitors have also shown efficacy in esophageal cancers. The KEYNOTE-590 trial evaluated pembrolizumab plus chemotherapy in advanced ESCCs (73%) and EACs.[32] In patients with PD-L1 CPS ≥10, pembrolizumab improved OS (13.5 vs 9.4 months) and PFS (6.3 vs 5.8 months). KEYNOTE-859 showed similar benefits in PD-L1 CPS ≥10 gastric and GEJ adenocarcinomas, with OS of 15.7 vs 11.8 months and PFS of 8.1 vs 5.6 months.[33] Tislelizumab, a PD-1 inhibitor with reduced Fc gamma receptor binding, improved survival in ESCC when combined with chemotherapy in the RATIONALE-306 trial.[34] Patients receiving tislelizumab and chemotherapy achieved longer OS compared with chemotherapy alone (17 vs 10 months) in those with PD-L1 CPS ≥1, as well as by Tumor Area Positivity (TAP) score, an alternative measure of PD-L1 expression.[87] In the RATIONALE-305 trial, tislelizumab plus chemotherapy also showed efficacy in frontline treatment of gastric and GEJ adenocarcinomas.[35] Its side effect profile is similar to other PD-1 inhibitors.[34,35]

While these trials collectively establish PD-1/PD-L1 blockade as a key treatment strategy, direct comparisons across studies are limited by differences in trial design including backbone chemotherapy regimen, PD-L1 scoring systems, histologic compositions and regional patient populations. To this point, multiple studies have attempted to better correlate PD-L1 levels and immunotherapy efficacy, and to elucidate potential discrepancies seen between studies.[88,89] Addition of immunotherapy to chemotherapy is likely to benefit patients with tumors that have high PD-L1 expression (CPS ≥10) and is unlikely benefit patients with low/negative expression (CPS < 1). The data is less clear for patients with intermediate

PD-L1 expression levels. Although a subset appears to derive clinical benefit—particularly among those with squamous cell carcinoma—better predictive biomarkers are needed to identify these patients.

CLDN18.2-Positive Esophageal Adenocarcinomas

CLDN18.2, a splice variant of a tight junction protein in normal gastric epithelium, is frequently overexpressed in subsets of gastroesophageal adenocarcinomas.[22] Zolbetuximab, a monoclonal antibody against CLDN18.2, promotes antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity.[90] CLDN18.2 positivity is defined by immunohistochemistry as strong (≥2+) membrane staining in ≥75% of adenocarcinoma cells.[91] The SPOTLIGHT trial enrolled patients with CLDN18.2-positive, HER2-negative gastric or GEJ adenocarcinomas and compared zolbetuximab plus chemotherapy to chemotherapy alone. Zolbetuximab improved OS (18.23 vs 15.54 months) and PFS (10.61 vs 8.67 months).[38] The GLOW trial similarly assessed zolbetuximab with chemotherapy, showing improved OS (14.39 vs 12.16 months) and PFS (8.21 vs 6.80 months) over chemotherapy alone.[39] Common adverse events (AEs) included nausea (82%), vomiting (67%), and decreased appetite (47%).[92]

Deficient MMR/MSI-High Esophageal Cancers

Deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) gastroesophageal cancers have impaired DNA repair, leading to high mutation rates and genomic instability.[93,94] They represent about 10% of gastroesophageal cancers.[16,17,95,96] Immune checkpoint inhibitors have shown benefit in this subset based on retrospective data from phase III trials. In CheckMate 649, subgroup analysis of 44 dMMR patients showed improved OS with nivolumab plus chemotherapy vs chemotherapy alone (38 vs 12 months).[31] Similarly, in KEYNOTE-859, 39 MSI-H patients had improved outcomes with pembrolizumab plus chemotherapy.[33] Immunotherapy alone may also be effective. In CheckMate 649, nivolumab plus ipilimumab improved OS vs chemotherapy in 21 MSI-H patients (OS not reached vs 10 months).[31] Pembrolizumab monotherapy also showed durable benefit in dMMR esophagogastric cancer based on exploratory analysis of the KEYNOTE-062, −059, and −061 trials.[40]

Angiogenesis-Targeted Therapies

Targeting the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) is an important second-line approach for advanced gastroesophageal cancers. Ramucirumab, a monoclonal antibody against VEGFR-2, has shown efficacy as monotherapy and combined with chemotherapy. The REGARD trial randomized previously treated advanced gastric or GEJ adenocarcinoma patients to ramucirumab or placebo.[43] Ramucirumab improved OS (5.2 vs 3.8 months) and PFS (2.1 vs 1.3 months). The RAINBOW trial assessed ramucirumab plus paclitaxel vs paclitaxel alone and showed improved OS (9.6 vs 7.4 months) and PFS (4.4 vs 2.9 months).[44] However, targeting this pathway has not shown efficacy in the frontline setting,[97,98] and current treatments are not biomarker driven.[99,100]

Locally Advanced Disease

While our focus has been on advanced metastatic EACs, recent shifts in treatment for locally advanced esophageal cancers are noteworthy. Previously, these cancers (EACs and ESCCs) were treated with preoperative chemoradiation using carboplatin and paclitaxel (the CROSS regimen).[101] Peri-operative FLOT chemotherapy (5-FU, leucovorin, oxaliplatin, and docetaxel), the standard for gastric and GEJ adenocarcinomas,[102] has recently shown superiority over CROSS for esophageal adenocarcinomas.[103] The ESOPEC trial demonstrated improved OS and PFS with peri-operative chemotherapy compared to neoadjuvant chemoradiation.

Checkpoint inhibitors have also shown utility in potentially curative, locally advanced esophageal cancers. Nivolumab improved disease-free survival compared to observation (22.4 vs 11.0 months) when given after neoadjuvant chemoradiotherapy in patients with pathologic residual disease at surgery.[104] More recently, durvalumab, a PD-L1 inhibitor, showed benefit in the perioperative setting. The MATTERHORN trial evaluated durvalumab with FLOT chemotherapy in resectable gastric and GEJ adenocarcinomas, showing improved two-year event-free survival (67.4% vs 58.5%) and higher pathologic complete response (pCR) rates (19.2% vs 7.2%).[36] Subgroup analyses from both studies suggest benefit may be greater in PD-L1-expressing tumors.[36,105] In contrast, pembrolizumab (KEYNOTE-585)[106,107]

and nivolumab (ATTRACTION-5)[108] added to chemotherapy have not shown clinical efficacy, and the DANTE trial is evaluating atezolizumab, another PD-L1 antibody, in this setting.[37] Notably, the subgroup in KEYNOTE-585 receiving FLOT (rather than cisplatin-based doublet) chemotherapy with pembrolizumab had outcomes similar to those in MATTERHORN.[106,107]

Neoadjuvant or peri-operative immunotherapy is being actively studied for localized dMMR/MSI-H esophageal cancers, with emerging evidence of clinical benefit. In KEYNOTE-585, adding pembrolizumab to peri-operative FLOT chemotherapy led to a 38.9% pCR rate.[106,107] Interim results from the DANTE trial showed a 63% pCR rate in the MSI-H subgroup with atezolizumab plus FLOT.[37] Immunotherapy alone is also under investigation, in the ongoing NEONIPIGA trial,[41] peri-operative nivolumab and ipilimumab treatment resulted in a 58.6% pCR rate. Similarly, the INFINITY trial reported a 60% pCR rate with the combination of tremelimumab (CTLA-4 antibody) and durvalumab.[42] These preliminary results, drawn from small cohorts, require confirmation in phase III trials before routine use in clinical practice.

Promising Future Therapies for Esophageal Cancers

Despite recent advances, prognosis in advanced esophageal cancer remains poor, and new effective therapies are needed. Strategies under investigation include adoptive cell therapies, ADCs, and novel approaches to targeting the TME, including new checkpoint inhibitors. Our discussion will focus on modalities with efficacy data, Table 2. While two-drug chemotherapy regimens have been the standard, three-drug regimens like FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin) have shown clinical efficacy.[109] In HER2-negative patients, FOLFIRINOX treatment achieved objective response rate (ORR) of 61%, PFS of 8.4 months, and OS of 15.5 months; in HER2-positive patients, adding trastuzumab improved outcomes (ORR 85%, PFS 13.8 months, OS 19.6 months). We will continue by discussing therapies by biomarker and mechanism of action.

HER2-Overexpressing Esophageal Adenocarcinomas

New approaches to blocking HER2 signaling are emerging for esophageal cancers. These include dual HER2 domain targeting bispecific antibodies such as zandidatamab.[110] In a phase II trial, zandidatamab plus chemotherapy displayed an ORR of 76.2%, PFS of 12.5 months, and OS of 36.5 months.[45] KN026 another HER2 bispecific antibody targeting two distinct HER2 domains,[111] demonstrated an ORR of 56% in HER2 high expressors (IHC 3+ or 2+/FISH-positive) in a phase II trial for pre-treated gastric and GEJ adenocarcinomas.[46]

Another HER2 blockade strategy involves novel monoclonal antibodies. HLX22 is a new anti-HER2 antibody that binds a different epitope than trastuzumab.[112] It was evaluated with a trastuzumab biosimilar, HLX02, and chemotherapy in a phase II trial.[47] Fifty-three first-line metastatic HER2-positive gastric/GEJ patients were randomized to HLX22 plus HLX02 and chemotherapy, or placebo plus HLX02 and chemotherapy. HLX22 improved PFS to 15.1 versus 8.2 months. A phase III trial is underway to assess HLX22 with trastuzumab and chemotherapy with and without pembrolizumab.[113]

Given the emergence of trastuzumab deruxtecan, additional HER2-targeting ADCs are in development. Interest is also growing to target HER2-low gastroesophageal cancers (IHC 2+/FISH-negative or IHC 1+), which account for up to 25% of cases.[114] The DESTINY-Gastric 01 trial analysis of HER2-low cohorts showed ORRs of 26.3% (IHC 2+/FISH-negative) and 9.5% (IHC 1+) with PFS of 4.4 months and 2.8 months, and OS of 7.8 months and 8.5 months, respectively.[48] Disitamab vedotin (DV, RC48) is a HER2 ADC with a monomethyl auristatin E payload.[115] In a phase I trial, DV plus anti-PD-1 toripalimab showed an ORR of 43%, PFS of 6.2 months, and OS of 16.8 months.[51] Responses were seen in HER2-positive and HER2-low patients. Common grade 3 AEs were neutropenia and leukopenia. A phase II trial has tested combinations of DV, toripalimab, chemotherapy, and trastuzumab.[52] For HER2-positive patients, DV with toripalimab and trastuzumab showed ORR of 82.4%, and for HER2-low patients, DV with toripalimab and chemotherapy showed ORR of 70.8% (76.9% with dose reduced chemotherapy). ARX788, another novel HER2 ADC utilizing a tubulin inhibitor payload showed ORR of 38%, PFS of 4.1 months, and OS of 10.7 months in heavily pretreated HER2-positive patients.[49] Common AEs included dry eye, thrombocytopenia, and elevated liver enzymes.[116]

Cellular therapies targeting HER2 are emerging for gastroesophageal cancers. HER2-directed chimeric antigen receptor (CAR) T cells have shown preclinical promise,[117] but still limited real clinical efficacy.[118] HER2 vaccines are

also in development. HER-Vaxx (IMU-131), a B-cell HER2 targeting vaccine showed improved OS of 13.9 versus 8.3 months when combined with chemotherapy in a phase II study.[50]

CLDN18.2-Positive Esophageal Adenocarcinomas

The approval of zolbetuximab for CLDN18.2 expressing gastroesophageal cancers has spurred additional interest in targeting this protein.[119] Osemitamab (TST001), a CLDN18.2 antibody with higher binding affinity and ADCC than zolbetuximab, showed promising results combined with nivolumab and chemotherapy in the TranStar102 phase I/II study resulting in ORR of 68%, PFS of 16.6 months, and OS of 20.4 months.[53] ASKB589, another CLDN18.2 antibody also showed early clinical efficacy combined with a PD-1 inhibitor and chemotherapy for CLDN18.2 expressing gastric/GEJ adenocarcinomas (ORR of 73.5%, 9-month PFS of 58.1%, and 12-month OS of 77.1%).[54] CLDN18.2-targeting ADCs are also in development. CMG901 in the KYM901 trial showed efficacy for treatment refractory gastroesophageal cancers with CLDN18.2 membrane staining intensity of at least 2+ in at least 5% of cancer cells with ORR of 29%, PFS of 3.7 months, and of OS 10.1 months.[55] Most responses (97%) occurred in tumors with ≥20% of cells showing expression. Common AEs were anemia, hypoalbuminemia, weight loss, nausea and vomiting. IBI343, another CLDN18.2 ADC, showed a similar ORR of 29% and PFS of 5.5 months in a phase I trial for treatment refractory CLDN18.2 high expressing gastric/GEJ adenocarcinoma patients.[56] Cellular therapies against CLDN18.2 are emerging as well. Satricabtagene autoleucel (satricel, CT041), an autologous CAR-T cell therapy targeting CLDN18.2,[120] improved PFS (3.25 vs 1.77 months) and OS (7.92 vs 5.49 months) versus physician's choice therapy in the phase II CT041-ST-01 trial.[57] Grade ≥3 cytopenias occurred in 99% and cytokine release syndrome in 95% of satricel-treated patients.

FGFR2-Overexpressing Esophageal Adenocarcinomas

Fibroblast growth factor receptor (FGFR) signalings are frequently altered in cancers.[121] *FGFR2* amplifications occur in 4–7% of gastric cancers[122] and FGF2b overexpression is seen in 4–30% of gastroesophageal cancers.[123,124] Bemarituzumab, an FGFR2b monoclonal antibody was assessed with chemotherapy in gastroesophageal cancer patients in the phase II FIGHT study.[58] Eligibility was based on FGFR2b overexpression (IHC 2+/3+ in >0% of tumor cells) or *FGFR2* amplification detected by circulating tumor DNA (ctDNA) sequencing. Bemarituzumab and chemotherapy improved PFS (9.5 vs 7.4 months) and OS (19.2 vs 13.5 months) compared with chemotherapy with greater benefit in tumors overexpressing FGFR2b in ≥10% of cells.[59] Corneal adverse events were commonly seen in the bemarituzumab treated arm (77.4%). The ongoing phase III FORTITUDE-101 trial has met its interim OS endpoint.[60] The benefit is therefore limited to selected patients with FGFR2b overexpression and ocular toxicity requires careful management.

TROP2-Overexpressing Esophageal Cancers

Trophoblast cell surface antigen 2 (TROP2), a calcium-transducing transmembrane protein, is overexpressed in 50–60% of gastric cancers[125,126] with similar rates in EACs[127] and ESCCs.[128] Sacituzumab tirumotecan (SKB264/MK2870) is a TROP2-directed ADC with a topoisomerase I payload.[129] Preliminary results from the phase II KL264-01 trial demonstrated early efficacy in treatment-refractory gastric and GEJ adenocarcinomas.[61] The ORR was 22.0%; in patients with ≥3 prior treatments, PFS was 3.7 months and OS was 7.6 months. Patients with medium/low TROP2 expression by immunohistochemistry showed an ORR of 21.7%, while high expressing patients had an ORR of 25.0%. Common AEs were anemia, decreased white blood cells, and neutropenia.

Targeting the Tumor Microenvironment PD-1/PD-L1 and Beyond

The emergence of PD-1 inhibitors (nivolumab, pembrolizumab, tislelizumab) and PD-L1 inhibitors (durvalumab) have prompted continued interest in targeting the TME in gastroesophageal cancers, especially ESCC. In the ESCORT-1st trial, camrelizumab, a PD-1 monoclonal antibody, plus chemotherapy improved OS (15.3 vs 12.0 months) and PFS (6.9 vs 5.6 months) over chemotherapy for metastatic ESCC patients with benefits seen regardless of PD-L1 expression.[62] Most common immune-related AE was reactive capillary endothelial proliferation. Similar outcomes were observed for additional PD-1 inhibitors when combined with chemotherapy compared to chemotherapy alone: in the JUPITER-06 trial with toripalimab (OS 17.0 vs 11.0 months),[63] and in the ORIENT-15 trial with sintilimab (OS 16.7 vs 12.5 months).[64]

Finally, the GEMSTONE-304 trial showed that the PD-L1 inhibitor, sugemalimab, improved OS to 15.3 from 11.5 months when added to chemotherapy in treatment-naïve advanced ESCC patients.[65]

Beyond PD-1/PD-L1, the tumor antigen, B7-H3 (CD276) has emerged as a novel target.[130] It is overexpressed in many cancers, including 45% of ESCCs,[131] and implicated in tumor progression and immune evasion.[132] YL201, a B7-H3-targeting ADC,[133] showed ORR of 25% and PFS of 4.8 months in a phase 1/1b trial of heavily pretreated ESCC patients.[66] Common grade ≥3 AEs were neutropenia, leukopenia, and anemia. Phase III trials assessing this ADC have begun for other tumor types, but not yet for esophageal cancers.

CTLA-4 is another immune checkpoint of interest,[134] particularly in combination with PD-1 blockade as shown in CheckMate 648 and 649 (discussed above). Cadonilimab a tetravalent anti-PD-1 and CTLA-4 bispecific antibody that is Fc-null for improved safety[135] was evaluated in the Chinese-centered COMPASSION-15 trial in untreated gastric/GEJ adenocarcinoma patients.[67] Cadonilimab plus chemotherapy improved OS to 14.1 vs 11.1 months compared to chemotherapy. In PD-L1 CPS ≥5 patients, OS was further improved to 15.3 compared to 10.9 months for chemotherapy alone. Common AEs were cytopenias and grade 1/2 hypothyroidism. Efficacy of cadonilimab internationally and compared to chemotherapy and PD-1 blockade will need to be addressed.

Lymphocyte-activation gene 3 (LAG-3) is an inhibitory receptor often co-expressed with PD-1 on T-cells.[136] Dual inhibition of LAG-3 and PD-1 has been found preclinically to have anti-tumor activity,[137] and LAG-3 has been found to be expressed in 40–50% of untreated gastroesophageal cancers.[138] In the RELATIVITY-60 study, combining relatlimab, a LAG-3 blocking antibody, with nivolumab and chemotherapy showed no OS benefit in patients with ≥1% LAG-3 expression.[68] Exploratory analyses showed a possible efficacy signal in patients with ≥5% LAG-3 expression and in patients with ≥1% LAG-3 expression combined with PD-L1 expression positivity (≥1 and <5). In neoadjuvant settings, relatlimab plus nivolumab with chemoradiation yielded 21.4% pCR and 93.8% 2-year OS vs 40% pCR and 75% 2-year OS with nivolumab alone.[69] Favezelimab, another anti-LAG-3 antibody, when combined with pembrolizumab in pretreated advanced gastric cancer patients showed modest activity (ORR 11.3%) with better outcomes in PD-L1-positive patients.[70] These results indicate gastroesophageal cancer patients may benefit from dual LAG-3 and PD-1 blockade, but better biomarkers are needed to select for these subsets of patients.

The lymphocyte inhibitor receptor, T cell immunoglobulin and ITIM domain (TIGIT), has also emerged as a new target to restore and augment anti-tumor responses combined with PD-1 blockade.[139] Rilvegostomig (AXD2936), a bispecific TIGIT and PD-1 antibody,[140] showed promising results in the GEMINI-Gastric phase II trial.[71] The combination of rilvegostomig with chemotherapy achieved an ORR of 67.5% (81.3% for CPS ≥5) in metastatic gastric/GEJ adenocarcinomas. Common AEs were nausea, neutropenia, and decreased appetite. Domvanalimab (AB154), a Fc-silent anti-TIGIT antibody, has been combined with zimberelimab (anti-PD-1 antibody) and chemotherapy in the EDGE-Gastric study.[72] ORR was 59% and PFS was 12.9 months; in patients with high PD-L1 expression (≥5% TAP score) ORR was 69% with PFS of 13.8 months.[141] Neutropenia, nausea, and anemia were the most common treatment-related AEs. The phase III STAR-221 trial is comparing this regimen to nivolumab with chemotherapy.[142] The TME includes immune targets beyond lymphocytes. Dickkopf-related protein (DKK1) is a secreted protein that controls tumor growth, is overexpressed in 50–70% of gastroesophageal adenocarcinomas,[143,144] and suppresses antitumor immune responses through regulation of tumor associated macrophages.[145] DKN-01, a DKK1 blocking antibody, was assessed in the phase II DisTinGuish trial with tislelizumab and chemotherapy.[73] The combination achieved ORR 73%, PFS of 11.3 months and OS of 19.5 months. *DKK1* expression was assessed using an RNAscope chromogenic in situ hybridization (CISH) assay, and a quantitate H-score was determined with ≥35 defined as DKK1-high. In patients with DKK1-high expression, ORR increased to 90%. Common AEs were fatigue, diarrhea, and neutropenia. A randomized trial is ongoing assessing the efficacy of adding DKN-01 to PD-1 blockade and chemotherapy.

During gastrointestinal cancer progression and treatment resistance, dysregulation of inflammatory toll-like receptor and interleukin-1 receptor activates the pro-survival and immunosuppressive NF-κB pathway.[146,147] Interleukin-1 Receptor Associated Kinase-4 (IRAK4) is a key regulator of this pathway and required for carcinogenesis.[148] Emavusertib (CA-4948), a small molecule IRAK4 inhibitor originally developed for hematologic malignancies,[149] is currently being evaluated in combination with chemotherapy for patients with untreated advanced gastroesophageal cancers.[74]

Gaps in Knowledge and Future Directions

Elucidating Tumor Heterogeneity

The difficulty in treating gastroesophageal cancers remains intratumoral and TME heterogeneity. Variability in biomarkers like HER2 and PD-L1 across tumor regions, over time, and after therapy complicates treatment;[150–152] overcoming this requires integrated higher-resolution analyses. The National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC) is advancing proteogenomic characterization using multi-omics to link genomic mutations with the transcriptome, epigenome, microbiome and proteome.[153] Beyond "bulk" analysis, single-cell and spatial sequencing now apply multi-omics at cellular resolution.[154] Tracking esophageal cancer at single-cell resolution could personalize treatment. Targeted RNA-sequencing marks a shift toward clinical use of additional "omics" approaches that may provide clinically meaningful information beyond genomic profiling.[155]

Improving Biomarkers

To find more clinically significant subtypes, better predictive and prognostic biomarkers are needed. Liquid biopsies and ctDNA, extracellular DNA from cancer cells,[156] offer real-time cancer detection and monitoring. CtDNA quantification may enable early detection and predict recurrence postoperatively.[157–159] It has shown strong concordance with tissue profiling in advanced gastroesophageal cancers.[160] Furthermore, longitudinal ctDNA monitoring during treatment is emerging as a way to personalize therapy sequencing.[26,161–164] Advanced technologies have enhanced the sensitivity of liquid biopsy "omics",[165,166] but clinical trials are needed to define their applicability in clinical practice.

PD-L1 expression assessed via CPS (as well as TPS and TAP) remains the best surrogate for immunotherapy response in gastroesophageal cancers.[88] However, IHC scoring is subjective and relies on a single marker to represent a complex immune environment. In addition, as discussed above, better predictive biomarkers are needed to identify patients who will benefit from immunotherapy among the patients with intermediate PD-L1 expression. Single-cell multi-omics have identified six distinct ecotypes (EC1-6) in gastroesophageal cancers[167] with biological and clinical implications.[168] EC3 and EC6, predominant in gastric cancers, comprise CD4/8 T, natural killer, and dendritic cells; and stromal and B cells, respectively. These ecotypes, particularly within the CIN group, further stratify survival, and clinically identifying ecotypes may improve selection for specific immunotherapy combinations.

Finally, improved biomarkers to guide, sequence and integrate current targeted therapies are also needed, especially for patients with HER2 negative, and dual CLDN18.2 and PD-L1 positive (CPS≥5) gastroesophageal adenocarcinomas. These double expressing tumors comprise almost half of all CLDN18.2 positive gastroesophageal adenocarcinomas.[169] Cross trial comparisons suggest that specific subsets of patients may derive differential benefit as GEJ adenocarcinomas and non-Asian subgroups showed less clinical benefit.[38,39] While the addition of zolbetuximab improved OS and PFS, there was no improvement in response rates when compared to immunotherapy trials.[38,39] Multiple trials, Table 2, are underway testing the combination of targeting CLDN18.2 and immunotherapy including zolbetuximab and pembrolizumab[170] that will lead to better biomarker driven guidance on optimal treatment selection.

Targeting Novel Tumor Intrinsic Vulnerabilities

Early *TP53* mutations drive genomic and phenotypic heterogeneity in gastroesophageal cancers and are early events in BE to EAC progression and ESCC carcinogenesis.[171–173] Targeting p53 loss-of-function is appealing but difficult due to mutation diversity.[174] Eprenetapopt (APR-246) binds mutated p53 cysteine residues triggering cell death.[175] Rezatapopt (PC14586) targets *TP53* Y220C mutations to reactivate p53 function,[176] while ELX-02, a small-molecule ribosomal selective glycoside, restores translation of *TP53* in *TP53* nonsense mutated cancers.[177] Wildtype p53 epitopes can also activate cytotoxic T lymphocytes using dendritic vaccines to target p53 mutated tumors.[178] Though mostly pre-clinical, early trials show promise for these strategies. For example, the PYNNACLE trial assessing rezatapopt in *TP53* Y220C tumors has shown a 33.3% ORR.[179]

Efforts to target mutated p53—a protein once considered "undruggable"—have encouraged the pursuit of other undruggable proteins including KRAS, which is mutated (3%) or amplified (14%) in gastroesophageal cancers.[180,181] Common mutations include G12D, G12V, and non-codon 12/13 variants.[180,182] Preclinical data show *KRAS* amplified gastric cancer models respond to SHP2, MEK, and CDK4/6 inhibition.[181,183] In addition, BI 3706674, a small molecule

inhibitor of the *KRAS* mutations and amplifications, has shown activity in tumors with *KRAS* G12V and copy number gains >10.[184] As technology advances, more protein targets are becoming druggable. One such emerging technology is proteolysis-targeting chimeras (PROTACs), which harness the cell's own ubiquitin-proteasome system to tag specific proteins with polyubiquitin chains, marking them for targeted proteasomal degradation.[185] While the challenges and applications of PROTACs are numbers,[185–187] preclinical development in gastroesophageal cancers has focused on targets such as FGFR2,[188] VEGFR-2,[189] and the histone demethylase, KDM4.[190]

While p53 and KRAS are common targets in solid tumors, efforts are underway to identify gastroesophageal-specific targets. Glycosylation aberrancies are common and may offer novel therapeutic avenues.[191] Mucin 1 (MUC1), α-fetoprotein (AFP) and carcinoembryonic antigen (CEA) have been assessed as glycoprotein targets for CAR-T cells.[192] Glycoprotein biology also drives carcinogenesis. Carbohydrate antigen 19–9 (CA19-9) induces pancreatitis and promotes pancreatic cancer with *KRAS* mutations,[193] and Mucin 6 (MUC6) loss induces gastric inflammation leading to cancer.[194] Abnormal glycosylation also affects the TME, as most immune checkpoints are glycoproteins, suggesting potential impact on future immunotherapy strategies.[195]

Most EACs have *TP53* mutations, *ERBB2* and *VEGFA* amplifications, and are classified as CIN tumors.[16] It has been recently recognized that CIN tumors harbor vulnerabilities that may be uniquely targeted.[196] CIN cancers, due to aneuploidy, show mitotic spindle defects and are sensitive to kinesin motor inhibition.[197] Inhibiting the kinesin motor, KIF18A, has shown preclinical efficacy[198] and early trials with the oral KIF18A inhibitor, VLS-1488, in solid tumors including esophageal cancers are promising[199] CIN tumors also activate the cGAS-STING immune pathway, and inhibiting this signaling may offer a novel treatment for chromosomally unstable esophageal cancers.[200]

Overcoming New Treatment Resistance

With advances in trastuzumab deruxtecan and zolbetuximab, understanding resistance mechanisms is critical. We will highlight a few areas, specifically, that will need to be addressed. The topic of immunotherapy resistance is beyond the scope of this review and has been well detailed.[201–203] Resistance to HER2 blockade with trastuzumab is well understood in breast oncology,[204] but strategies from breast cancer often do not translate to gastroesophageal cancers.[205] Known breast cancer HER2 ADC resistance involves HER2 downregulation and altered trafficking, payload resistance, and activation of alternative signaling pathways, including PI3K/AKT/mTOR.[206] Trastuzumab deruxtecan resistance may also be induced by changes in the tumor microenvironment and mutations in *SLX4* a gene involved in DNA repair.[207] Specific to gastroesophageal adenocarcinomas, *CCNE1* amplifications that induce cell cycle dysregulation,[208] human leukocyte antigens (HLAs) loss that may abrogate antibody-dependent cellular cytotoxicity, and upregulation of oxidative phosphorylation[209] are reported mechanisms of trastuzumab deruxtecan resistance. Novel HER2 ADCs, including disitamab vedotin,[210] and dual payload ADCs[211] are being investigated to overcome resistance these mechanisms, and combination approaches targeting alternative signaling pathways or dual HER2 targeting may also improve outcomes. Similar studies are needed to uncover resistance to zolbetuximab with the best evidence showing CLND18.2 expression downregulation.[212] Other suggested mechanisms may involve changes in the tumor microenvironment and compensatory growth pathways.[213] Overall, a systematic understanding of resistance including target modulation, intracellular signaling alterations, tumor heterogeneity and payload-specific mechanisms are needed to optimize next-generation HER2 and CLDN18.2-guided therapies.

Preventing Esophageal Cancer Development

Finally, all esophageal adenocarcinomas develop from Barrett's esophagus, making intestinal metaplasia a key target for prevention in western countries.[214,215] While dysplastic BE is managed with endoscopic therapy, preventing progression of non-dysplastic BE is critical.[216] The AspECT trial demonstrated proton pump inhibitors and aspirin reduce death and EAC/dysplasia,[217] providing the best evidence for BE chemoprevention. Tamoxifen, a selective estrogen receptor modulator, has been associated with decreased upper GI intestinal metaplasias[218] and altered gene expression in BE stroma.[219] In mice, selumetinib, a MEK inhibitor, reversed *Helicobacter pylori*-induced gastric intestinal metaplasia.[220] A phase I trial of trametinib, another MEK inhibitor, showed improvements in gastric oxyntic atrophy and intestinal metaplasia post-resection for early-stage gastric cancer patients.[221] These therapeutic strategies that may treat BE and prevent EAC development warrant further study.

Conclusion

Biomarker-driven therapies have transformed the management of advanced esophageal adenocarcinoma, with agents such as trastuzumab deruxtecan and zolbetuximab demonstrating significant improvements in patient outcomes. PD-L1, HER2, CLDN18.2, and MSI/MMR status now guide personalized treatment selection, yet anatomic, histologic, and molecular heterogeneity in tumor biology and overlapping actionable biomarkers complicate optimal therapy sequencing. New integrative multi-omics approaches provide deeper insights into tumor-intrinsic and microenvironmental mechanisms, offering potential strategies to overcome resistance and refine therapeutic interventions. Continued efforts are needed to translate basic science into clinical practice, and unique features of gastroesophageal cancers including *TP53* mutations, CIN molecular subtype, altered glycosylation, and intestinal metaplasia precursor lesions offer new exciting avenues for therapeutic intervention. Moving forward, the integration of new and more robust biomarkers with novel therapeutics will be essential to improve outcomes and guide precision-based management of esophageal cancers.

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References

1. Bray F, Laversanne M, Sung H. et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin*. 2025;75(1):10–45. doi:10.3322/caac.21871
3. Puhr HC, Pablik E, Berghoff AS, et al. Viennese risk prediction score for advanced gastroesophageal carcinoma based on Alarm Symptoms (VAGAS score): characterisation of alarm symptoms in advanced gastro-oesophageal cancer and its correlation with outcome. *ESMO Open*. 2020;5(2). doi:10.1136/esmoopen-2019-000623
4. Jin RU, Navo K, Park H. Chapter 15: esophageal and Gastric Cancer. In: Ramaswamy G, Daniel M, Armin G, editors. *The Washington Manual of Oncology*. 4th ed. Wolters Kluwer; 2021.
5. Spechler SJ, Souza RF. Barrett's esophagus. *N Engl J Med*. 2014;371(9):836–845. doi:10.1056/NEJMra1314704
6. Morgan E, Soerjomataram I, Rumgay H, et al. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates from GLOBOCAN 2020. *Gastroenterology*. 2022;163(3):649–658e2. doi:10.1053/j.gastro.2022.05.054
7. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg*. 2017;6(2):119–130. doi:10.21037/acs.2017.03.14
8. Siewert JR, Stein HJ. Carcinoma of the gastroesophageal junction - classification, pathology and extent of resection. *Dis Esophagus*. 1996;9(3):173–182. doi:10.1093/dote/9.3.173
9. Amin MB, American Joint Committee on Cancer, American Cancer Society. *AJCC Cancer Staging Manual*. 8th ed. American Joint Committee on Cancer, Springer; 2017:xvii,1024.
10. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers, Version 2.2023, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2023;21(4):393–422. doi:10.6004/jnccn.2023.0019
11. Chao J, Bedell V, Lee J, et al. Association between spatial heterogeneity within nonmetastatic gastroesophageal adenocarcinomas and survival. *JAMA Netw Open*. 2020;3(4):e203652. doi:10.1001/jamanetworkopen.2020.3652
12. Dinh HQ, Pan F, Wang G, et al. Integrated single-cell transcriptome analysis reveals heterogeneity of esophageal squamous cell carcinoma microenvironment. *Nat Commun*. 2021;12(1):7335. doi:10.1038/s41467-021-27599-5
13. Li X, Francies HE, Secrier M, et al. Organoid cultures recapitulate esophageal adenocarcinoma heterogeneity providing a model for clonality studies and precision therapeutics. *Nat Commun*. 2018;9(1):2983. doi:10.1038/s41467-018-05190-9
14. Stachler MD, Jin RU. Molecular pathology of gastroesophageal cancer. *Clin Lab Med*. 2024;44(2):239–254. doi:10.1016/j.cll.2023.08.005
15. Zeng Y, Jin RU. Molecular pathogenesis, targeted therapies, and future perspectives for gastric cancer. *Semin Cancer Biol*. 2022;86(Pt 3):566–582. doi:10.1016/j.semcancer.2021.12.004
16. Cancer Genome Atlas Research N, Analysis Working Group: Asan U, Agency BCC, et al. Integrated genomic characterization of oesophageal carcinoma. *Nature*. 2017;541(7636):169–175. doi:10.1038/nature20805

17. Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513(7517):202–209. doi:10.1038/nature13480
18. Sohn BH, Hwang JE, Jang HJ, et al. Clinical significance of four molecular subtypes of gastric cancer identified by the cancer genome Atlas project. *Clin Cancer Res*. 2017;23(15):4441–4449. doi:10.1158/1078-0432.CCR-16-2211
19. Network NCC. NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers. Available from: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed June 25, 2025.
20. Rodriguez GM, DePuy D, Aljehani M, et al. Trends in epidemiology of esophageal cancer in the US, 1975-2018. *JAMA Netw Open*. 2023;6(8):e2329497. doi:10.1001/jamanetworkopen.2023.29497
21. Thrift AP. Global burden and epidemiology of Barrett oesophagus and oesophageal cancer. *Nat Rev Gastroenterol Hepatol*. 2021;18(6):432–443. doi:10.1038/s41575-021-00419-3
22. Zeng Y, Lockhart AC, Jin RU. The preclinical discovery and development of zolbetuximab for the treatment of gastric cancer. *Expert Opin Drug Discov*. 2024;19(8):873–886. doi:10.1080/17460441.2024.2370332
23. Croft W, Evans RPT, Pearce H, Elshafie M, Griffiths EA, Moss P. The single cell transcriptional landscape of esophageal adenocarcinoma and its modulation by neoadjuvant chemotherapy. *Mol Cancer*. 2022;21(1):200. doi:10.1186/s12943-022-01666-x
24. Zhang X, Peng L, Luo Y, et al. Dissecting esophageal squamous-cell carcinoma ecosystem by single-cell transcriptomic analysis. *Nat Commun*. 2021;12(1):5291. doi:10.1038/s41467-021-25539-x
25. Ruschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. *Mod Pathol*. 2012;25(5):637–650. doi:10.1038/modpathol.2011.198
26. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in HER2-positive advanced gastric cancer: exploratory biomarker analysis of the randomized, phase 2 DESTINY-Gastric01 trial. *Nat Med*. 2024;30(7):1933–1942. doi:10.1038/s41591-024-02992-x
27. Shitara K, Van Cutsem E, Gumus M, et al. Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer. *N Engl J Med*. 2025. doi:10.1056/NEJMoa2503119
28. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the Phase 3 KEYNOTE-811 randomised placebo-controlled trial. *Lancet*. 2023;402(10418):2197–2208. doi:10.1016/S0140-6736(23)02033-0
29. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab in HER2-positive gastric cancer. *N Engl J Med*. 2024;391(14):1360–1362. doi:10.1056/NEJMc2408121
30. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. *N Engl J Med*. 2022;386(5):449–462. doi:10.1056/NEJMoa2111380
31. Janjigian YY, Ajani JA, Moehler M, et al. First-line nivolumab plus chemotherapy for advanced gastric, gastroesophageal junction, and esophageal adenocarcinoma: 3-year follow-up of the phase III CheckMate 649 trial. *J Clin Oncol*. 2024;42(17):2012–2020. doi:10.1200/JCO.23.01601
32. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2021;398(10302):759–771. doi:10.1016/S0140-6736(21)01234-4
33. Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2023;24(11):1181–1195. doi:10.1016/S1470-2045(23)00515-6
34. Xu J, Kato K, Raymond E, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. 2023;24(5):483–495. doi:10.1016/S1470-2045(23)00108-0
35. Qiu MZ, Oh DY, Kato K, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *BMJ*. 2024:385:e078876. doi:10.1136/bmj-2023-078876
36. Janjigian YY, Al-Batran SE, Wainberg ZA, et al. Perioperative durvalumab in gastric and gastroesophageal junction cancer. *N Engl J Med*. 2025. doi:10.1056/NEJMoa2503701
37. Lorenzen S, Gotze TO, Thuss-Patience P, et al. Perioperative atezolizumab plus fluorouracil, leucovorin, oxaliplatin, and docetaxel for resectable esophagogastric cancer: interim results from the randomized, multicenter, phase II/III DANTE/IKF-s633 trial. *J Clin Oncol*. 2024;42(4):410–420. doi:10.1200/JCO.23.00975
38. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*. 2023;401(10389):1655–1668. doi:10.1016/S0140-6736(23)00620-7
39. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med*. 2023;29(8):2133–2141. doi:10.1038/s41591-023-02465-7
40. Chao J, Fuchs CS, Shitara K, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol*. 2021;7(6):895–902. doi:10.1001/jamaoncol.2021.0275
41. Andre T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: the GERCOR NEONIPIGA phase II study. *J Clin Oncol*. 2023;41(2):255–265. doi:10.1200/JCO.22.00686
42. Raimondi A, Lonardi S, Murgioni S, et al. Tremelimumab and durvalumab as neoadjuvant or non-operative management strategy of patients with microsatellite instability-high resectable gastric or gastroesophageal junction adenocarcinoma: the INFINITY study by GONO. *Ann Oncol*. 2025;36(3):285–296. doi:10.1016/j.annonc.2024.11.016
43. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014;383(9911):31–39. doi:10.1016/S0140-6736(13)61719-5

44. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15(11):1224–1235. doi:10.1016/S1470-2045(14)70420-6
45. Elimova E, Ajani J, Burris H, et al. Zanidatamab plus chemotherapy as first-line treatment for patients with HER2-positive advanced gastro-oesophageal adenocarcinoma: primary results of a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2025;26(7):847–859. doi:10.1016/S1470-2045(25)00287-6
46. Xu J, Ying J, Liu R, et al. KN026 (anti-HER2 bispecific antibody) in patients with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancer. *Eur J Cancer*. 2023;178:1–12. doi:10.1016/j.ejca.2022.10.004
47. Li N, Qiu M, Zhang Y, et al. A randomized phase 2 study of HLX22 plus trastuzumab biosimilar HLX02 and XELOX as first-line therapy for HER2-positive advanced gastric cancer. *Med*. 2024;5(10):1255–1265e2. doi:10.1016/j.medj.2024.06.004
48. Yamaguchi K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in anti-human epidermal growth factor Receptor 2 treatment-naive patients with human epidermal growth factor receptor 2-low gastric or gastroesophageal junction adenocarcinoma: exploratory cohort results in a phase II trial. *J Clin Oncol*. 2023;41(4):816–825. doi:10.1200/JCO.22.00575
49. Barok M, Le Joncour V, Martins A, et al. ARX788, a novel anti-HER2 antibody-drug conjugate, shows anti-tumor effects in preclinical models of trastuzumab emtansine-resistant HER2-positive breast cancer and gastric cancer. *Cancer Lett*. 2020;473:156–163. doi:10.1016/j.canlet.2019.12.037
50. Tobias J, Maglakelidze M, Andric Z, et al. Phase II trial of HER-Vaxx, a B-cell peptide-based vaccine, in HER2-overexpressing advanced gastric cancer patients under platinum-based chemotherapy (HERIZON). *Clin Cancer Res*. 2024;30(18):4044–4054. doi:10.1158/1078-0432.CCR-24-0742
51. Wang Y, Gong J, Wang A, et al. Disitamab vedotin (RC48) plus toripalimab for HER2-expressing advanced gastric or gastroesophageal junction and other solid tumours: a multicentre, open label, dose escalation and expansion phase 1 trial. *EClinicalMedicine*. 2024;68:102415. doi:10.1016/j.eclinm.2023.102415
52. Shen L, Peng Z, Li C, et al. Disitamab vedotin (DV) plus toripalimab (Tor) and chemotherapy (C)/trastuzumab (Tra) as first-line (1L) treatment of patients (pts) with HER2-expressing locally advanced or metastatic (la/m) gastric cancer. *J Clin Oncol*. 2025;43(17_suppl):LBA4012. doi:10.1200/JCO.2025.43.17_suppl.LBA4012
53. Gong J, Liu D, Guo Z, et al. First-line osemitamab (TST001) plus nivolumab and CAPOX for advanced G/GEJ cancer (TranStar102): updated results of cohort G from a phase I/IIa study. *J Clin Oncol*. 2025;43(16_suppl):4032. doi:10.1200/JCO.2025.43.16_suppl.4032
54. Peng Z, Zhu H, Wang J, et al. Updated efficacy results of ASKB589 combined with CAPOX and PD-1 inhibitor as first-line treatment for metastatic gastric/gastro-esophageal junction (G/GEJ) adenocarcinoma from a phase Ib/II study. *J Clin Oncol*. 2025;43(4_suppl):454. doi:10.1200/JCO.2025.43.4_suppl.454
55. Ruan DY, Liu FR, Wei XL, et al. Claudin 18.2-targeting antibody-drug conjugate CMG901 in patients with advanced gastric or gastro-oesophageal junction cancer (KYM901): a multicentre, open-label, single-arm, phase 1 trial. *Lancet Oncol*. 2025;26(2):227–238. doi:10.1016/S1470-2045(24)00636-3
56. Liu J, Yang J, Sun Y, et al. CLDN18.2-targeting antibody-drug conjugate IBI343 in advanced gastric or gastroesophageal junction adenocarcinoma: a phase 1 trial. *Nat Med*. 2025;31(9):3028–3036. doi:10.1038/s41591-025-03783-8
57. Qi C, Liu C, Peng Z, et al. Claudin-18 isoform 2-specific CAR T-cell therapy (satri-cel) versus treatment of physician's choice for previously treated advanced gastric or gastro-oesophageal junction cancer (CT041-ST-01): a randomised, open-label, phase 2 trial. *Lancet*. 2025;405(10494):2049–2060. doi:10.1016/S0140-6736(25)00860-8
58. Wainberg ZA, Enzinger PC, Kang YK, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Oncol*. 2022;23(11):1430–1440. doi:10.1016/S1470-2045(22)00603-9
59. Wainberg ZA, Kang YK, Lee KW, et al. Bemarituzumab as first-line treatment for locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma: final analysis of the randomized phase 2 FIGHT trial. *Gastric Cancer*. 2024;27(3):558–570. doi:10.1007/s10120-024-01466-w
60. Amgen announces positive topline phase 3 results for bemarituzumab in fibroblast growth factor receptor 2b (FGFR2b) positive first-line gastric cancer; 2025.
61. Rodon J, Wainberg ZA, Zhang M, et al. Abstract CT038: preliminary efficacy and safety results of anti-TROP2 ADC SKB264 (MK-2870) in patients (pts) with previously treated advanced gastric (G) or gastroesophageal junction (GEJ) cancer from a phase 2 study. *Cancer Res*. 2024;84(7_Supplement):CT038. doi:10.1158/1538-7445.Am2024-ct038
62. Luo H, Lu J, Bai Y, et al. Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: the ESCORT-1st randomized clinical trial. *JAMA*. 2021;326(10):916–925. doi:10.1001/jama.2021.12836
63. Wang ZX, Cui C, Yao J, et al. Toripalimab plus chemotherapy in treatment-naive, advanced esophageal squamous cell carcinoma (Jupiter-06): a multi-center phase 3 trial. *Cancer Cell*. 2022;40(3):277–288e3. doi:10.1016/j.ccell.2022.02.007
64. Lu Z, Wang J, Shu Y, et al. Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double blind, phase 3 trial. *BMJ*. 2022;377:e068714. doi:10.1136/bmj-2021-068714
65. Li J, Chen Z, Bai Y, et al. First-line sugemalimab with chemotherapy for advanced esophageal squamous cell carcinoma: a randomized phase 3 study. *Nat Med*. 2024;30(3):740–748. doi:10.1038/s41591-024-02797-y
66. Ma Y, Yang Y, Huang Y, et al. A B7H3-targeting antibody-drug conjugate in advanced solid tumors: a phase 1/1b trial. *Nat Med*. 2025;31(6):1949–1957. doi:10.1038/s41591-025-03600-2
67. Shen L, Zhang Y, Li Z, et al. First-line cadonilimab plus chemotherapy in HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma: a randomized, double-blind, phase 3 trial. *Nat Med*. 2025;31(4):1163–1170. doi:10.1038/s41591-024-03450-4
68. Hegewisch-Becker S, Mendez G, Chao J, et al. First-line nivolumab and relatlimab plus chemotherapy for gastric or gastroesophageal junction adenocarcinoma: the phase II RELATIVITY-060 study. *J Clin Oncol*. 2024;42(17):2080–2093. doi:10.1200/JCO.23.01636

69. Kelly RJ, Landon BV, Zaidi AH, et al. Neoadjuvant nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable esophageal/gastroesophageal junction cancer: a phase Ib trial and ctDNA analyses. *Nat Med*. 2024;30(4):1023–1034. doi:10.1038/s41591-024-02877-z
70. Rha SY, Miller WH, MJd M, et al. Phase 1 trial of the anti-LAG3 antibody favezelimab plus pembrolizumab in advanced gastric cancer. *J Clin Oncol*. 2023;41(4_suppl):394. doi:10.1200/JCO.2023.41.4_suppl.394
71. Rivera Herrero F, Oh DY, Shitara K, et al. 1422P first-line rilvegostomig (rilve) + chemotherapy (CTx) in patients (pts) with HER2-negative (HER2−) locally advanced unresectable or metastatic gastric cancers: first report of GEMINI-gastric sub study 2. *Ann Oncol*. 2024;35:S887. doi:10.1016/j.annonc.2024.08.1488
72. Janjigian YY, Oh D-Y, Pelster M, et al. EDGE-gastric arm A1: phase 2 study of domvanalimab, zimberelimab, and FOLFOX in first-line (1L) advanced gastroesophageal cancer. *J Clin Oncol*. 2023;41(36_suppl):433248. doi:10.1200/JCO.2023.41.36_suppl.433248
73. Klempner SJ, Sonbol MB, Wainberg ZA, et al. DKN-01 in combination with tislelizumab and chemotherapy as first-line therapy in advanced gastric or gastroesophageal junction adenocarcinoma: DisTinGuish. *J Clin Oncol*. 2025;43(3):339–349. doi:10.1200/JCO.24.00410
74. Park H, Iglesia M, Pedersen KS, et al. Phase I trial of CA-4948, an IRAK4 inhibitor, in combination with FOLFOX/PD-1 inhibitor ± trastuzumab for untreated unresectable gastric and esophageal cancer. *J Clin Oncol*. 2022;40(16_suppl):TPS4168–TPS4168. doi:10.1200/JCO.2022.40.16_suppl.TPS4168
75. Bartley AN, Washington MK, Colasacco C, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. *J Clin Oncol*. 2017;35(4):446–464. doi:10.1200/JCO.2016.69.4836
76. Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer*. 2015;18(3):476–484. doi:10.1007/s10120-014-0402-y
77. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376(9742):687–697. doi:10.1016/S0140-6736(10)61121-X
78. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382(25):2419–2430. doi:10.1056/NEJMoa2004413
79. Van Cutsem E, Di Bartolomeo M, Smyth E, et al. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study. *Lancet Oncol*. 2023;24(7):744–756. doi:10.1016/S1470-2045(23)00215-2
80. Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. *ESMO Open*. 2022;7(4):100554. doi:10.1016/j.esmoop.2022.100554
81. Patsoukis N, Wang Q, Strauss L, Boussiotis VA. Revisiting the PD-1 pathway. *Sci Adv*. 2020;6(38). doi:10.1126/sciadv.abd2712
82. Yoon HH, Jin Z, Kour O, et al. Association of PD-L1 expression and other variables with benefit from immune checkpoint inhibition in advanced gastroesophageal cancer: systematic review and meta-analysis of 17 phase 3 randomized clinical trials. *JAMA Oncol*. 2022;8(10):1456–1465. doi:10.1001/jamaoncol.2022.3707
83. Ahn S, Kim KM. PD-L1 expression in gastric cancer: interchangeability of 22C3 and 28-8 pharmDx assays for responses to immunotherapy. *Mod Pathol*. 2021;34(9):1719–1727. doi:10.1038/s41379-021-00823-9
84. Kulangara K, Zhang N, Corigliano E, et al. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. *Arch Pathol Lab Med*. 2019;143(3):330–337. doi:10.5858/arpa.2018-0043-OA
85. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27–40. doi:10.1016/S0140-6736(21)00797-2
86. Shitara K, Ajani JA, Moehler M, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. *Nature*. 2022;603(7903):942–948. doi:10.1038/s41586-022-04508-4
87. Xu J, Kato K, Hubner R, et al. First-line tislelizumab plus chemotherapy for esophageal squamous cell carcinoma with programmed death-ligand 1 expression >/= 1%: a retrospective analysis of RATIONALE-306. *Adv Ther*. 2025;42(5):2269–2284. doi:10.1007/s12325-025-03115-9
88. Formica V, Morelli C, Fornaro L, et al. PD-L1 thresholds predict efficacy of immune checkpoint inhibition in first-line treatment of advanced gastroesophageal adenocarcinoma. A systematic review and meta-analysis of seven phase III randomized trials. *ESMO Open*. 2024;9(11):103967. doi:10.1016/j.esmoop.2024.103967
89. Zhao JJ, Yap DWT, Chan YH, et al. Low programmed death-ligand 1-expressing subgroup outcomes of first-line immune checkpoint inhibitors in gastric or esophageal adenocarcinoma. *J Clin Oncol*. 2022;40(4):392–402. doi:10.1200/JCO.21.01862
90. Mitnacht-Kraus R, Kreuzberg M, Utsch M, Sahin U, Türeci Ö. 378P - Preclinical characterization of IMAB362 for the treatment of gastric carcinoma. *Ann Oncol*. 2017;28:v126. doi:doi:10.1093/annonc/mdx367.012
91. Fassan M, Kuwata T, Matkowskyj KA, Rocken C, Ruschoff J. Claudin-18.2 immunohistochemical evaluation in gastric and gastroesophageal junction adenocarcinomas to direct targeted therapy: a practical approach. *Mod Pathol*. 2024;37(11):100589. doi:10.1016/j.modpat.2024.100589
92. Shitara K, Pophale R, Matsangou M, et al. Management of nausea and vomiting (N/V) following first-line (1L) zolbetuximab + chemotherapy treatment in claudin-18.2 (CLDN18.2)+, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: analysis from the phase 3 SPOTLIGHT and GLOW studies. *J Clin Oncol*. 2024;42(3_suppl):372. doi:10.1200/JCO.2024.42.3_suppl.372
93. Jiricny J. The multifaceted mismatch-repair system. *Nat Rev Mol Cell Biol*. 2006;7(5):335–346. doi:10.1038/nrm1907
94. Li GM. Mechanisms and functions of DNA mismatch repair. *Cell Res*. 2008;18(1):85–98. doi:10.1038/cr.2007.115
95. van Velzen MJM, Derks S, van Grieken NCT, Haj Mohammad N, van Laarhoven HWM. MSI as a predictive factor for treatment outcome of gastroesophageal adenocarcinoma. *Cancer Treat Rev*. 2020;86:102024. doi:10.1016/j.ctrv.2020.102024
96. de la Fouchardiere C, Cammarota A, Svrcek M, et al. How do I treat dMMR/MSI gastro-oesophageal adenocarcinoma in 2025? A position paper from the EORTC-GITCG gastro-esophageal task force. *Cancer Treat Rev*. 2025;134:102890. doi:10.1016/j.ctrv.2025.102890
97. Yoon HH, Bendell JC, Braiteh FS, et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. *Ann Oncol*. 2016;27(12):2196–2203. doi:10.1093/annonc/mdw423

98. Fuchs CS, Shitara K, Di Bartolomeo M, et al. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20 (3):420–435. doi:10.1016/S1470-2045(18)30791-5
99. Fuchs CS, Tabernero J, Tomasek J, et al. Biomarker analyses in REGARD gastric/GEJ carcinoma patients treated with VEGFR2-targeted antibody ramucirumab. *Br J Cancer*. 2016;115(8):974–982. doi:10.1038/bjc.2016.293
100. Van Cutsem E, Muro K, Cunningham D, et al. Biomarker analyses of second-line ramucirumab in patients with advanced gastric cancer from RAINBOW, a global, randomized, double-blind, phase 3 study. *Eur J Cancer*. 2020;127:150–157. doi:10.1016/j.ejca.2019.10.026
101. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366 (22):2074–2084. doi:10.1056/NEJMoa1112088
102. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948–1957. doi:10.1016/S0140-6736(18)32557-1
103. Hoeppner J, Brunner T, Schmoor C, et al. Perioperative chemotherapy or preoperative chemoradiotherapy in esophageal cancer. *N Engl J Med*. 2025;392(4):323–335. doi:10.1056/NEJMoa2409408
104. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *N Engl J Med*. 2021;384 (13):1191–1203. doi:10.1056/NEJMoa2032125
105. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): first results of overall survival (OS) from CheckMate 577. *J Clin Oncol*. 2025;43(16_suppl):4000. doi:10.1200/JCO.2025.43.16_suppl.4000
106. Shitara K, Rha SY, Wyrwicz LS, et al. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study. *Lancet Oncol*. 2024;25 (2):212–224. doi:10.1016/S1470-2045(23)00541-7
107. Shitara K, Rha SY, Wyrwicz L, et al. Pembrolizumab plus chemotherapy versus chemotherapy as perioperative therapy in locally advanced gastric and gastroesophageal junction cancer: final analysis of the randomized, phase III KEYNOTE-585 study. *J Clin Oncol*. 2025: JCO2500486. doi:10.1200/JCO-25-00486
108. Kang YK, Terashima M, Kim YW, et al. Adjuvant nivolumab plus chemotherapy versus placebo plus chemotherapy for stage III gastric or gastro-oesophageal junction cancer after gastrectomy with D2 or more extensive lymph-node dissection (ATTRACTION-5): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2024;9(8):705–717. doi:10.1016/S2468-1253(24)00156-0
109. Park H, Jin RU, Wang-Gillam A, et al. FOLFIRINOX for the treatment of advanced gastroesophageal cancers: a phase 2 nonrandomized clinical trial. *JAMA Oncol*. 2020;6(8):1231–1240. doi:10.1001/jamaoncol.2020.2020
110. Weisser NE, Sanches M, Escobar-Cabrera E, et al. An anti-HER2 biparatopic antibody that induces unique HER2 clustering and complement-dependent cytotoxicity. *Nat Commun*. 2023;14(1):1394. doi:10.1038/s41467-023-37029-3
111. Wei H, Cai H, Jin Y, et al. Structural basis of a novel heterodimeric Fc for bispecific antibody production. *Oncotarget*. 2017;8(31):51037–51049. doi:10.18632/oncotarget.17558
112. Zhu X, Ding Y, Wang Q, Yang G, Zhou L, Wang Q. HLX22, an anti-HER-2 monoclonal antibody, in patients with advanced solid tumors overexpressing human epidermal growth factor receptor 2: an open-label, dose-escalation, phase 1 trial. *Invest New Drugs*. 2023;41(3):473–482. doi:10.1007/s10637-023-01338-7
113. Ajani JA, Kato K, Yang F, Wang Q, Shen L. A randomized, double-blinded, international phase III trial comparing HLX22 in combination with trastuzumab and chemotherapy versus trastuzumab and chemotherapy with or without pembrolizumab for first-line treatment for HER2-positive locally advanced or metastatic G/GEJ cancer. *J Clin Oncol*. 2025;43(16_suppl):TPS4206. doi:10.1200/JCO.2025.43.16_suppl.TPS4206
114. Nakayama I, Takahari D, Chin K, et al. Incidence, clinicopathological features, and clinical outcomes of low HER2 expressed, inoperable, advanced, or recurrent gastric/gastroesophageal junction adenocarcinoma. *ESMO Open*. 2023;8(4):101582. doi:10.1016/j.esmoop.2023.101582
115. Li H, Yu C, Jiang J, et al. An anti-HER2 antibody conjugated with monomethyl auristatin E is highly effective in HER2-positive human gastric cancer. *Cancer Biol Ther*. 2016;17(4):346–354. doi:10.1080/15384047.2016.1139248
116. Zhang Y, Qiu MZ, Wang JF, et al. Phase 1 multicenter, dose-expansion study of ARX788 as monotherapy in HER2-positive advanced gastric and gastroesophageal junction adenocarcinoma. *Cell Rep Med*. 2022;3(11):100814. doi:10.1016/j.xcrm.2022.100814
117. Song Y, Tong C, Wang Y, et al. Effective and persistent antitumor activity of HER2-directed CAR-T cells against gastric cancer cells in vitro and xenotransplanted tumors in vivo. *Protein Cell*. 2018;9(10):867–878. doi:10.1007/s13238-017-0384-8
118. Feng K, Liu Y, Guo Y, et al. Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. *Protein Cell*. 2018;9(10):838–847. doi:10.1007/s13238-017-0440-4
119. Nakayama I, Qi C, Chen Y, Nakamura Y, Shen L, Shitara K. Claudin 18.2 as a novel therapeutic target. *Nat Rev Clin Oncol*. 2024;21(5):354–369. doi:10.1038/s41571-024-00874-2
120. Jiang H, Shi Z, Wang P, et al. Claudin18.2-specific chimeric antigen receptor engineered T cells for the treatment of gastric cancer. *J Natl Cancer Inst*. 2019;111(4):409–418. doi:10.1093/jnci/djy134
121. Katoh M. Fibroblast growth factor receptors as treatment targets in clinical oncology. *Nat Rev Clin Oncol*. 2019;16(2):105–122. doi:10.1038/s41571-018-0115-y
122. Su X, Zhan P, Gavine PR, et al. FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study. *Br J Cancer*. 2014;110(4):967–975. doi:10.1038/bjc.2013.802
123. Sato S, Rhodes SL, Aoki Y, et al. Clinical characterization of FGFR2b expression in patients with advanced gastric or gastroesophageal junction adenocarcinoma. *ESMO Open*. 2025;10(7):105322. doi:10.1016/j.esmoop.2025.105322
124. Ahn S, Lee J, Hong M, et al. FGFR2 in gastric cancer: protein overexpression predicts gene amplification and high H-index predicts poor survival. *Mod Pathol*. 2016;29(9):1095–1103. doi:10.1038/modpathol.2016.96
125. Muhlmann G, Spizzo G, Gostner J, et al. TROP2 expression as prognostic marker for gastric carcinoma. *J Clin Pathol*. 2009;62(2):152–158. doi:10.1136/jcp.2008.060590
126. Zhao W, Zhu H, Zhang S, et al. Trop2 is overexpressed in gastric cancer and predicts poor prognosis. *Oncotarget*. 2016;7(5):6136–6145. doi:10.18632/oncotarget.6733

127. Hoppe S, Meder L, Gebauer F, et al. Trophoblast cell surface antigen 2 (TROP2) as a predictive bio-marker for the therapeutic efficacy of sacituzumab govitecan in adenocarcinoma of the esophagus. *Cancers*. 2022;14(19). doi:10.3390/cancers14194789
128. Yao Z, Wei G, Song P, et al. Trop2, Nectin-4, and PD-L1 expression profiles in esophageal squamous cell carcinoma: implications for combined immunotherapy and ADC targeted therapies. *Pathol Res Pract*. 2025;271:156032. doi:10.1016/j.prp.2025.156032
129. Cheng Y, Yuan X, Tian Q, et al. Preclinical profiles of SKB264, a novel anti-TROP2 antibody conjugated to topoisomerase inhibitor, demonstrated promising antitumor efficacy compared to IMMU-132. *Front Oncol*. 2022;12:951589. doi:10.3389/fonc.2022.951589
130. Kontos F, Michelakos T, Kurokawa T, et al. B7-H3: an attractive target for antibody-based immunotherapy. *Clin Cancer Res*. 2021;27(5):1227–1235. doi:10.1158/1078-0432.CCR-20-2584
131. Maruki Y, Takashima A, Miyamoto T, et al. Expression of B7-H3 (CD276) in surgically resected esophageal squamous cell carcinoma. *J Clin Oncol*. 2018;36(4_suppl):70. doi:10.1200/JCO.2018.36.4_suppl.70
132. Xiong G, Chen Z, Liu Q, et al. CD276 regulates the immune escape of esophageal squamous cell carcinoma through CXCL1-CXCR2 induced NETs. *J Immunother Cancer*. 2024;12(5). doi:10.1136/jitc-2023-008662
133. Xu J, Zong Q, Wang W, Liu Q, Stann S, Cai J. Abstract 6304: preclinical development of a next generation antibody drug conjugate (ADC) targeting B7-H3 for treatment of solid tumors. *Cancer Res*. 2023;83(7_Supplement):6304. doi:10.1158/1538-7445.Am2023-6304
134. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol*. 2016;39(1):98–106. doi:10.1097/COC.0000000000000239
135. Pang X, Huang Z, Zhong T, et al. Cadonilimab, a tetravalent PD-1/CTLA-4 bispecific antibody with trans-binding and enhanced target binding avidity. *MAbs*. 2023;15(1):2180794. doi:10.1080/19420862.2023.2180794
136. Aggarwal V, Workman CJ, Vignali DAA. LAG-3 as the third checkpoint inhibitor. *Nat Immunol*. 2023;24(9):1415–1422. doi:10.1038/s41590-023-01569-z
137. Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res*. 2012;72(4):917–927. doi:10.1158/0008-5472.CAN-11-1620
138. Ulase D, Behrens HM, Kruger S, et al. LAG3 in gastric cancer: it's complicated. *J Cancer Res Clin Oncol*. 2023;149(12):10797–10811. doi:10.1007/s00432-023-04954-1
139. Harjunpaa H, Guillerey C. TIGIT as an emerging immune checkpoint. *Clin Exp Immunol*. 2020;200(2):108–119. doi:10.1111/cei.13407
140. Rohrberg KS, Brandão M, Alvarez EC, et al. Safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of AZD2936, a bispecific antibody targeting PD-1 and TIGIT, in checkpoint inhibitor (CPI)-experienced advanced/metastatic non-small-cell lung cancer (NSCLC): first report of ARTEMIDE-01. *J Clin Oncol*. 2023;41(16_suppl):9050. doi:10.1200/JCO.2023.41.16_suppl.9050
141. Rha SY, Oh DY, Pelster M, et al. 130MO EDGE-gastric Arm A1: phase II study of domvanalimab (D), zimberelimab (Z), and FOLFOX in first-line (1L) advanced gastroesophageal (GE) cancer. *Ann Oncol*. 2024;35:S1455. doi:10.1016/j.annonc.2024.10.156
142. Klempner SJ, Shitara K, Sison A, et al. STAR-221: a randomized, open-label, multicenter, phase 3 trial of domvanalimab, zimberelimab, and chemotherapy versus nivolumab and chemotherapy in previously untreated, locally advanced, unresectable or metastatic gastric, gastroesophageal junction, and esophageal adenocarcinoma. *J Clin Oncol*. 2023;41(16_suppl):TPS4206. doi:10.1200/JCO.2023.41.16_suppl.TPS4206
143. Wang Z, Lin L, Thomas DG, et al. The role of Dickkopf-3 overexpression in esophageal adenocarcinoma. *J Thorac Cardiovasc Surg*. 2015;150(2):377–385e2. doi:10.1016/j.jtcvs.2015.05.006
144. Hong SA, Yoo SH, Lee HH, et al. Prognostic value of Dickkopf-1 and ss-catenin expression in advanced gastric cancer. *BMC Cancer*. 2018;18(1):506. doi:10.1186/s12885-018-4420-8
145. Shi T, Zhang Y, Wang Y, et al. DKK1 promotes tumor immune evasion and impedes anti-PD-1 treatment by inducing immunosuppressive macrophages in gastric cancer. *Cancer Immunol Res*. 2022;10(12):1506–1524. doi:10.1158/2326-6066.CIR-22-0218
146. Zhang D, Li L, Jiang H, et al. Constitutive IRAK4 activation underlies poor prognosis and chemoresistance in pancreatic ductal adenocarcinoma. *Clin Cancer Res*. 2017;23(7):1748–1759. doi:10.1158/1078-0432.CCR-16-1121
147. Li Q, Chen Y, Zhang D, et al. IRAK4 mediates colitis-induced tumorigenesis and chemoresistance in colorectal cancer. *JCI Insight*. 2019;4(19). doi:10.1172/jci.insight.130867
148. Somani VK, Zhang D, Dodhiawala PB, et al. IRAK4 signaling drives resistance to checkpoint immunotherapy in pancreatic ductal adenocarcinoma. *Gastroenterology*. 2022;162(7):2047–2062. doi:10.1053/j.gastro.2022.02.035
149. Gummadi VR, Boruah A, Ainan BR, et al. Discovery of CA-4948, an orally bioavailable IRAK4 inhibitor for treatment of hematologic malignancies. *ACS Med Chem Lett*. 2020;11(12):2374–2381. doi:10.1021/acsmedchemlett.0c00255
150. Pectasides E, Stachler MD, Derks S, et al. Genomic heterogeneity as a barrier to precision medicine in gastroesophageal adenocarcinoma. *Cancer Discov*. 2018;8(1):37–48. doi:10.1158/2159-8290.CD-17-0395
151. He WZ, Yang YZ, Yin CX, et al. Evolution of HER2-low expression from primary to paired metastatic gastric cancer lesions. *NPJ Precis Oncol*. 2025;9(1):108. doi:10.1038/s41698-025-00881-1
152. Zhou KI, Peterson B, Serritella A, et al. Spatial and temporal heterogeneity of PD-L1 expression and tumor mutational burden in gastroesophageal adenocarcinoma at baseline diagnosis and after chemotherapy. *Clin Cancer Res*. 2020;26(24):6453–6463. doi:10.1158/1078-0432.CCR-20-2085
153. Li Y, Dou Y, Da Veiga Leprevost F, et al. Proteogenomic data and resources for pan-cancer analysis. *Cancer Cell*. 2023;41(8):1397–1406. doi:10.1016/j.ccell.2023.06.009
154. Wang Y, Jin RU, Xu J, et al. Harnessing technologies to unravel gastric cancer heterogeneity. *Trends Cancer*. 2025. doi:10.1016/j.trecan.2025.04.011
155. Siddaway R, Glembocki AI, Arnoldo A, et al. Clinical utility of targeted RNA sequencing in cancer molecular diagnostics. *Nat Med*. 2025. doi:10.1038/s41591-025-03848-8
156. Alese OB, Cook N, Ortega-Franco A, Ulanja MB, Tan L, Tie J. Circulating tumor DNA: an emerging tool in gastrointestinal cancers. *Am Soc Clin Oncol Educ Book*. 2022;42:1–20. doi:10.1200/EDBK_349143
157. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*. 2018;359(6378):926–930. doi:10.1126/science.aar3247
158. Huffman BM, Aushev VN, Budde GL, et al. Analysis of circulating tumor DNA to predict risk of recurrence in patients with esophageal and gastric cancers. *JCO Precis Oncol*. 2022;6:e2200420. doi:10.1200/PO.22.00420

159. Lander EM, Aushev VN, Huffman BM, et al. Circulating Tumor DNA as a Prognostic Biomarker for Recurrence in Patients With Locoregional Esophagogastric Cancers With a Pathologic Complete Response. *JCO Precis Oncol*. 2024:8:e2400288. doi:10.1200/PO.24.00288
160. Kato S, Okamura R, Baumgartner JM, et al. Analysis of circulating tumor DNA and clinical correlates in patients with esophageal, gastroesophageal junction, and gastric adenocarcinoma. *Clin Cancer Res*. 2018;24(24):6248–6256. doi:10.1158/1078-0432.CCR-18-1128
161. Jogo T, Nakamura Y, Shitara K, et al. Circulating tumor DNA analysis detects FGFR2 amplification and concurrent genomic alterations associated with FGFR inhibitor efficacy in advanced gastric cancer. *Clin Cancer Res*. 2021;27(20):5619–5627. doi:10.1158/1078-0432.CCR-21-1414
162. Kim ST, Cristescu R, Bass AJ, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med*. 2018;24(9):1449–1458. doi:10.1038/s41591-018-0101-z
163. Catenacci DVT, Moya S, Lomnicki S, et al. Personalized Antibodies for Gastroesophageal Adenocarcinoma (PANGEA): a phase II study evaluating an individualized treatment strategy for metastatic disease. *Cancer Discov*. 2021;11(2):308–325. doi:10.1158/2159-8290.CD-20-1408
164. Lee J, Kim ST, Kim K, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: the VIKTORY umbrella trial. *Cancer Discov*. 2019;9(10):1388–1405. doi:10.1158/2159-8290.CD-19-0442
165. Kandimalla R, Xu J, Link A, et al. EpiPanGI Dx: a cell-free DNA methylation fingerprint for the early detection of gastrointestinal cancers. *Clin Cancer Res*. 2021;27(22):6135–6144. doi:10.1158/1078-0432.CCR-21-1982
166. Jby S, Kapoor R, Zhu F, et al. Development and validation of a serum microRNA biomarker panel for detecting gastric cancer in a high-risk population. *Gut*. 2021;70(5):829–837. doi:10.1136/gutjnl-2020-322065
167. Luca BA, Steen CB, Matusiak M, et al. Atlas of clinically distinct cell states and ecosystems across human solid tumors. *Cell*. 2021;184 (21):5482–5496e28. doi:10.1016/j.cell.2021.09.014
168. Wang R, Song S, Qin J, et al. Evolution of immune and stromal cell states and ecotypes during gastric adenocarcinoma progression. *Cancer Cell*. 2023;41(8):1407–1426e9. doi:10.1016/j.ccell.2023.06.005
169. Kubota Y, Kawazoe A, Mishima S, et al. Comprehensive clinical and molecular characterization of claudin 18.2 expression in advanced gastric or gastroesophageal junction cancer. *ESMO Open*. 2023;8(1):100762. doi:10.1016/j.esmoop.2022.100762
170. Klempner SJ, Lee KW, Shitara K, et al. ILUSTRO: phase II multicohort trial of zolbetuximab in patients with advanced or metastatic claudin 18.2-positive gastric or gastroesophageal junction adenocarcinoma. *Clin Cancer Res*. 2023;29(19):3882–3891. doi:10.1158/1078-0432.CCR-23-0204
171. Redston M, Noffsinger A, Kim A, et al. Abnormal TP53 predicts risk of progression in patients with Barrett's esophagus regardless of a diagnosis of dysplasia. *Gastroenterology*. 2022;162(2):468–481. doi:10.1053/j.gastro.2021.10.038
172. Stachler MD, Camarda ND, Deitrick C, et al. Detection of mutations in Barrett's esophagus before progression to high-grade dysplasia or adenocarcinoma. *Gastroenterology*. 2018;155(1):156–167. doi:10.1053/j.gastro.2018.03.047
173. Chen XX, Zhong Q, Liu Y, et al. Genomic comparison of esophageal squamous cell carcinoma and its precursor lesions by multi-region whole-exome sequencing. *Nat Commun*. 2017;8(1):524. doi:10.1038/s41467-017-00650-0
174. Shah PA, Wiman KG, Cichowski K, Rodon Ahnert J. Capturing unicorns: targeting cancers with TP53 mutations, RAS alterations beyond G12C, and MTAP loss-no target is out of the realm of possibility. *Am Soc Clin Oncol Educ Book*. 2025;45(3):e473616. doi:10.1200/EDBK-25-473616
175. Cluzeau T, Sebert M, Rahme R, et al. Eprenetapopt plus azacitidine in TP53-mutated myelodysplastic syndromes and acute myeloid leukemia: a phase II study by the Groupe Francophone des Myelodysplasies (GFM). *J Clin Oncol*. 2021;39(14):1575–1583. doi:10.1200/JCO.20.02342
176. Puzio-Kuter AM, Xu L, McBrayer MK, et al. Restoration of the tumor suppressor function of Y220C-mutant p53 by rezatapopt, a small-molecule reactivator. *Cancer Discov*. 2025;15(6):1159–1179. doi:10.1158/2159-8290.CD-24-1421
177. Crawford DK, Alroy I, Sharpe N, Goddeeris MM, Williams G. ELX-02 generates protein via premature stop codon read-through without inducing native stop codon read-through proteins. *J Pharmacol Exp Ther*. 2020;374(2):264–272. doi:10.1124/jpet.120.265595
178. Yamada M, Tazawa H, Suemori K, et al. Oncolytic virus-mediated p53 activation boosts the antitumor immunity of a p53-transduced dendritic cell vaccine. *NPJ Vaccines*. 2025;10(1):158. doi:10.1038/s41541-025-01219-5
179. Schram AM, Shapiro GI, Johnson ML, et al. Abstract LB_A25: updated phase 1 results from the PYNNACLE phase 1/2 study of PC14586, a selective p53 reactivator, in patients with advanced solid tumors harboring a TP53 Y220C mutation. *Mol Cancer Therap*. 2023;22 (12_Supplement):LB_A25. doi:10.1158/1535-7163.Targ-23-lb_a25
180. Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. *Nat Med*. 2024;30(4):969–983. doi:10.1038/s41591-024-02903-0
181. Li T, Kikuchi O, Zhou J, et al. Developing SHP2-based combination therapy for KRAS-amplified cancer. *JCI Insight*. 2023;8(3). doi:10.1172/jci.insight.152714
182. Wang L, Saeedi BJ, Mahdi Z, Krasinskas A, Robinson B. Analysis of KRAS mutations in gastrointestinal tract adenocarcinomas reveals site-specific mutational signatures. *Mod Pathol*. 2023;36(2):100014. doi:10.1016/j.modpat.2022.100014
183. Wong GS, Zhou J, Liu JB, et al. Targeting wild-type KRAS-amplified gastroesophageal cancer through combined MEK and SHP2 inhibition. *Nat Med*. 2018;24(7):968–977. doi:10.1038/s41591-018-0022-x
184. Tedeschi A, Peng DH, Schischlik F, et al. Abstract 3317: KRASmulti inhibitor BI 3706674 shows efficacy in KRAS-driven preclinical models of cancer that supports clinical testing in patients with tumors harbouring KRASG12V mutations and KRAS wild-type amplifications. *Cancer Research*. 2024;84(6_Supplement):3317. doi:10.1158/1538-7445.AM2024-3317
185. Rutherford KA, McManus KJ. PROTACs: current and future potential as a precision medicine strategy to combat cancer. *Mol Cancer Ther*. 2024;23(4):454–463. doi:10.1158/1535-7163.MCT-23-0747
186. Chen Y, Yang Q, Xu J, et al. PROTACs in gastrointestinal cancers. *Mol Ther Oncolytics*. 2022;27:204–223. doi:10.1016/j.omto.2022.10.012
187. Zhong G, Chang X, Xie W, Zhou X. Targeted protein degradation: advances in drug discovery and clinical practice. *Signal Transduct Target Ther*. 2024;9(1):308. doi:10.1038/s41392-024-02004-x
188. Feng Z, Wang S, Yu S, Qu C, Chu B, Qian Z. Synthesis and identification of a selective FGFR2 degrader with potent antiproliferative effects in gastric cancer. *Eur J Med Chem*. 2024;277:116780. doi:10.1016/j.ejmech.2024.116780
189. Wang XR, Wang S, Mu HX, et al. Discovery of novel VEGFR-2-PROTAC degraders based on the localization of lysine residues via recruiting VHL for the treatment of gastric cancer. *Eur J Med Chem*. 2022;244:114821. doi:10.1016/j.ejmech.2022.114821
190. Rao D, Wang Y, Yang X, et al. Discovery of a first-in-class PROTAC degrader of histone lysine demethylase KDM4. *Eur J Med Chem*. 2025;288:117410. doi:10.1016/j.ejmech.2025.117410
191. Das KK, Brown JW. 3'-sulfated Lewis(A/C): an oncofetal epitope associated with metaplastic and oncogenic plasticity of the gastrointestinal foregut. *Front Cell Dev Biol*. 2023;11:1089028. doi:10.3389/fcell.2023.1089028

192. Xu N, Wu Z, Pan J, Xu X, Wei Q. CAR-T cell therapy: advances in digestive system malignant tumors. *Mol Ther Oncol*. 2024;32(4):200872. doi:10.1016/j.omton.2024.200872
193. Engle DD, Tiriac H, Rivera KD, et al. The glycan CA19-9 promotes pancreatitis and pancreatic cancer in mice. *Science*. 2019;364(6446):1156–1162. doi:10.1126/science.aaw3145
194. Arai J, Hayakawa Y, Tateno H, et al. Impaired glycosylation of gastric mucins drives gastric tumorigenesis and serves as a novel therapeutic target. *Gastroenterology*. 2024;167(3):505–521e19. doi:10.1053/j.gastro.2024.03.037
195. Ren X, Lin S, Guan F, Kang H. Glycosylation targeting: a paradigm shift in cancer immunotherapy. *Int J Biol Sci*. 2024;20(7):2607–2621. doi:10.7150/ijbs.93806
196. Al-Rawi DH, Lettera E, Li J, DiBona M, Bakhoum SF. Targeting chromosomal instability in patients with cancer. *Nat Rev Clin Oncol*. 2024;21(9):645–659. doi:10.1038/s41571-024-00923-w
197. Cohen-Sharir Y, McFarland JM, Abdusamad M, et al. Aneuploidy renders cancer cells vulnerable to mitotic checkpoint inhibition. *Nature*. 2021;590(7846):486–491. doi:10.1038/s41586-020-03114-6
198. Marquis C, Fonseca CL, Queen KA, et al. Chromosomally unstable tumor cells specifically require KIF18A for proliferation. *Nat Commun*. 2021;12(1):1213. doi:10.1038/s41467-021-21447-2
199. Dumbrava EE, Mathews CA, O'Neil B, et al. Preliminary results from a first-in-human, phase I/II study of VLS-1488, an oral KIF18A inhibitor, in patients with advanced solid tumors. *J Clin Oncol*. 2025;43(16_suppl):3012. doi:10.1200/JCO.2025.43.16_suppl.3012
200. Li J, Hubisz MJ, Earlie EM, et al. Non-cell-autonomous cancer progression from chromosomal instability. *Nature*. 2023;620(7976):1080–1088. doi:10.1038/s41586-023-06464-z
201. Fares CM, Van Allen EM, Drake CG, Allison JP, Hu-Lieskovan S. Mechanisms of resistance to immune checkpoint blockade: why does checkpoint inhibitor immunotherapy not work for all patients? *Am Soc Clin Oncol Educ Book*. 2019;39:147–164. doi:10.1200/EDBK_240837
202. Sharma P, Hu-Lieskovan S, Wargo JA, Primary RA. Adaptive, and acquired resistance to cancer immunotherapy. *Cell*. 2017;168(4):707–723. doi:10.1016/j.cell.2017.01.017
203. Luo D, Zhou J, Ruan S, et al. Overcoming immunotherapy resistance in gastric cancer: insights into mechanisms and emerging strategies. *Cell Death Dis*. 2025;16(1):75. doi:10.1038/s41419-025-07385-7
204. Vernieri C, Milano M, Brambilla M, et al. Resistance mechanisms to anti-HER2 therapies in HER2-positive breast cancer: current knowledge, new research directions and therapeutic perspectives. *Crit Rev Oncol Hematol*. 2019;139:53–66. doi:10.1016/j.critrevonc.2019.05.001
205. Samson P, Lockhart AC. Biologic therapy in esophageal and gastric malignancies: current therapies and future directions. *J Gastrointest Oncol*. 2017;8(3):418–429. doi:10.21037/jgo.2016.11.13
206. Saleh K, Khoury R, Khalife N, et al. Mechanisms of action and resistance to anti-HER2 antibody-drug conjugates in breast cancer. *Cancer Drug Resist*. 2024;7:22. doi:10.20517/cdr.2024.06
207. Mosele F, Deluche E, Lusque A, et al. Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial. *Nat Med*. 2023;29(8):2110–2120. doi:10.1038/s41591-023-02478-2
208. Yamaguchi K, Ito M, Isobe T, et al. Impact of genomic alterations on efficacy of trastuzumab deruxtecan against human epidermal growth factor receptor-2-positive advanced gastric cancer. *JCO Precis Oncol*. 2024:8:e2300681. doi:10.1200/PO.23.00681
209. Sheng T, Sundar R, Srivastava S, et al. Spatial profiling of patient-matched HER2 positive gastric cancer reveals resistance mechanisms to trastuzumab and trastuzumab deruxtecan. *medRxiv*. 2024:2024.10.29.24316248. doi:10.1101/2024.10.29.24316248
210. Pourjamal N, Le Joncour V, Vereb G, et al. Abstract 1704: overcoming resistance in HER2-positive gastric and breast cancers: efficacy of disitamab vedotin in preclinical models resistant to trastuzumab emtansine and trastuzumab deruxtecan. *Cancer Research*. 2025;85(8_Supplement_1):1704. doi:10.1158/1538-7445.Am2025-1704
211. Mullard A. Dual-payload ADCs move into first oncology clinical trials. *Nat Rev Drug Discov*. 2025. doi:10.1038/d41573-025-00121-y
212. Yamamoto K, Nakayama I, Sakamoto N, et al. Temporal dynamics of CLDN18.2 expression following zolbetuximab treatment in advanced gastric cancer. *ESMO Gastrointest Oncol*. 2025;9. doi:10.1016/j.esmogo.2025.100206
213. Tojjari A, Idrissi YA, Saeed A. Emerging targets in gastric and pancreatic cancer: focus on claudin 18.2. *Cancer Lett*. 2024;611:217362. doi:10.1016/j.canlet.2024.217362
214. Curtius K, Rubenstein JH, Chak A, Inadomi JM. Computational modelling suggests that Barrett's oesophagus may be the precursor of all oesophageal adenocarcinomas. *Gut*. 2020. doi:10.1136/gutjnl-2020-321598
215. Wang GQ, Abnet CC, Shen Q, et al. Histological precursors of oesophageal squamous cell carcinoma: results from a 13 year prospective follow up study in a high risk population. *Gut*. 2005;54(2):187–192. doi:10.1136/gut.2004.046631
216. Rubenstein JH, Sawas T, Wani S, et al. AGA clinical practice guideline on endoscopic eradication therapy of Barrett's esophagus and related neoplasia. *Gastroenterology*. 2024;166(6):1020–1055. doi:10.1053/j.gastro.2024.03.019
217. Jankowski JAZ, de Caestecker J, Love SB, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. *Lancet*. 2018;392(10145):400–408. doi:10.1016/S0140-6736(18)31388-6
218. Moon CM, Kim SH, Lee SK, et al. Chronic tamoxifen use is associated with a decreased risk of intestinal metaplasia in human gastric epithelium. *Dig Dis Sci*. 2014;59(6):1244–1254. doi:10.1007/s10620-013-2994-1
219. Zhu H, Nittolo T, To S, et al. A novel co-culture system to validate results of a phase I trial testing new treatment for Barrett's esophagus. *J Clin Oncol*. 2025;43(16_suppl):e15099. doi:10.1200/JCO.2025.43.16_suppl.e15099
220. Yang Q, Yasuda T, Choi E, et al. MEK inhibitor reverses metaplasia and allows re-emergence of normal lineages in helicobacter pylori-infected gerbils. *Gastroenterology*. 2019;156(3):577–581e4. doi:10.1053/j.gastro.2018.10.049
221. Goldenring JR, Jang B, Gotoda T, et al. Safety and efficacy of MEK inhibitor treatment for gastric precancerous lesions. *Gastroenterology*. 2025. doi:10.1053/j.gastro.2025.05.023

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