Gastric cancer

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Gastric cancer remains a major health challenge worldwide, with nearly 1 million new cases annually contributing to more than 650 000 deaths. Epidemiologically, gastric cancer shows substantial geographical variation in incidence, with higher rates in Asia, South America, and eastern Europe, and a rapid increase in early-onset cases among people younger than 50 years. Key risk factors for gastric cancer include *Helicobacter pylori* infection, diet, obesity, smoking, and genetic predisposition. Early detection through comprehensive diagnostic procedures is crucial for optimising treatment outcomes. Standard treatment approaches for locally advanced gastric cancer include surgical resection, particularly D2 lymphadenectomy, complemented by chemotherapy and radiotherapy. There is increasing implementation of minimally invasive surgical techniques for operable disease and integration of immune checkpoint inhibitors and targeted therapies for advanced stages. Emerging therapies, such as novel targeted treatments and next-generation immunotherapies, show promise in improving survival and quality of life. Future directions in the management of gastric cancer focus on precision medicine, continued advancement in immunotherapy, novel early detection methods, and a multidisciplinary approach to care. These strategies aim to enhance the overall effectiveness of treatment and prognosis worldwide.

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Introduction

Gastric cancer remains a formidable global health challenge, characterised by diverse risk factors and causes, aggressive nature, and often late-stage diagnosis. This Seminar aims to provide an in-depth description and analysis of gastric cancer, from molecular mechanisms to the latest therapeutic strategies, highlighting emerging trends and promising avenues for improved patient care.

Epidemiology

Gastric cancer ranks as the fifth leading cancer for both mortality and morbidity, with almost 1 million new cases diagnosed annually, leading to more than 650 000 deaths worldwide (GLOBOCAN 2022 data).[1,2] The incidence of gastric cancer varies globally, with the highest rates in Asia, South America, and eastern Europe, and the disease is more prevalent in males than females (figure 1). First-generation immigrants from high-incidence regions continue to show an increased risk of gastric cancer even after migrating to low-incidence regions.[4] During the past century, the age-standardised incidence of gastric cancer has decreased, but the total number of cases has increased, potentially because of the ageing population in Asia.[5] Incidence varies by anatomical location and subtype. The incidence of stomach tumours related to diet and *Helicobacter pylori* has fallen over the past two decades, but the incidence of proximal tumours linked to obesity and sociodemographic factors is rising.[6]

The incidence of early-onset gastric cancer (ie, diagnosis in people younger than 50 years) is rising, particularly in those born between 1980 and 1994, in whom rates are double those in people born in the 1950s.[7] Early-onset gastric cancer was conventionally associated with hereditary syndromes such as hereditary diffuse gastric cancer and Lynch syndrome. However, these syndromes contribute to only 3% of all early-onset cases.[8] Most early-onset cases are sporadic, potentially related to behavioural, lifestyle, nutritional, microbial, and environmental factors.[8] Early-onset gastric cancer seems to have a distinct biology, occurring more commonly in females than males.[9] These tumours show more aggressive characteristics, such as undifferentiated tumours, a diffuse histology subtype, and signet ring cells, and have different genomic characteristics, leading to a poor prognosis.[10,11] Reduced clinical suspicion leading to late diagnosis and presentation at advanced stages, along with concerns about fertility preservation and psychosocial aspects, are some of the issues that can affect management of early-onset gastric cancer.

The prognosis of gastric cancer depends on cancer stage, treatment, biological characteristics, and patient-related factors such as nutrition and sex. Mismatch repair deficiency (dMMR) or microsatellite instability (MSI) have favourable prognostic value. Overall, mortality from gastric cancer has been decreasing over the past two decades, correlated with global sociodemographic improvements.[12]

Symptoms and diagnosis

Gastric cancer commonly presents with symptoms such as dyspepsia, poor appetite, weight loss, and abdominal

Search strategy and selection criteria

We searched PubMed for articles published in any language from Jan 1, 1950, to June 1, 2024. Additional studies were identified through a review of American Society of Clinical Oncology and European Society for Medical Oncology conference abstracts and proceedings from Jan 1, 2000, to March 1, 2025. Search terms were "gastric cancer", "gastroesophageal cancer", "gastroesophageal junction cancer", "stomach neoplasm", "epidemiology", "incidence", "symptoms", "diagnosis", "risk factors", "tumour microenvironment", "advanced gastric cancer", "metastatic gastric cancer", "classification", "heterogeneity", "subtypes", "surgery", "radiation therapy", "chemoradiation", "biomarkers", "nutrition", "supportive care", "targeted therapy", and "immunotherapy".

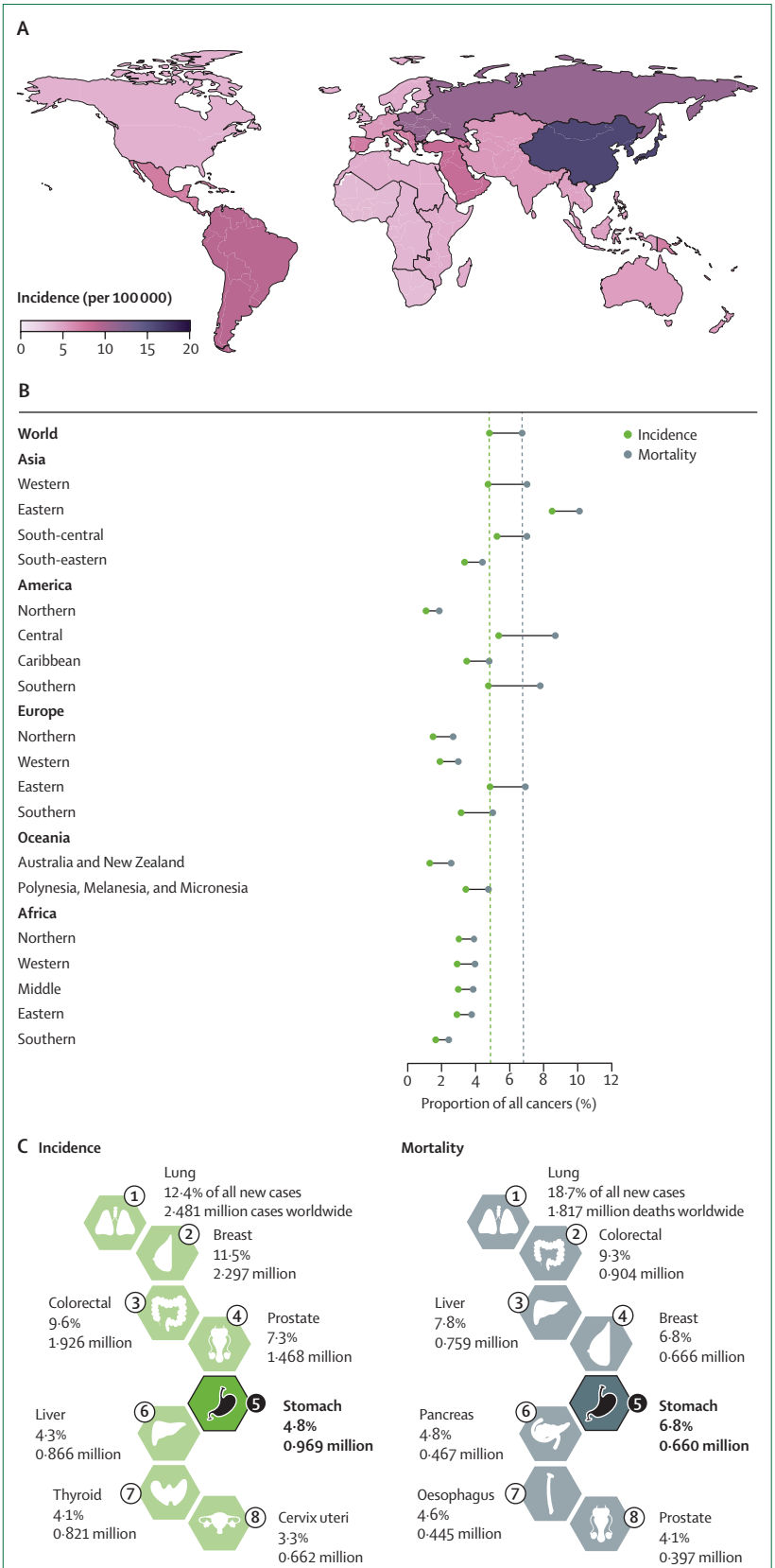

Figure 1: **Worldwide perspective on stomach cancer**
(A) Stomach cancer age-standardised incidence rate, in both sexes, grouped by UN region. Map created from data given in reference 2. (B) Stomach cancer incidence and mortality (age-standardised rates) as a percentage of all cancers, grouped by UN region (Polynesia, Melanesia, and Micronesia were combined). Dotted lines denote the world average for incidence (green) and mortality (grey). Created from data given in reference 2. (C) Ranking of most common cancers by incidence and mortality. Created from data given in reference 3.

pain. Dysphagia or regurgitation might occur in patients with proximal or gastro-oesophageal junction tumours.

Diagnosis involves endoscopic examination for tumour localisation and biopsy, followed by clinical staging to determine the treatment approach. CT is the gold standard to assess for metastatic disease. Data supporting routine use of staging PET-CT are controversial. PET helps in some cases, such as for detection of occult metastases when staging locally advanced tumours for curative intent therapy. Although [^{18}F]fluorodeoxyglucose-PET is not always useful in diffuse gastric cancer, novel tracers are emerging.[13,14] Endoscopic ultrasound helps identify early-stage, non-metastatic tumours that might be candidates for endoscopic resection. Peritoneal involvement is frequent and might be missed on cross-sectional imaging. Diagnostic laparoscopy is highly recommended for complete perioperative staging in the absence of radiographic evidence of metastatic disease. Positive cytology on peritoneal lavage is deemed to be micrometastatic stage IV disease and routine surgery is not recommended because of the high risk of recurrence; however, surgery is increasingly considered in some patients with clear cytology after chemotherapy.[15]

Gastric cancer classification

Gastric cancer is a heterogeneous disease. Historically, the Laurén classification divided gastric cancer into intestinal and diffuse subtypes. Intestinal-type gastric cancer is linked to *H pylori* infection and displays glandular or papillary differentiated structures. Diffuse-type gastric cancer consists of poorly cohesive, dedifferentiated tumour cells within a rich cellular stroma. The presence of signet ring cells typically portends resistance to systemic therapy and a poor prognosis.[16] Although alternative histopathological classifications exist, variations do not guide gastric cancer treatment and management.[17]

In the genomics era, The Cancer Genome Atlas consortium identified distinct molecular subtypes of gastric cancer: chromosomal instability (CIN), MSI, genome stability, and Epstein–Barr virus (EBV) positive. EBV-positive gastric cancers mainly occur in the proximal stomach, often affecting patients younger than 60 years, and have poorly differentiated histology and high levels of immune cell infiltration expressing PD-L1 and PD-L2—proteins that have a crucial role in the regulation of the immune system. EBV infection can induce hypermethylation, silencing tumour suppressor genes,

and EBV-positive gastric tumours are associated with recurrent mutations in *PIK3CA*, *ARID1A*, and *BCOR*. MSI gastric tumours result from impaired DNA mismatch repair, and show dense lymphocyte infiltration and widespread immune-checkpoint protein expression, highlighting their high immunogenicity. CIN tumours are characterised by aneuploidy, and have frequent *TP53* mutations and recurrent amplifications of genes encoding receptor tyrosine kinases. Genome stability tumours lack the characteristics of other subtypes, manifest in the non-junctional stomach, are often of diffuse histological subtype, and show molecular features such as *CDH1* or *RHOA* mutations associated with epithelial-to-mesenchymal transition and *CLDN18–ARHGAP* fusions.[18] The Asian Cancer Research Group identified subtypes as *TP53* active, *TP53* inactive, mesenchymal-like, and MSI.[19] These genomic classifications have limitations, focusing on surgically resected primary tumours and having few data on premalignant lesions or metastatic sites. Additionally these studies focused on samples with high tumour content, which might have downplayed the role of stromal cell types and the tumour microenvironment, now recognised as a crucial component of the tumour ecosystem. Laurén's classification remains widely used in clinical trials, and the clinical significance of molecular subgroups, except for the MSI subtype, is not yet firmly established for prognosis and therapy response.

Risk factors

The Correa cascade[20] is a model that outlines progression of normal gastric mucosa to gastric cancer through a series of histological changes: chronic infection leads to chronic gastritis, gastric atrophy, intestinal metaplasia, dysplasia, and finally gastric cancer. Genetic and epigenetic changes such as chromosomal instability, copy number alterations, and DNA methylation accrue through this process.[21]

H pylori infection, a strong risk factor for gastric cancer (75% attributable risk), is recognised as a class 1 carcinogen by WHO.[22] Although half of the population is infected worldwide, only about 3% of people who are infected with *H pylori* develop gastric cancer.[23] *H pylori* is associated with both intestinal-type and diffuse-type gastric cancer. However, chronic inflammation is not necessary for diffuse-type cancers, indicating distinct mechanisms in *H pylori*-induced malignant disease.[24] Bacterial constituents of virulence, such as cytotoxin-associated gene A protein (CagA) and vacuolating cytotoxin A (VacA), substantially damage host cell DNA and initiate cell survival pathways. There is an increasing effort to study the cost-effectiveness and feasibility of population-based *H pylori* search-test-and-treat programmes in targeted high-risk areas.[25] Indications for *H pylori* eradication include personal history of gastric neoplasia and family history of gastric cancer.[26,27]

Environmental factors, such as high salt intake, often from traditional diets with salted fish, have been implicated in the pathogenesis of gastric cancer. Obesity, gastro-oesophageal reflux, and Barrett's oesophagus are associated with gastro-oesophageal junction cancer.[28] EBV infection is associated with 5–10% of all gastric cancers.[29] Other risk factors for gastric cancer include smoking, alcohol, older age, familial predisposition, socioeconomic status, and pernicious anaemia.

Familial aggregation occurs in about 10% of all cases of gastric cancer, although known heritable mutations account for only about 1–3% of the global burden.[30] Hereditary diffuse gastric cancer is characterised by a high prevalence of diffuse gastric cancer and lobular breast cancer, mainly caused by mutations in *CDH1*. Prophylactic total gastrectomy is recommended for pathogenic *CDH1* variant carriers, with guidelines acknowledging variability in gastric cancer risk between families, advancements in surveillance, and newer relaxed genetic testing criteria and endoscopic surveillance options.[31] Gastric cancer is more frequent in patients with germline pathogenic variants of genes encoding homologous recombination deficiency (*ATM, PALB2, BRCA1,* and *BRCA2*), especially in those with *H pylori* co-infection.[32] Other hereditary syndromes are also associated with a higher incidence of gastric cancer, including Lynch syndrome and familial adenomatous polyposis.[30]

Screening and prevention

Upper endoscopy is the primary screening method for gastric cancer, because it is sensitive and allows biopsy samples to be taken for diagnosis of precancerous lesions and gastric cancer. Contrast radiography can detect malignant gastric ulcers and early cancers, but false-negative results are common. The effectiveness of screening varies by population risk, and has reduced mortality in high-incidence areas. In these high-incidence areas such as Japan and South Korea, population-based screening is implemented with recommended intervals of 2–3 years.[33,34] In low-incidence areas, screening is reserved for high-risk subgroups such as those with gastric adenomas and intestinal metaplasia, pernicious anaemia, and familial syndromes. Cost-effectiveness is favourable in high-risk groups but less so in low-incidence areas. *H pylori* eradication reduces gastric cancer risk in high-incidence areas but is not recommended for routine prevention in low-incidence areas in people without other risk factors.[26]

Surgery for gastric cancer

Principles of surgical resection

The core principles of surgical resection for gastric cancer consist of (1) resection of the primary cancer with clear margins (R0 resection) and adequate lymphadenectomy for improved survival; (2) minimisation of postoperative complications to allow

adjuvant systemic therapy; and (3) reconstruction with restoration of gastrointestinal continuity to enhance quality of life.

Endoscopic surgery

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are the main treatments for early gastric cancer. EMR has a shorter learning curve, while ESD results in en-bloc specimens, improved completeness of resection, and fewer recurrences.[35,36] The main concern regarding endoscopic resection is the risk of lymph node metastases, which can be up to 20% in patients with stage T1b cancer.[37] Sentinel node surgery with ESD might reduce the risk of locoregional recurrence but requires further research.[38]

Extent of lymphadenectomy

The debate about D1 versus D2 lymphadenectomy has been resolved by findings from randomised trials, which favoured D2 lymphadenectomy.[39,40] D2 lymphadenectomy is now the standard of care for patients with locally advanced gastric cancer (figure 2). Although standard in Asian countries, the quality of lymphadenectomy varies in American and European centres. Intraoperative photography and video assessments are crucial for improving surgical standards in non-Asian centres. Several studies are exploring the role of resection of isolated metastatic retroperitoneal or para-aortic lymph nodes, balancing oncological benefits against potential surgical risks.

Method of reconstruction

Research has focused on long-term sequelae after gastrectomy, such as dumping, reflux, early satiety, and weight loss.[41] Pylorus-preserving surgery does not reduce complications compared with traditional distal gastrectomy but increases the risk of pyloric stenosis.[42]

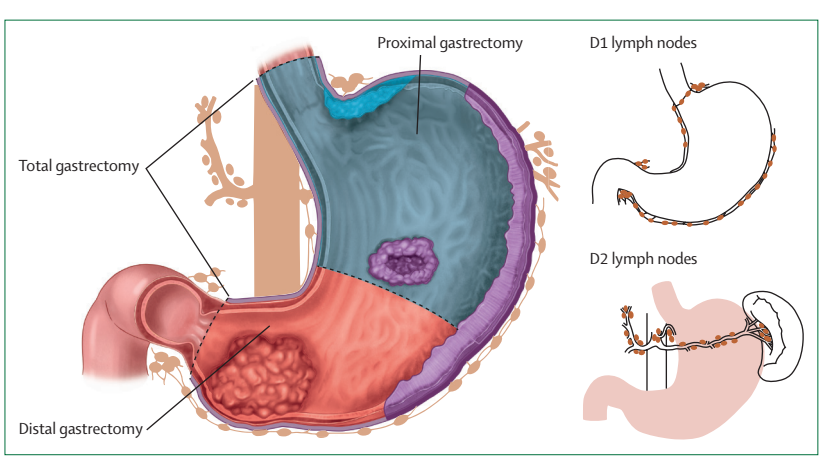

Figure 2: **Surgery for gastric cancer**
Illustration of the most common types of surgery for gastric cancer, according to tumour location: distal gastrectomy (red) for pyloric tumours, proximal gastrectomy (blue) for cardia and lower gastro-oesophageal junction tumours, and total gastrectomy (purple) for body or more extensive tumours. Insets show the lymph node distribution of D1 and D2 lymph nodes.

Roux-en-Y reconstruction for distal gastric cancer offers superior outcomes in bile reflux, nausea, and reflux symptoms compared with Billroth II reconstruction.[43] Total gastrectomy with Roux-en-Y reconstruction is the preferred approach for locally advanced, proximal gastric cancer. Some centres have explored the role of Merendino or double tract procedures to preserve gastric volume in early-stage gastric cancer. Findings from the KLASS-05 randomised controlled trial[44] showed that short-term outcomes and quality of life did not differ significantly between laparoscopic proximal gastrectomy with double-tract reconstruction and laparoscopic total gastrectomy.

Surgical access

The safety of minimally invasive (laparoscopic or robotic) approaches has been established for early and advanced gastric cancer.[45–47] Findings from randomised trials have shown non-inferiority for laparoscopic gastrectomy compared with open techniques, while other studies suggest improved postoperative results might reflect surgeons' gains in proficiency with the technique.[48–50] Laparoscopic gastrectomy is gaining acceptance, but evidence comparing robotic and laparoscopic approaches is limited. Early trials noted similar infection rates but fewer severe complications with robotic surgery; a larger trial is underway.[51,52]

Advanced indications for surgery; oligometastatic and peritoneal disease

Potentially the most exciting area of surgical research in gastric cancer involves advanced indications for surgery and extending curative treatments. The European OMEC study group has defined oligometastatic disease from oesophageal and gastric cancers. Systematic reviews suggest a prognostic benefit from resection of oligometastatic disease in the liver and lymph nodes.[53,54] However, findings from the randomised RENAISSANCE trial[55] showed that in patients with limited metastatic gastric or gastro-oesophageal junction cancers, surgical resection after initial chemotherapy did not improve overall survival compared with continuing chemotherapy alone. Subgroup analyses showed that surgical resection might benefit patients with distant lymph node metastases, whereas resection in patients with peritoneal metastases fared worse.[55] Other local ablative therapies (eg, stereotactic radiotherapy and radiofrequency ablation) can be considered to avoid the risk of surgical complications. Research on hyperthermic intraperitoneal chemotherapy and pressurised intraperitoneal aerosol chemotherapy in peritoneal disease is ongoing but remains investigational.[15,56] The true benefit of aggressive local therapy in oligometastatic disease might be best assessed after a period of disease regression or stabilisation after systemic therapy. Future studies should also include quality-of-life outcomes for these techniques.

Multimodal therapy for locally advanced gastric cancer

The intent of treatment for locally advanced gastric cancer is curative. The choice of adjunctive therapy alongside surgery for operable gastric cancer varies by geographical region. However, as the epidemiology evolves over time, corresponding shifts in treatment strategies are beginning to occur. These changes and differences are reflected in various prominent guidelines such as the National Comprehensive Cancer Network,[57] European Society for Medical Oncology,[58] and the Pan-Asian guidelines endorsed by several national societies.[59]

Adjuvant therapy

In east Asia, where more patients are diagnosed with early-stage gastric cancer compared with other regions, adjuvant chemotherapy after D2 gastrectomy is recommended for patients at high risk of recurrence.[59–62] For Asian patients with a modest risk of recurrence (stage II), or with comorbidities that preclude doublet chemotherapy, S-1 (a combination of tegafur, gimeracil, and oteracil) monotherapy for 1 year is the standard of care, whereas patients with moderate-risk or high-risk resected gastric cancer (stage III) are recommended doublet chemotherapy with either 6 months of capecitabine and oxaliplatin (CAPOX), S-1 and oxaliplatin (SOX), or docetaxel and S-1.[63–65] Adjuvant chemotherapy without a neoadjuvant component did not improve survival in non-Asian patients with gastric cancer, although meta-analysis suggests a small benefit of adjuvant chemotherapy.[66] CAPOX can also be recommended as adjuvant chemotherapy for non-Asian patients.

Neoadjuvant therapy

Outside Asia, patients are more commonly diagnosed with locally advanced but operable gastric cancer, which is also more likely to be proximal in location. Neoadjuvant or perioperative chemotherapy to downstage tumours before surgery improves survival compared with surgery alone and is the standard of care outside Asia for operable gastric or gastro-oesophageal junction cancer, with the most evidence for the triplet FLOT regimen (5-fluorouracil, oxaliplatin, and docetaxel).[67] Doublet platinum and fluoropyrimidine regimens can be considered for patients in whom toxicity is a concern.[68] After neoadjuvant chemotherapy and surgery, completion adjuvant chemotherapy is recommended, and seems to improve survival even in high-risk patients, although tolerability remains a challenge.[69,70] Use of neoadjuvant chemotherapy is evolving in Asia for locally advanced or bulky tumours (cT4). The PRODIGY trial[71] assessed neoadjuvant docetaxel, oxaliplatin, and S-1 plus D2 surgery and adjuvant S-1 in patients with resectable locally advanced gastric cancer and showed an overall survival benefit compared with surgery plus adjuvant S-1 alone. Findings from the RESOLVE trial[72] showed improved survival with perioperative SOX compared with adjuvant CAPOX chemotherapy in patients undergoing D2 gastrectomy. Consequently, in Asia, recommendations for perioperative chemotherapy are restricted to patients with stage T4a disease with node positive or large size of lymph node metastasis.[59]

Addition of radiotherapy

Historically, chemoradiotherapy was an option for resected gastric cancer. However, findings from trials including CRITICS[73] and ARTIST-2[74] showed no benefit of radiotherapy after surgery, even in high-risk patients. As a result, radiotherapy is no longer recommended routinely after surgical resection (with the exception of D0 or D1 lymphadenectomy or R1 resection).[75] Patients with type 1 and type 2 gastro-oesophageal junction cancer can receive either perioperative chemotherapy or neoadjuvant chemoradiotherapy on the basis of findings from the CROSS trial,[76] further discussion of which is included in oesophageal cancer literature.[77] The ESOPEC trial[78] noted the superiority of perioperative FLOT over neoadjuvant CROSS (chemoradiation with carboplatin and paclitaxel) for patients with operable oesophageal or gastro-oesophageal junction adenocarcinoma, with improvement in overall survival and progression-free survival. As a result of the ESOPEC outcome, chemoradiotherapy is not the preferred choice for junctional tumours. The TOPGEAR trial[79] compared preoperative chemo-radiotherapy plus perioperative chemotherapy versus perioperative chemotherapy alone in patients with resectable gastric or gastro-oesophageal junction cancer. The addition of preoperative chemoradiotherapy did not improve overall survival or progression-free survival, with similar treatment-related toxic effects in both groups.

Targeted therapy and immunotherapy

Although many antibody-based therapies are effective in enhancing survival outcomes for advanced gastro-oesophageal junction or gastric cancer, none have yet obtained approval for use in operable disease contexts. The HERFLOT,[80] PETRARCA,[81] and INNOVATION[82] phase 2 trials assessed the efficacy of trastuzumab and trastuzumab–pertuzumab combination chemotherapy regimens in patients with HER2-positive gastro-oesophageal junction or gastric cancer. Findings from these trials showed enhanced pathological complete response rates with these regimens; however, the statistical power of the trials, possibly because of small sample sizes, has been insufficient to definitively establish a survival benefit.

The KEYNOTE-585 trial[83] investigated the addition of immune checkpoint inhibitors to chemotherapy in operable gastric or gastro-oesophageal cancer. Patients treated with pembrolizumab and chemotherapy had improved pathological complete response rates compared with those receiving chemotherapy alone, but neither event-free survival nor overall survival differed between

treatment groups. These results might be attributable to statistical design. In the VESTIGE trial,[70] adjuvant immunotherapy with nivolumab and ipilimumab was inferior to continuing adjuvant chemotherapy in patients with high-risk (node-positive or R1) gastro-oesophageal cancer. Similarly, in the Asian ATTRACTION-5 trial,[84] adjuvant nivolumab plus CAPOX or S-1 did not improve survival compared with CAPOX or S-1 alone in patients with pathological stage III gastric or gastro-oesophageal junction tumours that had undergone a D2 gastrectomy. In the DANTE trial,[85] the addition of the PD-L1 antibody atezolizumab to perioperative FLOT chemotherapy in patients with resectable oesophagogastric adenocarcinoma improved postoperative stage and histopathological regression without increasing the proportion of adverse events. At the time of writing, the international randomised phase 3 MATTERHORN trial,[86] which assessed the addition of durvalumab to perioperative FLOT chemotherapy, has been reported as having a positive outcome for event-free survival; however, no more details are available.

Biomarkers including dMMR

dMMR or MSI subtypes are more common in operable than in advanced disease. dMMR or MSI tumours have an excellent prognosis with surgery alone and seem more resistant to platinum and fluoropyrimidine chemotherapy.[87,88] The necessity of adjuvant chemotherapy should be carefully considered. For neoadjuvant chemotherapy to downstage resectable tumours, FLOT has shown good pathological responses. For non-resectable tumours (eg, cT4b), a combination of chemotherapy and immune checkpoint inhibitors can be considered, followed by re-evaluation.[85] Small trials such as NEONIPIGA[89] and INFINITY[90] reported about 60% pathological complete responses and encouraging disease-free survival with neoadjuvant doublet immunotherapy (anti-CTLA4, anti-PD-1, or anti-PD-L1) in resectable MSI or dMMR gastric or gastro-oesophageal cancer.[83] Results from trials investigating a surgery-free or organ-sparing approach using immune checkpoint inhibitors for dMMR or MSI cancer are awaited, but in view of the excellent survival of this group of patients following surgery, the non-operative approach should be considered experimental for now.

Beyond dMMR or MSI gastric cancer, robust prognostic and predictive biomarkers for operable gastric cancer are scarce. Circulating tumour DNA (ctDNA) has been investigated in several series; the presence of ctDNA in plasma after surgery is associated with a heightened risk of recurrence.[91–93] Prospective clinical trials are required to establish whether ctDNA can be used postoperatively to risk stratify for adjuvant therapy.

Nutrition, exercise, and supportive care

Nutrition and supportive care are integral components in the comprehensive management of gastric cancer, from diagnosis to advanced disease stages. Common complications include malnutrition, weight loss, and sarcopenia, which can have pronounced effects on treatment response, immune function, and quality of life. Nutritional support mitigates treatment-related toxicities but also enhances therapy tolerance and overall outcomes.[94,95] In operable cases, presurgical jejunostomy tube placement can facilitate neoadjuvant chemotherapy delivery, while stents can alleviate dysphagia or gastric outlet obstruction in advanced disease. Supervised exercise programmes improve cardiorespiratory fitness and quality of life, particularly in the postoperative period.[96] Appetite stimulants such as olanzapine can enhance oral intake, and parenteral feeding can serve as a bridge to chemotherapy in patients with intestinal obstruction.

Evidence from randomised trials highlights the survival benefits of early supportive and palliative care for patients with advanced gastric cancer. Multidisciplinary collaboration between oncologists, surgeons, dietitians, nurses, and allied professionals is essential for delivering comprehensive care tailored to each individual patient's needs. The long-term symptomatic and psychological burden and functional recovery following gastrectomy for cancer is clearly an important consideration in patients receiving curatively intended treatment. Adequate preoperative counselling for patients, paired with long-term survivorship support with dedicated specialist clinics, is crucial to ensure patients are adequately supported during and beyond treatment.

Systemic therapy for patients with advanced gastric cancer

Evidence from several clinical trials unequivocally supports the role of systemic chemotherapy in improving overall survival and quality of life in patients diagnosed with unresectable advanced, recurrent, or metastatic gastro-oesophageal junction or gastric cancer.[58,59] Median overall survival of patients with advanced gastric cancer who receive systemic therapy is currently about 13–20 months.[97–99] Active cytotoxic chemotherapy drugs in advanced disease include fluoropyrimidines (5-fluorouracil, capecitabine, and S-1), platinums (cisplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), irinotecan, and trifluridine–tipiracil (an oral nucleoside analogue plus thymidine phosphorylase inhibitor). Several effective molecular targeted therapies are available for the treatment of advanced gastric cancer. Many clinical trials of advanced disease have included patients with adenocarcinoma of the oesophagus or gastro-oesophageal junction, and effective drugs used for advanced gastric cancer can also be beneficial for treating these adenocarcinomas.[100] There are regional disparities in drug approval and reimbursement, which substantially affect treatment outcomes, underscoring the need for a more uniform approach to advanced gastric cancer treatment worldwide.[59]

Biomarker testing for advanced gastric cancer

Biomarker testing for advanced gastric cancer is crucial for precision oncology and personalised decision making. Contemporary targeted (and immunotherapy) trials frequently include biomarker-selected subgroup analyses, showing clear survival benefits. As these drugs gain approval, their associated biomarker tests become essential for identification of patients who will most likely benefit. HER2 (also known as ERBB2), the first biomarker showing therapeutic relevance for targeted treatment in advanced disease, is measured by immunohistochemistry. In situ hybridisation can be used for additional confirmation.[101] dMMR or MSI status is assessed by immunohistochemistry or PCR, respectively, and can be used to predict for sensitivity to immunotherapy.[102] PD-L1 expression on tumour and immune cells, measured via immunohistochemistry and calculated with the combined positive score (CPS) or tumour area proportion, has been incorporated as the key biomarker for most anti-PD-1 or anti-PD-L1 trials. Although various immunohistochemistry assays are used clinically, there is little standardisation, which creates challenges with interpretation and affects the selection of optimum therapies.[103] HER2, MMR, and PD-L1 were considered established biomarkers and are highly recommended to be tested before beginning first-line treatment for advanced gastric cancer. CLDN18.2 is a new biomarker for anti-CLDN18.2 therapy (zolbetuximab) in advanced disease, which attained regulatory approval in 2024.[99]

Gastric cancer shows substantial intratumoural genomic and phenotypic heterogeneity, which might be one reason for many negative targeted therapy trials.[104,105] For example, HER2-positive gastric tumours show varying levels of HER2 expression, even exceeding the heterogeneity seen in HER2-positive breast cancer.[106] Patients with heterogeneous HER2 expression in their primary tumours who are treated with trastuzumab-containing first-line chemotherapy regimens often have shorter progression-free survival than patients with homogeneous HER2 expression.[107] Furthermore, discordant HER2 expression between primary tumours and metastatic lesions occurs in a notable subset of gastric cancers.[108] These data highlight the crucial need for accurate definitions regarding the timing and anatomical location of molecular assessments to guide treatments effectively. This need is particularly relevant for HER2, for which second-line HER2 blockade with trastuzumab deruxtecan is possible. Consequently, repeated biopsies or the use of ctDNA to monitor HER2 expression dynamics during treatment are being considered.[109]

First-line cytotoxic chemotherapy

For the initial treatment of patients with advanced gastric cancer, a platinum–fluoropyrimidine doublet is the preferred backbone cytotoxic chemotherapy.[57,58] Fluoropyrimidine alone or in combination with taxanes or irinotecan can be considered for patients intolerant of or unfit for platinum-based chemotherapy.[110,111] Clinical evidence from randomised trials consistently supports the addition of reduced-dose oxaliplatin to fluoropyrimidine for less medically fit or older patients in the first-line setting, with oxaliplatin being preferred over cisplatin because of its superior safety profile, including a lower risk of thromboembolic events and renal dysfunction.[112–114] Pivotal trials have established oxaliplatin as the standard platinum agent.[97–99] Infusional 5-fluorouracil and oral fluoropyrimidines show comparable efficacy, although capecitabine is associated with higher rates of hand–foot syndrome.[114] S-1, an oral fluoropyrimidine used in Asia, has limited use in non-Asian populations because of pharmacogenomic disparities.[115]

Doublet versus triplet chemotherapy

Although findings from initial studies hinted at a small survival benefit with triplet chemotherapy (cisplatin, 5-fluorouracil, and docetaxel) in patients with advanced gastric cancer, subsequent trials produced conflicting results.[116–119] Toxicity concerns and absence of consistently superior outcomes with triplet regimens have made doublet chemotherapy the preferred choice for advanced gastric cancer. However, the novel triplet regimen TFOX or modified FLOT might remain an option for some patients, particularly those with a high fitness level, requiring rapid responses, and no access to targeted therapies such as anti-PD-1, anti-HER2, or anti-CLDN18.2.

Immunotherapy for patients with advanced gastric cancer

Immune checkpoint inhibition combined with platinum doublet chemotherapy has emerged as a standard of care globally for treatment-naive patients with HER2-negative advanced gastric cancer. Although in many countries anti-PD-1 is licensed independent of PD-L1 expression, there is consensus that the major benefits of immune checkpoint inhibitors are generally reserved for patients with higher levels of PD-L1 expression on their tumour. The US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee voted against the risk–benefit profile of PD-1 inhibitors for first-line treatment of HER2-negative advanced disease with PD-L1 CPS less than one, following discussions and data presentations from several clinical trials.[120] Findings from the randomised phase 3 CheckMate-649 trial[97] showed a significant improvement in overall survival and progression-free survival in patients who received nivolumab plus chemotherapy compared with those who received placebo plus chemotherapy, with the survival benefit more pronounced in patients whose tumours had a CPS of five or more. In this trial and others, the combination of immune checkpoint inhibitors and chemotherapy was highly effective in patients with dMMR or MSI tumours, although they make up fewer

than 5% of patients with advanced disease.[97,102,121,122] By contrast, the Asian randomised phase 3 trial ATTRACTION-4[123] showed that the combination of an immune checkpoint inhibitor and chemotherapy improved progression-free survival in patients with HER2-negative disease compared with placebo plus chemotherapy, yet the absence of a significant difference in overall survival could be attributed to the high proportion of patients receiving subsequent immune checkpoint inhibitors in both trial groups.

Although first-line chemotherapy with nivolumab is approved for HER2-negative advanced gastric cancer in the USA and Asian countries, the European Medicines Agency (EMA) has restricted its approval to patients with high PD-L1 expression (CPS ≥5). There is a general consensus on nivolumab use alongside chemotherapy for patients with a CPS of five or more and for those with dMMR or MSI tumours, although its usefulness in those with a CPS of less than five remains debatable.[124,125] Findings of the KEYNOTE-859 trial[98] showed efficacy of pembrolizumab in combination with chemotherapy in participants with locally advanced or metastatic HER2-negative gastric cancer, with the degree of benefit being greatest in participants with PD-L1-positive tumours. Results from several other randomised clinical trials have corroborated the effectiveness of immunochemotherapy with different anti-PD-1 or anti-PD-L1 monoclonal antibodies such as tislelizumab, sintilimab, and sugemalimab in first-line treatment for HER2-negative advanced gastric cancer.[126–128] However, the usefulness of PD-L1 expression as a biomarker for selection of patients for immune checkpoint inhibitor therapy remains suboptimum, with different antibodies (28-8, 22C3, and SP263) and evaluation methods (CPS, tumour proportion score, and tumour area positivity score) used across trials, and several consistency and other assay-related issues remaining unresolved (figure 3).[103]

Biologics in first-line advanced gastric cancer

HER2 targeted therapy

HER2 belongs to the epidermal growth factor receptor (EGFR) tyrosine kinase family and is situated on the cell membrane. Amplification and overexpression of HER2 are implicated in the pathogenesis of gastric cancer, occurring in about 15% of patients.[18] Findings from the ToGA trial[101] showed that the addition of trastuzumab, an antibody targeting HER2, to first-line capecitabine plus cisplatin or fluorouracil plus cisplatin significantly improved overall survival compared with chemotherapy alone in patients with HER2-positive advanced gastric cancer. HER2-positive tumours were defined as tumours scoring 3+ on immunohistochemistry or if they were positive on in situ hybridisation (*HER2*:*CEP17* ratio ≥2).[58,59,101] However, by contrast with HER2-positive breast cancer, the use of trastuzumab beyond progression after first-line treatment and dual blockade with trastuzumab and pertuzumab did not confer clinical benefit.[129,130] Intratumour heterogeneity of HER2 expression and loss of HER2 expression during trastuzumab treatment underlie primary and acquired resistance to HER2-directed therapy in advanced gastric cancer.[131–133] Findings from the randomised phase 3 KEYNOTE-811 trial[134] showed a significant increase in objective response rate with pembrolizumab plus trastuzumab and chemotherapy compared with trastuzumab plus chemotherapy alone in first-line treatment of HER2-positive advanced disease, leading to FDA accelerated approval. Subsequently, significant extension in progression-free survival and overall survival, particularly in patients with a PD-L1 CPS of one or more, resulted in EMA approval of pembrolizumab for HER2-positive and PD-L1-expressing (CPS ≥1) advanced gastric cancer in first-line treatment.[135,136] The use of pembrolizumab for HER2-positive advanced gastric cancer was also amended and restricted to patients with a PD-L1 CPS of one or more in the USA.[137] These results highlight the importance of assessment of immune context when adding immune checkpoint inhibitors to targeted therapy.

CLDN18.2 targeted therapy

CLDN18.2 is a tight junction molecule expressed on normal gastric mucosa cells and over-expressed in advanced gastric cancer.[138] Zolbetuximab is a first-in-class monoclonal antibody targeting CLDN18.2.[139] Findings from two randomised international phase 3 trials (SPOTLIGHT[99] and GLOW[140]) showed that zolbetuximab in combination with chemotherapy improved overall survival and progression-free survival compared with chemotherapy alone in the treatment of HER2-negative, CLDN18.2-positive treatment-naive disease. CLDN18.2-positive advanced gastric cancer was defined as tumours with moderate to strong protein expression of CLDN18.2 in at least 75% of cancer cells. Notable toxic effects of zolbetuximab include on-target nausea and vomiting, most commonly occurring at first infusion.[141] Various other anti-CLDN18.2 targeted therapies are under investigation.[138]

Second-line and beyond systemic therapy for advanced gastric cancer

For patients in good general condition, second-line chemotherapy becomes a viable option; taxane and irinotecan monotherapy have comparable efficacy and extend survival compared with best supportive care alone after progression on first-line chemotherapy. Findings from the phase 3 RAINBOW trial[142,143] showed the adjunctive benefits of adding ramucirumab, an anti-VEGFR2 monoclonal antibody, to paclitaxel in second-line therapy. Irinotecan-based chemotherapy offers an alternative treatment for early recurrence following perioperative FLOT or adjuvant docetaxel plus S-1 chemotherapy. Trifluridine–tipiracil improved overall survival compared with best supportive care in patients

with heavily pretreated metastatic gastric cancer in the randomised phase 3 TAGS trial.[144] In the ATTRACTION-2 trial,[145] which recruited patients only in Asia, nivolumab monotherapy improved survival in third-line or later treatment, and could be a treatment option if not used in the first-line setting.

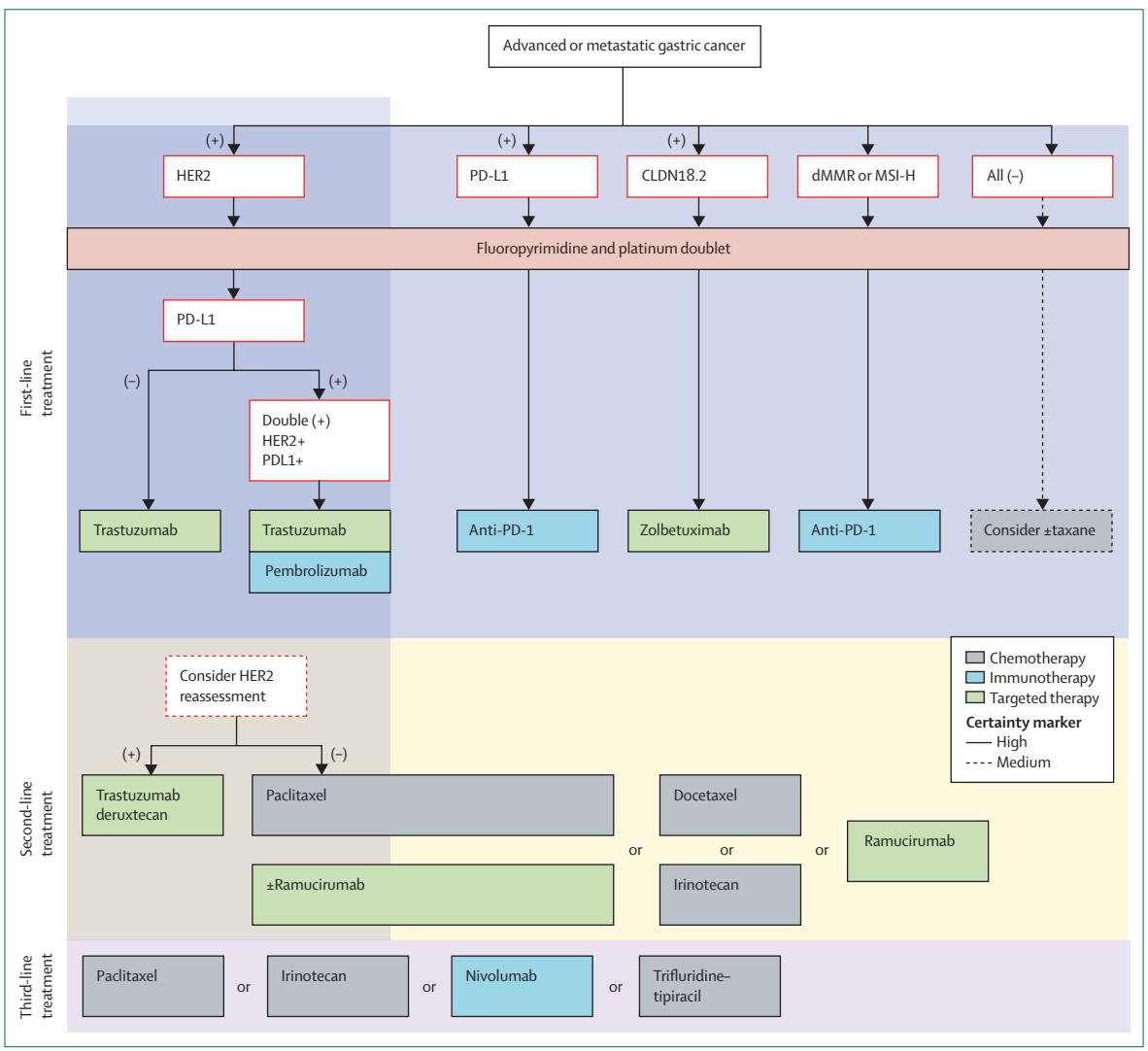

Figure 3: **Therapeutic algorithm for advanced or metastatic gastric cancer**
Upfront testing of all gastric cancer biomarkers is recommended at diagnosis. HER2 immunohistochemistry, PD-L1 immunohistochemistry to calculate CPS, and detection of dMMR by immunohistochemistry or MSI-H by PCR or next-generation sequencing are strongly recommended. Testing for CLDN18.2 by immunohistochemistry is recommended if drug or clinical trials are available. Recommended first-line treatment consists of a fluoropyrimidine and platinum doublet chemotherapy backbone, combined with other therapies depending on biomarker status. For HER2-positive tumours, if PD-L1 positive (defined as CPS ≥1), the recommended treatment is a combination of trastuzumab and pembrolizumab with fluoropyrimidine or platinum doublet chemotherapy; if PD-L1 negative (CPS <1), only trastuzumab is combined with doublet chemotherapy. There is much controversy surrounding PD-L1 testing, including which assay (antibody clone), scoring method (CPS or tumour area positivity score), and cutoff level (1, 5, or 10) are appropriate. Various trials with different drugs have used different assays and cutoff levels to achieve regulatory approval for several anti-PD-1 and anti-PD-L1 inhibitors. Details and nuances are beyond the scope of this Seminar and are extensively discussed elsewhere. For simplicity, the addition of an anti-PD-1 inhibitor to chemotherapy is recommended for PD-L1 positive tumours. For dMMR or MSI-H tumours, the addition of anti-PD-1 therapies is recommended. In regions where zolbetuximab is approved and available, recommended first-line treatment for CLDN18.2-positive tumours is zolbetuximab combined with chemotherapy. If all biomarkers are negative, and for high volume disease, requiring rapid responses, the addition of taxane chemotherapy to fluoropyrimidine and platinum can be considered in fit patients. There is a possibility of overlap of biomarker positivity: for HER2-positive tumours, following the HER2 pathway is recommended. However, if PD-L1 and CLDN18.2 are both positive, there are insufficient data to provide guidance on best choice of treatment and both anti-PD-1 or zolbetuximab remain possible options. In second-line treatment, for HER2-positive tumours, if feasible, a rebiopsy of the tumour should be done to test HER2 status. If HER2 negative, paclitaxel and ramucirumab combination is standard of care, similar to that for HER2-negative tumours. Less preferred, but viable, alternatives include docetaxel, irinotecan, or ramucirumab. For HER2-positive tumours, trastuzumab deruxtecan can be considered for second-line or third-line treatment (if not given second line). Other third-line options for HER2-negative tumours include paclitaxel, irinotecan, nivolumab, or trifluridine–tipiracil. (+)=positive. (–)=negative. ±=with or without. CPS=combined positive score. dMMR=mismatch repair deficiency. MSI-H=microsatellite instability high.

Although ramucirumab plus paclitaxel is established as the standard second-line treatment, its use in the first-line setting or beyond disease progression has not shown improved treatment outcomes.[146] Regorafenib, a multikinase inhibitor targeting the VEGF pathway, showed modest improvement in survival in third-line or later treatment in the INTEGRATE IIa study.[147] Apatinib, another angiogenesis inhibitor, has shown positive results mainly in China,[148] but findings from the international ANGEL study[149] did not show a statistically significant improvement in overall survival in patients given apatinib plus best supportive care versus placebo plus best supportive care.

In later treatment lines, targeting HER2-positive advanced gastric cancer with the antibody–drug conjugate trastuzumab emtansine did not improve overall survival or progression-free survival compared with paclitaxel in second-line therapy.[150] However, trastuzumab deruxtecan, a novel antibody–drug conjugate linked to a topoisomerase I inhibitor payload and a cleavable linker, thus allowing bystander cell killing, showed promising results in Asia and in North America and Europe. Findings from the DESTINY-Gastric01 trial[151,152] showed superior objective response rate and overall survival over third-line chemotherapy and antitumour activity in patients with HER2-positive advanced disease. On the basis of these findings and additional trial data, trastuzumab deruxtecan is approved by the US FDA and EMA as a second-line or later treatment for HER2-positive disease.[153] Findings from the international randomised phase 3 trial DESTINY-Gastric04 (NCT04704934) showed the efficacy of trastuzumab deruxtecan against ramucirumab plus paclitaxel in the second-line setting with an improvement in overall survival.[154]

Novel targets and approaches in gastric cancer

Several new therapeutic vulnerabilities are being investigated in clinical trials in advanced gastric cancer (figure 4). The FGFR2b receptor is a promising therapeutic target. Initial success with bemarituzumab, an anti-FGFR2b antibody, in the FIGHT trial[155] has led to ongoing phase 3 trials investigating its efficacy in combination with chemotherapy (FORTITUDE-101, NCT05052801) and additionally, nivolumab and chemotherapy (FORTITUDE-102, NCT05111626). Other currently investigated targets include TROP2,[156] CAPRIN1,[157] and DKK1.[158] Beyond monoclonal antibodies, for established targets such as HER2 and CLDN18.2, novel approaches including antibody–drug conjugates, bispecific antibodies, chimeric antigen receptor T-cell therapies, and bispecific T-cell engagers are being actively explored in clinical trials.[138,159]

Several combinations of targeted therapies and immunotherapies for advanced gastric cancer are being explored. These combinations include multikinase inhibitors paired with PD-1 inhibitors, which are being investigated in phase 3 trials.[160–162] Novel immune checkpoints such as TIGIT are being studied as putative therapeutic targets. Results from the phase 2 EDGE-Gastric study[163] showed promising antitumour activity

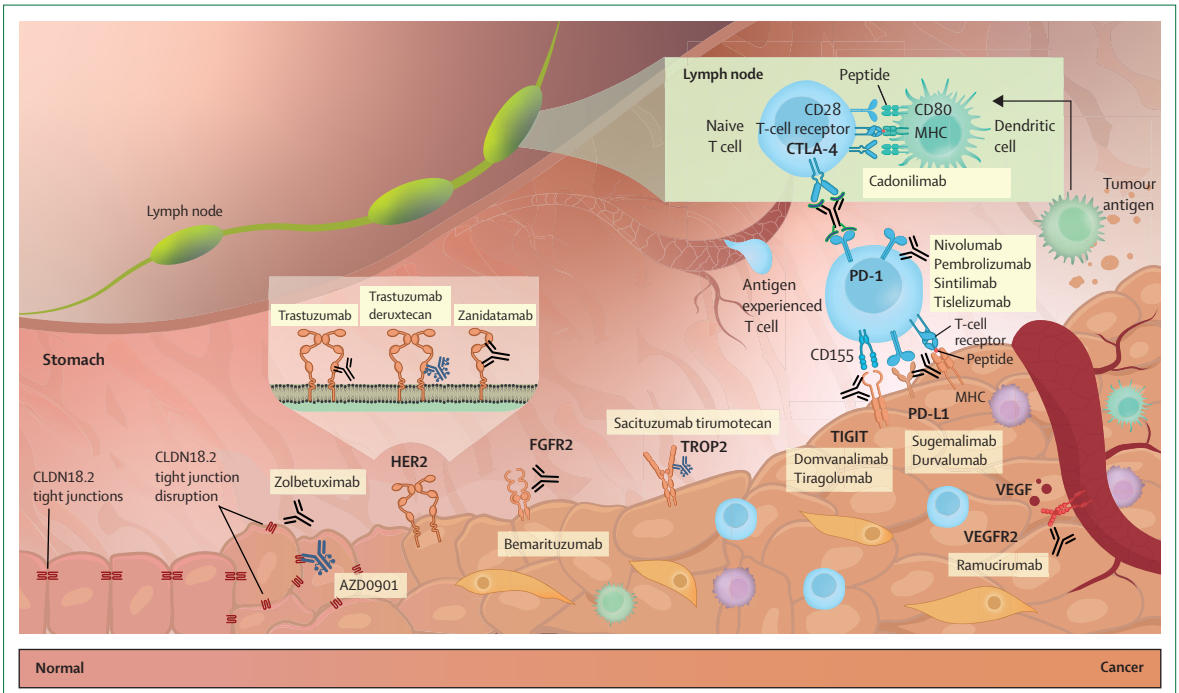

Figure 4: **Present and emerging targets and therapies in gastric cancer**
Illustration of gastric cancer tumour and microenvironment with targets and drugs. The figure is not meant to be comprehensive, but highlights current and emerging therapeutic strategies in gastric cancer.

with the addition of domvanalimab (anti-TIGIT) and zimberelimab (anti-PD-1) to chemotherapy. The ongoing randomised phase 3 STAR221 trial (NCT05502237) is comparing the efficacy of anti-TIGIT and PD-1 therapy with chemotherapy versus nivolumab and chemotherapy. Targeting CTLA4 with enhanced approaches is also being investigated (COMPASSION-15, NCT06251973).

Ongoing challenges and future directions

Gastric cancer poses persistent hurdles in the realms of diagnosis, treatment, and management. Despite substantial progress in understanding its molecular characteristics and the development of targeted therapies and immunotherapies, several challenges remain, including the heterogeneity of the disease, treatment resistance, and poor access to novel therapies in several regions across the globe. Targets that were previously considered undruggable, such KRAS and TP53, which are commonly mutated in gastric cancer, now have drugs that are entering clinical trials, albeit in very early stages. Understanding biomarker co-expression and optimum therapy sequencing will be crucial in advanced gastric cancer. Many targets, such as CLDN18.2 and PD-L1, are not oncogenic drivers and can co-occur frequently, complicating treatment decisions. Moving forward, addressing these challenges necessitates a multifaceted approach that integrates advances in precision medicine, immunotherapy, and targeted therapies. Additionally, efforts to improve early detection and implement multidisciplinary care models are crucial for optimising patient outcomes. Collaborative research endeavours, innovative clinical trial designs, and international cooperation will be instrumental in shaping the future directions of gastric cancer management, ultimately striving towards more effective and personalised approaches to combat this complex disease.

Contributors

RS and ECS wrote the initial draft of the manuscript. All authors contributed to writing of the manuscript. All authors approved the final version.

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