



Review

Gastric cancer: French intergroup clinical practice guidelines for diagnosis, staging, treatment and follow-up (TNCD, SNFGE, FFCD, UNICANCER, GERCOR, SFCD, SFED, AFEF, SFRO, SFP, SFR, ACHBPT, RENAPE, SNFCP)[☆]

Aziz Zaanan^{a,*}, Juliette Palle^a, Florence Renaud^b, Maximilien Barret^c,
Meher Ben Abdelghani^d, Bruno Buecher^e, Nicolas Chapelle^f, Olivier Dubreuil^g,
Jerome Durand-Labrunie^h, Nadim Faresⁱ, Johan Gagniere^j, Marine Jary^k, Antoine Mariani^l,
Lola-Jade Palmieri^m, Michel Ducreuxⁿ, Olivier Bouché^o

^a Department of Gastroenterology and Digestive Oncology, Hôpital Européen Georges Pompidou, AP-HP centre, Institut du Cancer Paris CARPEM, Université Paris-Cité, Paris, France

^b Department of Pathology, Pitié-Salpêtrière Hospital, APHP, Sorbonne University, Inserm UMRS938, CURAMUS, Paris, France

^c Department of Gastroenterology, Clinique de Bizet, Paris, France

^d Department of Medical Oncology, Institut Strauss, Strasbourg, France

^e Department of Genetics, Institut Curie, Université Paris Sciences et Lettres, Paris, France

^f Gastroenterology Unit, UMR 1064 Center for Research in Transplantation and Translational Immunology, Nantes University Hospital, Nantes, France

^g Medical Oncology, Diaconesses-Croix St Simon Hospital, Paris, France

^h Department of Radiation Oncology, Gustave Roussy, Villejuif, France

ⁱ Digestive Oncology Department, Rangueil Hospital, Toulouse University Hospital, Toulouse University, Toulouse, France

^j Department of Digestive and Hepatobiliary Surgery, University Hospital of Clermont-Ferrand, U1071 Inserm/UCA, M2iSH, Clermont-Ferrand, France

^k Department of Digestive Surgery, Clermont-Ferrand University Hospital, Clermont-Ferrand, France, U1071 Inserm/UCA, M2iSH, Clermont-Auvergne University, Clermont-Ferrand, France

^l Department of Digestive Surgery, Hôpital Européen Georges Pompidou, AP-HP centre, Institut du Cancer Paris CARPEM, Université Paris-Cité, Paris, France

^m Department of Medical Oncology, Institut Bergonié, Bordeaux, France

ⁿ Department of Medical Oncology, Gustave Roussy, Université Paris-Saclay, Inserm U1279 Tumor Cell Dynamics, Villejuif, France

^o Department of Gastroenterology and Digestive Oncology, CHU Reims, Université Reims Champagne-Ardenne (URCA), Reims, France

ARTICLE INFO

Keywords:

Guidelines

Gastric cancer

Chemotherapy

Perioperative

Immunotherapy

Targeted therapy

ABSTRACT

Introduction: The updated edition of the French intergroup guidelines for the management of patients with gastric and gastroesophageal junction adenocarcinoma is a collaborative work of several national medical societies, and available on the website of the French Society of Gastroenterology (SNFGE) (www.tncd.org).

Methods: The recommendations are graded into three categories (A, B, and C), based on the level of scientific evidence published until January 2026.

Results: Initial staging and risk assessment should include physical evaluation, endoscopy and computed tomography-scan of the thorax, abdomen, and pelvis. For resectable disease, endoscopic ultrasonography can be used for T and N staging, while laparoscopic exploration may be performed to exclude occult peritoneal metastases, especially for cT3/cT4 and poorly cohesive tumors. Endoscopic or surgical resection alone is appropriate for very early cT1N0 tumors. For locally advanced disease $\geq$ cT2 and/or cN+, the perioperative FLOT chemotherapy is recommended as the standard of care. Recently, the addition of durvalumab to perioperative

[☆] on behalf of the Thésaurus National de Cancérologie Digestive (TNCD): Société Nationale Française de Gastroentérologie (SNFGE), Fédération Francophone de Cancérologie Digestive (FFCD), Fédération Nationale des Centres de Lutte Contre le Cancer (UNICANCER), Groupe Coopérateur multidisciplinaire en Oncologie (GERCOR), Société Française de Chirurgie Digestive (SFCD), Société Française d'Endoscopie Digestive (SFED), Association Française pour l'Etude du Foie (AFEF), Société Française de Radiothérapie Oncologique (SFRO), Société Française de Pathologie (SFP), Société Française de Radiologie (SFR), Association de Chirurgie Hépatobilio-Pancréatique et Transplantation (ACHBPT), Réseau National de Référence des Tumeurs Rares du Péritoine (RENAPE), Société Nationale Française de Colo-Proctologie (SNFCP).

* Correspondence to: Aziz Zaanan, Department of Gastroenterology and Digestive Oncology, European Georges Pompidou Hospital, University Paris Cité, 20 rue Leblanc, Paris 75015, France

E-mail address: aziz.zaanan@aphp.fr (A. Zaanan).

<https://doi.org/10.1016/j.ejca.2026.116697>

Received 4 February 2026; Received in revised form 16 March 2026; Accepted 19 March 2026

Available online 24 March 2026

0959-8049/© 2026 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

FLOT followed by durvalumab for 10 months as maintenance therapy was associated with a significant improvement of survival. For metastatic disease, the first-line chemotherapy is based on platinum–fluoropyrimidine combination. The addition of targeted therapy and/or immunotherapy to doublet chemotherapy depends on the tumor biomarker profile, including HER2 (trastuzumab), claudin18.2 (zolbetuximab), PD-L1 and dMMR/MSI phenotype (anti-PD1 monoclonal antibodies). The addition of docetaxel, based on the triplet TFOX regimen may be considered for selected patients with biomarker-negative tumors. Resection of primary tumor and metastases cannot be recommended but may be considered on an individual basis in highly selected patients with oligometastatic disease who respond to systemic treatment. Various drugs are indicated beyond first-line of treatment, including trastuzumab-deruxtecan for HER2-positive tumors.

Conclusion: These national guidelines on gastric cancer are intended to facilitate decision-making in daily clinical practice. These recommendations are subject to ongoing review. Each individual case should be discussed within a multidisciplinary team.

1. Introduction

This guideline is a collaborative work involving most French medical societies (SNFGE, FFCD, UNICANCER, GERCOR, SFCD, SFED, AFEF, SFRO, SFP, SFR, ACHBPT, RENAPE, SNFCP) from different specialties engaged in the management of gastric cancer (gastric surgeons, pathologists, radiation oncologists, medical oncologists and gastroenterologists). The treatment of esophageal adenocarcinomas is addressed in the esophageal chapter of the French guidelines [1], whereas adenocarcinomas of the gastroesophageal junction (GEJ), often included in gastric cancer studies regardless of Siewert classification, are covered in the present guidelines. Recommendations were based on previous guidelines of the French intergroup, and data published in the literature until January 2026 using the following keywords in PubMed "gastric and gastroesophageal junction cancer", "incidence", "early cancer", "chemotherapy", "surgical treatment". Results from unpublished studies presented as oral communication at the "American Society of Clinical Oncology" (ASCO), "American Society of Clinical Oncology Gastrointestinal Cancers Symposium" (ASCO GI), "European Society of Medical Oncology" (ESMO) or "European Society of Medical Oncology Gastrointestinal Cancers Congress" (ESMO GI) meetings were included. These guidelines reflect a consensus process involving several national scientific societies representing the different specialties involved in the management of gastric and GEJ adenocarcinoma. In this context, the recommendations are not based on a formal voting procedure. Rather, they result from a process of multidisciplinary discussions and exchanges among experts designated by the participating societies. The available scientific evidence is reviewed and the proposed statements are discussed collectively until a consensus is reached. Levels of evidence were specified according to standard definition with grade A (large meta-analyses or large randomized trial), grade B (small randomized trials), grade C (prospective non-randomized study), and expert opinion (when no scientific evidence was validated) (Table 1). All the statements in the current article completely match the original full French guidelines available on the website of the French Society of Gastroenterology (SNFGE) (www.tnecd.org).

Table 1
Grade of recommendations.

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on highly robust scientific evidence (large metanalysis or large randomized trial)
B	Moderate	Usually recommended based on scientific presumption (small randomized trials)
C	Low	Option according to expert opinion based on weak scientific evidence (prospective non randomized study)
Expert agreement	Very low	No scientific evidence validated

2. Epidemiology

Gastric cancer ranks as the fifth most diagnosed malignancy worldwide with almost 1 million new cases diagnosed annually, leading to more than 650,000 deaths worldwide [2]. The incidence of gastric cancer varies globally, with the highest rates in Asia and South America, and the disease is more prevalent in males than females [2]. In Europe, approximately 135,000 incident gastric cancer cases and 95,000 deaths were estimated in 2022 [2]. Recently, some data suggest an increase in the incidence of gastric cancer in individuals under 50 years old, particularly in countries with low incidence where the prevalence of *Helicobacter pylori* infection is low [3]. The suggested hypotheses involve gastric microbiota dysbiosis, possibly linked to contemporary lifestyle factors, along with increasing rates of obesity and autoimmune disorders in younger populations [4]. In France, gastric cancer incidence rate has been decreasing over the past 20 years (–1.8%/year), reaching a plateau in the last years (6550 and 6557 new cases diagnosed in 2012 and 2019, respectively) [5]. This decrease is due notably to a better control of the risk factors, particularly *Helicobacter pylori* infection. The other risk factors are pernicious anemia (Biermer disease), smoking, alcohol consumption, Epstein-Barr virus infection, high-salt diet, history of partial gastrectomy (more than 10 years) and ethnic origins [6]. Gastric cancer demonstrates familial aggregation in approximately 10% of cases, and an inherited genetic predisposition is observed in 1–3% of patients.

3. Diagnosis, risk assessment and clinical staging, biomarkers

Algorithms for diagnosis and staging investigations in gastric cancer patients are summarized in Figure 1. The histological diagnosis is reported according to the "World Health Organization" (WHO) and Lauren classification (Table 2). TNM stage should be determined according to the latest edition of the "American Joint Committee on Cancer" (AJCC) – "Union for International Cancer Control" (UICC) guidelines [7] (Tables 3 and 4).

3.1. Diagnosis

Upper gastrointestinal endoscopy with biopsies is the most appropriate diagnostic method. When superficial (T1) neoplasia is suspected, biopsies from the lesion should be limited to prevent fibrosis that could compromise endoscopic treatment, while additional biopsies should be taken from other gastric areas to evaluate for intestinal metaplasia and dysplasia. The detection rate is improved by endoscopy with virtual chromoendoscopy. For endoscopically unresectable lesions, at least 10 biopsies should be performed to evaluate the histological subtypes and differentiation (Table 2), and to analyze different biomarkers for the treatment strategy. In linitis plastica, endoscopic biopsies have low sensitivity (50%) [8]. In case of negative standard biopsies, deep (bite on bite) biopsies, macrobiopsy or endoscopic ultrasound-guided fine-needle biopsy may be proposed.

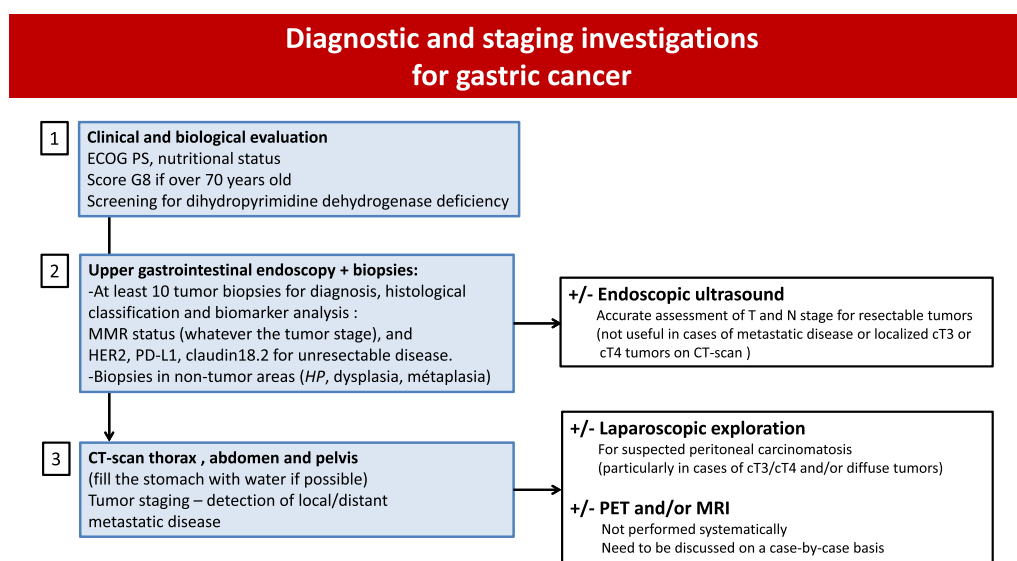


Fig. 1. Diagnostic and staging investigations in gastric cancer. **Abbreviation:** CT, computed tomography; EUS, endoscopic ultrasound; T, tumor; N, node; PET, positron emission tomography; MRI, magnetic resonance imaging; HP, *Helicobacter pylori*.

3.2. Risk assessment and clinical staging

Physical assessment is essential to ensure that patients are correctly selected for specific treatments (Figure 1). Nutritional status and history of weight loss should be assessed, as well as comorbidities to identify those requiring additional support. A geriatric evaluation should be considered for patients aged 70 years and older before treatment decisions. In clinical practice, the G8 screening tool assesses nutritional status, mobility, neuropsychological status, medication use, and comorbidities, with scores ranging from 0 to 17. A score of 14 or below indicates the need for a full comprehensive geriatric assessment, while lower scores (e.g., 12 or 10) reflect increasing frailty and higher risk of treatment-related complications [9]. Patients should be tested for dihydropyrimidine dehydrogenase (DPD) deficiency before starting treatment with 5-fluorouracil or capecitabine.

Initial tumor staging should include computed tomography (CT)-scan +/- endoscopic ultrasonography (EUS) and laparoscopy (Figure 1). Thoracic, abdominal and pelvis CT-scan is required for

staging assessment before treatment and to detect distant metastases [10,11]. The performance of CT-scan for diagnosis of locoregional lymph node and parietal gastric extension may be improved by filling the stomach with water. Endoscopic ultrasonography is more sensitive than CT-scan for evaluating superficial tumor infiltration and locoregional lymph node involvement. Endoscopic ultrasonography is useful when preoperative treatment is discussed, but not in case of metastatic disease or localized cT3 and cT4 tumors on CT-scan. Laparoscopic exploration with or without peritoneal cytology could be discussed for resectable gastric cancer to exclude peritoneal carcinomatosis, especially for cT3/cT4 tumors or poorly cohesive carcinomas [12] (Figure 1).

Other imaging explorations are optional and should be discussed on a case-by-case basis depending on the context. Magnetic Resonance Imaging is not systematically performed but may be complementary to CT-scan, notably for the diagnosis of hepatic metastases. Positron emission tomography (FDG-PET) could be used in potential surgical candidates but its indication is not clearly defined and validated in gastric cancer and may not be informative for mucinous or diffuse/

Table 2

Histological classifications of gastric cancer.

Lauren classification
Intestinal
Diffuse
Mixed
World Health Organization “WHO” classification
Adenocarcinoma
Papillary adenocarcinoma
Tubular adenocarcinoma
Mucinous adenocarcinoma
Poorly cohesive adenocarcinoma (including signet ring cell carcinoma and other variants)
Adenosquamous carcinoma
Mixed adenocarcinoma
Carcinoma with lymphoid stroma (medullary carcinoma)
Hepatoid adenocarcinoma
Squamous cell carcinoma
Undifferentiated carcinoma
Neuroendocrine neoplasm
Differentiation category
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
Gx Not evaluable

Table 3

TNM staging of gastric cancer according to the UICC 9th Edition.

Primary tumor (T)
Tis Carcinoma in situ; intra-epithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1 Tumor invades lamina propria or muscularis mucosae or submucosa
T1a Tumor invades lamina propria or muscularis mucosae or submucosa
T1b Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades subserosa
T4 Tumor perforates subserosa (visceral peritoneum) or invades adjacent structures
T4a Tumor perforates subserosa (visceral peritoneum)
T4b Tumor invades adjacent structures
Regional lymph nodes (N)
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–2 regional lymph nodes
N2 Metastasis in 3–6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes
N3a Metastasis in 7–15 regional lymph nodes
N3b Metastasis in 16 or more regional lymph nodes
Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Table 4
Tumor stage group for gastric cancer according to the UICC 9th Edition.

Stage group	T stage	N stage	M stage
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1,N2	M0
	T4b	N0	M0
Stage IIIB	T1	N3b	M0
	T2	N3b	M0
	T3	N3a	M0
	T4a	N3a	M0
	T4b	N1,N2	M0
Stage IIIC	T3	N3b	M0
	T4a	N3b	M0
	T4b	N3a, N3b	M0
Stage IV	Any T	Any N	M1

poorly cohesive carcinomas [13]. Tumor markers (CEA and CA 19–9) could be useful for the treatment evaluation or detection of recurrence.

3.3. Biomarkers

Several biomarkers are needed to guide the treatment of gastric cancer: MMR status for both localized and metastatic settings (also useful for Lynch syndrome screening), and HER2, PD-L1 and claudin18.2 expression for metastatic disease. Reflex testing should be performed for MMR, HER2, PD-L1 and claudin18.2 at the time of diagnosis in order to save tumor tissue and provide faster results than sequential analysis.

MMR. Diagnosis of dMMR/MSI or pMMR/MSS status is evaluated with immunohistochemistry (IHC) by using antibodies against the 4 MMR proteins (MLH1, MSH2, MSH6 and PMS2) to detect the loss of expression of MMR heterodimers, and/or with molecular biology by using polymerase chain reaction (PCR) [14,15]. Regarding the tumor sample for the MMR assessment, IHC can be used even when the tumor cells content is very low, whereas conventional PCR techniques require at least 20% of tumor cells [14,15]. Both tests are recommended to confirm dMMR/MSI status before starting immunotherapy treatment (<https://www.cancer.fr>).

HER2. Screening of HER2 overexpression is evaluated by IHC + /- in situ hybridization (ISH) with the Ruschhoff-Hofmann scoring system [16]. The absence of membrane staining in IHC is scored 0, while weak, moderate and intense staining are respectively scored 1, 2 and 3. Tumors with an IHC score of 0 or 1 + are considered HER2 negative. Tumors with an IHC score of 2 + should be analyzed by ISH to determine HER2 status. Tumors with an IHC score of 3 + or 2+/ISH+ are considered HER2 positive.

PD-L1. Expression of PD-L1 is assessed by IHC using either the “Combined Positive Score” (CPS) or the “Tumor Area Positivity” (TAP) score. These two scoring methods appear concordant, are considered clinically comparable, and can guide treatment decision for anti-PD1agents in metastatic disease [17].

The CPS (Combined Positive Score) is a cell-counting-based

approach that calculates the ratio of the total number of cells PD-L1 positives (including tumor cells, mononuclear lymphocytes, and tumor-associated macrophages) to the total number of viable tumor cells (X 100).

The TAP (Tumor Area Positivity) score is an alternate PD-L1 scoring system based on visual estimation. The TAP score is assessed on IHC slide as the ratio of the area occupied by PD-L1-positive tumor cells and all immune cells to the total tumor area, without counting the cells precisely.

For both CPS and TAP score, a minimum of 100 invasive viable tumor cells is required for assessment of PD-L1 expression.

Claudin18.2. Screening of claudin18.2 overexpression is evaluated by IHC [18]. The expected staining pattern is membranous and evaluated semi-quantitatively, taking into account both the intensity of the staining (weak, moderate, strong) and the percentage of tumor cells stained at each intensity level. Claudin 18.2 positive is currently defined by $\geq 2 +$ intensity in $\geq 75\%$ of tumor cells. A minimum of 50 invasive viable tumor cells is required for assessment.

3.4. Recommendations

- Diagnosis should be made from upper gastrointestinal endoscopy with multiple biopsies (at least 10), being reviewed according to the WHO and Lauren classification [**expert agreement**].
- Initial clinical staging should include biological and physical assessment, CT-scan of the thorax, abdomen and pelvis + /- EUS for T and N staging in case of resectable disease [recommendation: **grade C**].
- Magnetic Resonance Imaging and FDG–PET can be performed but are not routinely recommended [recommendation: **grade B**].
- Laparoscopy + /- peritoneal cytology could be performed for resectable disease in case of locally advanced (cT3/T4) or poorly cohesive tumors [**expert agreement**].
- The dMMR/MSI test should be performed routinely regardless of tumor stage, as it is a predictive marker of response to immune checkpoint inhibitors and contributes to the screening of Lynch syndrome [recommendation: **grade C**].
- HER2, PD-L1 (based on CPS and TAP score) and claudin18.2 status are predictive biomarkers for response to anti-HER2 drugs, immunotherapy and zolbetuximab, respectively, and should be assessed in patients with advanced disease [recommendation: **grade A**].

4. Therapeutic management of local/locoregional disease

A multidisciplinary board meeting is required before any treatment. Therapeutic algorithm is summarized in [Figure 2](#).

4.1. Endoscopic resection for early cancer

Despite advances in endoscopic devices, less than 5% of gastric cancers are diagnosed at an early stage (T1N0) and treated by endoscopic resection [19]. Two different techniques can be used for endoscopic resection: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). As compared to EMR, ESD is associated with a higher “en-bloc” resection rate, higher R0 resection rate, and a lower recurrence rate, but with a longer procedure time and a higher perforation risk [20].

The endoscopic treatment is preferentially proposed in case of intestinal adenocarcinoma, and requires an initial endoscopic assessment of the extension in surface and depth (using virtual chromoendoscopy + /- EUS). The resection must be “en-bloc” and therefore performed preferably by ESD. Due to a higher risk of lymph node invasion, endoscopic resection is not recommended for (i) poorly differentiated lesions larger than 2 cm or with ulceration, (ii) or for ulcerated well-differentiated lesions larger than 3 cm [21].

Even after an R0 resection of a gastric lesion, additional surgery with

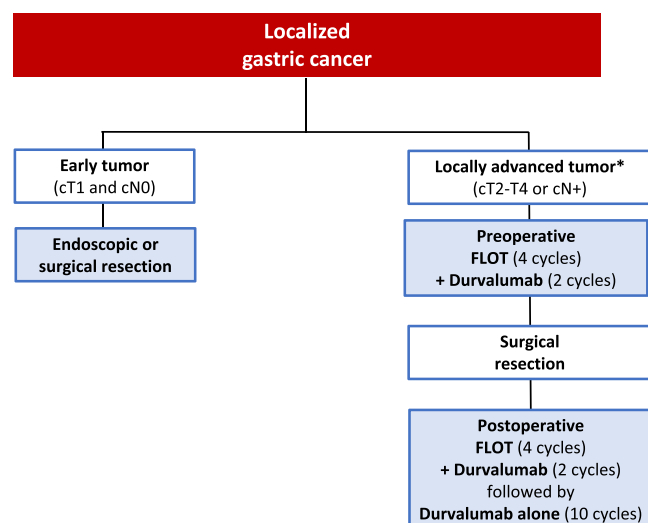


Fig. 2. Treatment algorithm for localized gastric cancer. Criteria for endoscopic instead of surgical resection are specified in the text. *Perioperative chemotherapy with FLOT is the standard of care for localized gastric cancer $\geq$ cT2 or cN + , with the addition of durvalumab for $\geq$ cT3 or cN + disease. The CRITICS and TOPGEAR trials found no survival benefit in adding post- or pre-operative chemoradiotherapy to perioperative chemotherapy. Consider neoadjuvant or perioperative immune checkpoint inhibitors (if available) without chemotherapy for $\geq$ cT2 or cN + dMMR/MSI tumors.

lymph node dissection should be considered (taking into account surgical morbidity and mortality) in the presence of lymphovascular invasion, submucosal lesions (pT1sm1) that are either ulcerated or predominantly poorly differentiated, or submucosal invasion $> 500 \mu\text{m}$ (pT1sm2). In case of deep (vertical) R1 resection margins, surgical resection with lymph node dissection should be offered as a salvage treatment. In cases of lateral (horizontal) R1 margins, repeat endoscopic resection may be considered [20].

After endoscopic resection of early gastric cancer, careful surveillance endoscopies with chromoendoscopy (virtual chromoendoscopy +/- zoom) should be performed at 3–6 months after resection, and annually thereafter [20]. *Helicobacter pylori* infection must be treated to reduce the metachronous cancer risk.

4.2. Surgery

For the distal gastric cancer, a distal subtotal gastrectomy remains the standard for non-signet-ring cells [22,23], while a total gastrectomy should be performed in case of signet-ring cells; however, a distal subtotal gastrectomy could be proposed in case of signet-ring cells if the proximal resection R0 margin is $> 8 \text{ cm}$. For tumors at other locations, a total gastrectomy should be performed regardless of the histological subtypes. All resections should be performed in “mono-bloc”, especially for T4 tumors. The recommended proximal gastric and distal duodenal macroscopic surgical margins are $\geq 5 \text{ cm}$ and $\geq 1 \text{ cm}$, respectively. The type of reconstruction remains at surgeon’s discretion. D1 lymphadenectomy is indicated for early gastric cancers (cT1/N0), while a spleen-preserving D2 lymphadenectomy removing at least 16 lymph nodes is the standard approach for locally advanced gastric cancer ($\geq$ cT2 or cN+) [24–26]. Extended lymphadenectomies are not recommended and should be considered only in clinical trials [27].

Laparoscopic compared to open surgery has the potential benefit of decreased postoperative morbidity and reduced recovery with a similar R0 lymphadenectomy and tumor resection rate. For the distal gastrectomy, several Asian studies have shown that laparoscopic was non-inferior to laparotomy in terms of survival, even for T4a gastric cancer, and appeared to offer better postoperative safety [28–30]. For the total gastrectomy, two randomized trials have been conducted in

western countries, the STOMACH study (total gastrectomy) [31] and the LOGICA study (total or subtotal gastrectomy) [32], and showed similar short-term results, with non-inferior recurrence-free survival for the laparoscopic versus open surgical approach in expert centers. The main limitation of these studies is the insufficient hindsight to analyze long-term results. Laparoscopic total gastrectomy is possible in expert centers.

Robotic gastrectomy is an evolving minimally invasive technique for gastric cancer, potentially offering improved surgical precision, although its oncologic benefit over laparoscopy and cost-effectiveness remain under investigation [33]. Robotic gastrectomy is currently being considered as an option in some expert centers.

After curative surgery, histological report should include the following items:

- Macroscopic data (type of resection, location, and tumor size)
- Histological subtype according to Lauren and/or WHO classification
- Differentiation grade
- Tumor (T) and lymph node (N) extension (number of invaded/analyzed lymph nodes)
- Measurement of proximal, distal, and radial resection margins to qualify the resection as R0, R1 or R2
- Existence of vascular emboli, lymphatic invasion or perineural invasion
- Response to neoadjuvant therapy, if applicable

4.3. Perioperative treatment

Perioperative chemotherapy is the standard of care for tumors $\geq$ cT2 and/or N + . Two randomized phase 3 studies of perioperative chemotherapy versus surgery alone have shown a significant improvement in survival with the ECF (Epirubicin-Cisplatin–5-fluorouracil) and 5FU-cisplatin regimens [34,35]. Thereafter, the FLOT4 study showed a significant improvement of survival in the perioperative FLOT arm (4 cycles in pre- and post-operative setting) compared to perioperative ECF arm in terms of recurrence-free survival (median: 30 versus 18 months) and overall survival (median: 50 versus 35 months), with a 5-year survival rate at 45% versus 36%. All subgroups benefited from perioperative FLOT, including GEJ location or diffuse forms. In the FLOT study, surgery was performed according to current quality standards (D2 lymphadenectomy) [36].

Recently, the MATTERHORN phase III trial has evaluated in patients with resectable $\geq$ cT3 and/or N + gastric and GEJ adenocarcinoma, the perioperative FLOT plus either durvalumab (D-FLOT) or placebo, followed by up to 10 months of durvalumab or placebo maintenance therapy. The event-free survival (HR 0.71, $p < 0.001$), pCR rates (19.2% versus 7.2%), and overall survival (HR 0.78, $p = 0.021$) were significantly improved in favor of the durvalumab arm, with a 3-year survival rate at 68.6% versus 61.9%. Toxicity was comparable between treatment arms [37,38]. In March 2026, durvalumab received EMA approval for this indication, along with a positive opinion for early access in France pending reimbursement decision.

4.4. Post-operative treatment

In patients who did not receive preoperative chemotherapy, a meta-analysis showed that fluoropyrimidine-based adjuvant chemotherapy was associated with a significant improvement of survival in 3838 patients from 17 clinical trials (HR, 0.82; $p < 0.001$) [39]. In the Korean CLASSIC randomized phase III trial, the CAPOX adjuvant chemotherapy was associated with a significant improvement of survival compared with surgery alone [40].

Postoperative chemoradiotherapy was shown superior to surgery alone in the MACDONALD et al phase 3 trial published in 2001 [41]. However, several criticisms of this trial were raised concerning i) lymph node resection, which was D0 in 54% of cases, ii) the toxicity of an

obsolete chemotherapy regimen (FUFOL) and iii) the 2D radiotherapy technique. As compared to perioperative chemotherapy, the phase III CRITICS study did not show a significant improvement of survival by adding post-operative chemoradiotherapy in patients treated with pre-operative chemotherapy [42]. In addition, two other studies in Asian populations did not confirm the benefit of postoperative chemoradiotherapy versus adjuvant chemotherapy alone after surgery and D2 lymph node resection [43], even in node-positive diseases [44]. Post-operative chemoradiotherapy is therefore not recommended in cases of R0 resection after adequate surgery and lymph node resection.

4.5. Special case of dMMR/MSI tumors

Patients with localized dMMR/MSI gastric and GEJ adenocarcinomas who undergo surgery have a better prognosis than those with pMMR/MSS tumor phenotype [45]. Retrospective analyses of randomized trials suggest no added survival benefit from adjuvant or perioperative chemotherapy in this population [45]. The two phase 2 trials NEONIPIGA [46] and INFINITY [47] reported in small groups (29 and 15 patients, respectively) of dMMR/MSI resectable tumors ($\geq$ cT2 and/or cN+) high pCR rates (around 60%) with neoadjuvant dual immunotherapy alone (nivolumab and ipilimumab in NEONIPIGA; durvalumab and tremelimumab in INFINITY). Furthermore, in the small subgroups of dMMR/MSI patients included in two randomized trials, the pCR rate was improved with the addition of anti-PD-L1 monoclonal antibody to perioperative FLOT chemotherapy from 27% to 63% (atezolizumab) in the DANTE study (n = 23) [48], and from 8.3% to 28.3% (durvalumab) in the MATTERHORN study (n = 49) [37].

4.6. Recommendations

- Endoscopic resection is recommended for very early tumors (T1) with a low risk of lymph-node invasion [recommendation: **grade A**]. ESD is the reference technique [recommendation: **grade B**] and should be performed in an expert center.
- D1 lymphadenectomy is recommended for early gastric cancers (cT1/cN0), while a spleen-preserving D2 lymphadenectomy removing at least 16 lymph nodes is the standard approach for locally advanced gastric cancer ($\geq$ cT2 or cN+) [recommendation: **grade B**].
- For locally advanced tumors $\geq$ cT2 or cN+, perioperative FLOT chemotherapy is the standard of care [recommendation: **grade A**]. Based on the Matterhorn trial, the addition of durvalumab to perioperative FLOT is recommended for tumors $\geq$ cT2 or cN+ [recommendation: **grade A**].
- For patients with stage pT2 or pN+ tumors who underwent surgery without preoperative treatment, adjuvant fluoropyrimidine-based chemotherapy for 6 months is recommended [recommendation: **grade B**].
- For dMMR/MSI tumors, preoperative immunotherapy if available is recommended for locally advanced tumors $\geq$ cT2 or cN+ [recommendation: **grade C**].

5. Therapeutic management of metastatic disease

Most pivotal randomized trials evaluating systemic therapies in metastatic gastric cancer have enrolled patients with both gastric and GEJ adenocarcinomas. Therefore, the treatment strategies described in this section for metastatic gastric cancer are also applicable to GEJ adenocarcinoma. The management of metastatic disease is based on systemic drug therapy aimed at prolonging survival while maintaining quality of life. Active management of symptoms is crucial, along with all nutritional, psychosocial, and comfort support measures. With the increasing use of immunotherapy and targeted therapies in advanced gastric cancer, a subset of patients may experience prolonged responses and long-term survival. In this context, treatment duration, maintenance

strategies, and the balance between therapeutic efficacy and treatment-related toxicity are important considerations in clinical practice. In several trials, immune checkpoint inhibitors were continued as maintenance therapy after combination with chemotherapy, highlighting the potential role of treatment continuation in responders [49]. Although chemotherapy de-escalation was not assessed in most of randomized clinical trials, interruption of platinum agent administration can be considered after 4–6 months of treatment [expert agreement]. In addition, quality-of-life outcomes should be considered when selecting systemic treatments, particularly in the metastatic setting where maintaining symptom control and functional status remains a major objective of care.

The role of surgery in oligometastatic gastric cancer remains uncertain. Early retrospective studies and meta-analysis suggested a potential survival benefit in selected patients, and the phase II FLOT3 study reported encouraging outcomes in patients undergoing resection after response to chemotherapy [50,51]. However, in the randomized phase III RENAISSANCE trial presented at the ASCO Meeting in 2024 (not published yet), the addition of surgery to systemic chemotherapy did not improve overall survival compared with chemotherapy alone in patients with limited metastatic disease [52]. The role of surgery is also debated in the specific setting of peritoneal metastases [53]. In the randomized GASTRIPEC trial, all patients with peritoneal carcinomatosis underwent cytoreductive surgery and were randomized to receive hyperthermic intraperitoneal chemotherapy (HIPEC) or not; the addition of HIPEC did not significantly improve overall survival [54]. Ongoing randomized trials are evaluating the role of cytoreductive surgery (with or without HIPEC) compared with systemic therapy alone in this setting, including the CONVERGENCE trial (NCT07241715). On the basis of the currently available evidence, surgical resection of metastases cannot be routinely recommended, but may be considered in highly selected patients with oligometastatic disease who achieve a favorable response to systemic therapy, following discussion in a multidisciplinary tumor board [expert agreement].

Palliative endoscopic treatments can be discussed with metallic endoscopic stents for stenosing tumors invading the cardia or gastroenterostomy for gastric outlet obstruction. Recent randomized trials demonstrated the superiority of endoscopic gastrojejunostomies over surgical approach, regarding to oral intake, need for reinterventions or supplemental nutrition, length of hospitalization, quality of life and treatment costs [55,56]. Bleeding tumors can be treated with sclerosis, argon plasma, radiotherapy or hemostatic powder, with a high risk of failure or bleeding recurrence [57]. Palliative gastrectomy may be discussed in cases of occlusion or bleeding symptoms uncontrolled by other therapeutic approaches [58].

5.1. First-line treatment

The current recommended therapeutic algorithm is summarized in Figure 3a.

5.1.1. Chemotherapy

Chemotherapy has been the cornerstone of first-line treatment for metastatic gastric cancer for several decades. Compared with best supportive care alone, systemic chemotherapy has been shown to improve overall survival and quality of life [59]. In addition, randomized studies demonstrated that doublet chemotherapy regimens provide superior survival outcomes compared with single-agent fluoropyrimidine therapy, with a median overall survival of approximately 11 months [59]. Consequently, doublet regimens based on a fluoropyrimidine combined with a platinum compound have long been considered the standard first-line treatment backbone in advanced gastric cancer. Several trials have demonstrated equivalence in terms of efficacy for the fluoropyrimidine (5FU and capecitabine), and the platinum salts (cisplatin and oxaliplatin) [60,61]. In elderly patients ($>$ 65–70 years), oxaliplatin has a better safety profile than cisplatin and may be associated with better

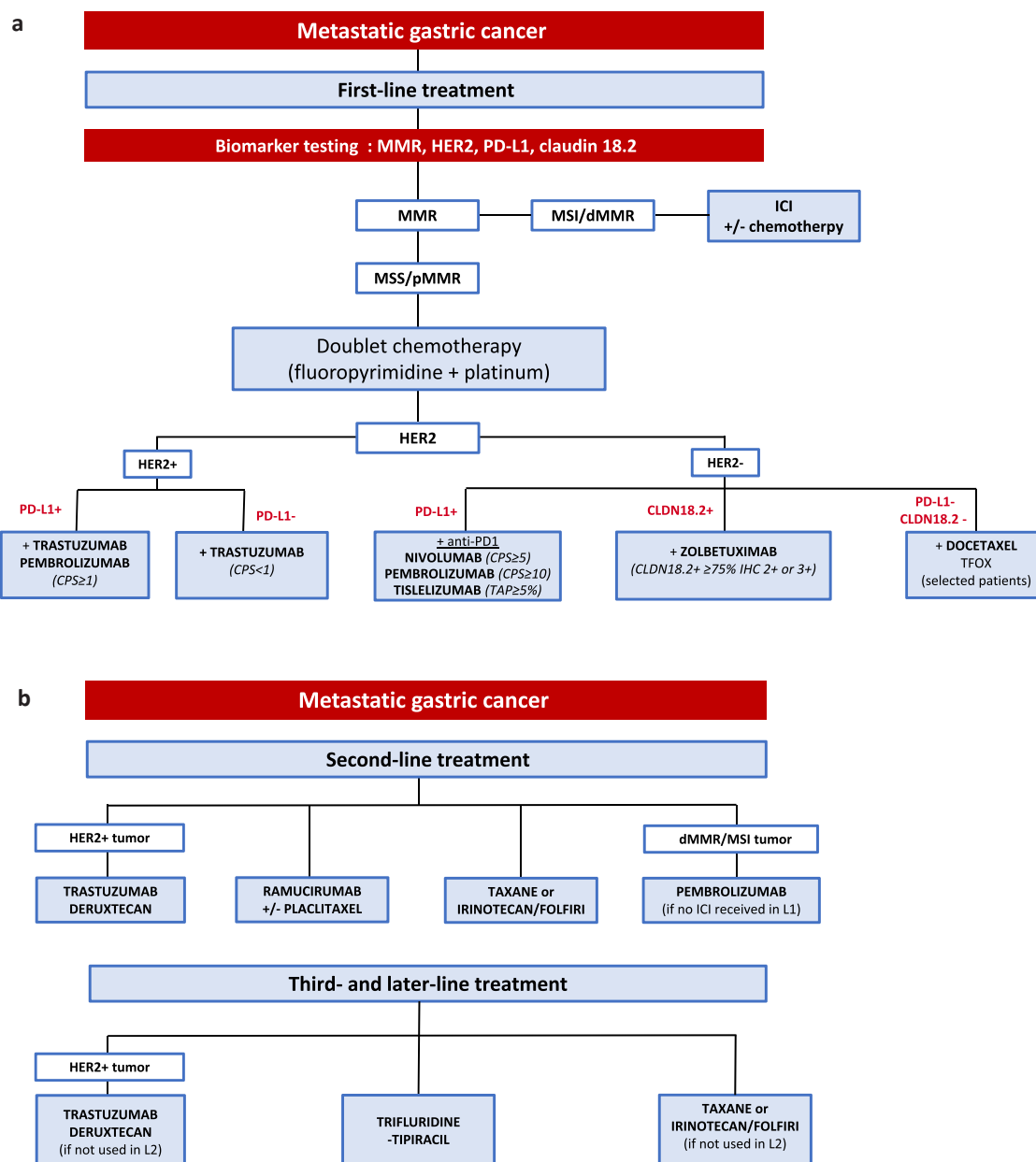


Fig. 3. Treatment algorithm for metastatic gastric cancer. Figure 3a. Treatment algorithm for first-line therapy of metastatic gastric cancer. Figure 3b. Treatment algorithm beyond the first-line therapy of metastatic gastric cancer. **Abbreviation:** CPS, combined positive score; TAP, tumor area positivity; dMMR, deficient mismatch repair; MSI, microsatellite instability-high; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; PD-1, programmed cell-death protein 1; PD-L1, programmed death-ligand 1.

survival [60].

Docetaxel-based triplet chemotherapy, combining high dose of cisplatin, 5FU and docetaxel, administered every 3 weeks (DCF protocol), was shown to be better than the doublet 5FU-cisplatin but was associated with substantial toxicity (particularly hematological and infectious), thus limiting its use in clinical practice [62]. The alternative docetaxel-based triplet TFOX regimen with a lower dose of drugs administered every two weeks (5FU, oxaliplatin, docetaxel) significantly improved survival and objective response rate compared to FOLFOX, and appeared to have a better hematological safety profile than the DCF regimen. In subgroup analysis of the GASTFOX trial, the benefit of TFOX was even greater for young (aged less than 70 years), and fit patients (ECOG PS 0), or for patients with diffuse histological form [63].

Irinotecan combined with 5FU (FOLFIRI) has also shown efficacy in first-line treatment in a French phase 3 trial [64], and may be a therapeutic option if platinum salts are contraindicated.

5.1.2. HER2-negative tumor

5.1.2.1. Anti-PD1 monoclonal antibody. The phase 3 Checkmate 649 study showed that the addition of nivolumab (anti-PD1) to CAPOX or FOLFOX doublet chemotherapy was associated with a significant improvement in progression-free survival (HR=0.68) and overall survival (HR=0.71) in tumors with CPS ≥ 5, leading to EMA approval in 2021 and subsequent reimbursement in France for this subgroup of patients [65]. The phase 3 Keynote 859 study confirmed the overall survival benefit of pembrolizumab (anti-PD1) combined with doublet chemotherapy in the overall population (HR=0.78) [66]. In this study, the survival benefit was greater in subgroups of patients with tumors CPS ≥ 1 (HR=0.74) and CPS ≥ 10 (HR=0.65). Based on these results, pembrolizumab was approved in the EU in 2023 for tumors CPS ≥ 1 although reimbursement in France is limited to tumors CPS ≥ 10. More recently, the phase 3 RATIONALE 305 trial also demonstrated the

efficacy of tislelizumab (anti-PD1) in combination with platinum-based doublet chemotherapy. Median overall survival was improved in the overall population (HR=0.80), with a greater survival benefit observed in tumors with TAP $\geq$ 5% (HR=0.74) [67]. Based on these results, tislelizumab was approved by the EMA in 2024 for this subgroup, and reimbursement in France has been granted accordingly.

5.1.2.2. Anti-claudin18.2 monoclonal antibody. Zolbetuximab is a monoclonal antibody directed against the 18.2 isoform of claudin, a protein involved in intercellular tight junctions. Two international phase 3 randomized trials demonstrated that the addition of zolbetuximab to oxaliplatin-based doublet chemotherapy (FOLFOX for the SPOTLIGHT study, and CAPOX for the GLOW study) significantly improved progression-free survival and overall survival in patients with tumors overexpressing claudin18.2 in moderate to intense IHC for $\geq$ 75% of tumor cells [68,69]. Nausea and vomiting frequently occur during the initial infusions of zolbetuximab. To manage these effects, antiemetic prophylaxis in line with guidelines for highly emetogenic chemotherapy should be administered at least during the initial cycles. The infusion rate of zolbetuximab may be also reduced if such symptoms occur [70]. Following these results, zolbetuximab received EMA approval in 2024, and early access has been available in France since January 2025 for patients with HER2-negative tumors and CPS $<$ 5, pending formal reimbursement.

5.1.3. HER2-positive tumor

5.1.3.1. Trastuzumab. Trastuzumab is a monoclonal antibody targeting one extracellular domain (ECD4) on the HER2 receptor. The ToGA phase III trial showed that the addition of trastuzumab to platinum-based doublet chemotherapy was associated with increased overall survival in patients with HER2-positive tumors (IHC3 + or HIS+) [71]. The benefit was greater for tumor IHC3 + or IHC2 + / ISH + for which trastuzumab was approved. As trastuzumab is cardiotoxic, monitoring of left ventricular ejection fraction every 3 months is recommended.

5.1.3.2. Zanidatamab. Zanidatamab is a bispecific monoclonal antibody directed against two extracellular domains (ECD2 and ECD4) on the HER2 receptor. According to the first interim analysis from the phase 3 HERIZON-GEA-01 trial presented at the 2026 ASCO-GI meeting, the doublet chemotherapy plus zanidatamab significantly improved progression-free survival (median, 12.4 vs 8.1 months, HR=0.65; $p < 0.0001$) and delivered an overall survival advantage (median, 24.4 vs 19.2 months, HR=0.80; $p = 0.056$) over doublet chemotherapy plus trastuzumab in first-line treatment of HER2-positive metastatic disease. The most common treatment-related event was diarrhea in the experimental arm (20% of grade $\geq$ 3), generally occurring in the first cycle [72]. The results of the final overall survival analysis are still pending.

5.1.3.3. Anti-PD1 monoclonal antibody. The phase 3 Keynote-811 trial evaluated the addition of pembrolizumab to trastuzumab plus doublet chemotherapy. Final results demonstrated a statistically significant improvement in survival, with greater benefit in tumors with CPS $\geq$ 1 for both progression-free survival (HR=0.70) and overall survival (HR=0.79) [73,74]. Based on these data, pembrolizumab in combination with trastuzumab and chemotherapy was approved by the EMA for HER2-positive/CPS $\geq$ 1 tumors, and early access has been granted in France since February 2025 while reimbursement is pending.

In the phase 3 HERIZON-GEA-01 trial, the combination of chemotherapy, zanidatamab, and tislelizumab significantly improved progression-free survival (median 12.4 vs 8.1 months; HR=0.63; $p < 0.0001$) and overall survival (median 26.4 vs 19.2 months; HR=0.72; $p = 0.0043$) compared with chemotherapy plus trastuzumab. The most frequent treatment-related adverse event in the experimental arm was diarrhea (24% grade $\geq$ 3), typically occurring during the first

cycle [72]. Results from the comparison of chemotherapy plus zanidatamab with or without tislelizumab are still pending. At the time of writing these guidelines, zanidatamab has not yet received EMA approval for patients with HER2-positive metastatic disease.

5.1.4. Special case of dMMR/MSI tumors

The dMMR/MSI phenotype represents a major predictive biomarker of response to immune checkpoint inhibitors. However, there is no randomized trial dedicated to patients with advanced dMMR/MSI gastric and GEJ adenocarcinoma. In the first-line treatment of dMMR/MSI metastatic disease, subgroup analyses of several randomized phase 3 trials have suggested remarkable efficacy of anti-PD1 in combination with doublet chemotherapy [65–67]. A recent phase II single arm study showed an ORR of 62.1% and median PFS of 13.8 months (median OS was not reached) with a dual immune checkpoint inhibitors combining nivolumab and ipilimumab in first-line treatment of 29 patients with dMMR/MSI advanced disease [75]. There is no EMA approval for immunotherapy in the first-line treatment of dMMR/MSI advanced gastroesophageal adenocarcinoma; however, these tumors are often PD-L1 positive, which may support the use of immune checkpoint inhibitor-based therapies.

5.2. Second-line treatment

The current recommended therapeutic algorithm is summarized in Figure 3b.

5.2.1. Chemotherapy

Cytotoxic chemotherapy with taxane [76] or irinotecan [77] has demonstrated its efficacy in phase 3 trials by significantly improving patient survival compared to best supportive care alone. These two drugs appear to have equivalent efficacy [78,79]. Irinotecan can be combined with 5FU (FOLFIRI) based on a randomized phase 3 trial evaluating the sequence of FOLFIRI in first-line followed by ECX in second-line, or the inverse strategy with ECX first followed by FOLFIRI [64].

5.2.2. Ramucirumab

Ramucirumab is a monoclonal antibody targeting VEGF receptor 2, which has shown its efficacy as monotherapy [80] or combined with paclitaxel [81]. In these two phase 3 studies, ramucirumab provided a statistically significant improvement in progression-free survival and overall survival in second-line treatment. However, although ramucirumab received EMA approval, the French « High Authority for Health » (HAS) estimated that the clinical benefit ('service médical rendu') was insufficient to support reimbursement in France.

5.2.3. Trastuzumab-deruxtecan

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate consisting of a humanized anti-HER2 monoclonal antibody covalently linked to a topoisomerase I inhibitor cytotoxic payload (DXd). Preliminary data from 2 phase II trials (DG-01 and DG-02) showed anti-tumor activity in second and third/late-line treatment for patients with pretreated HER2 positive advanced gastric and GEJ adenocarcinoma [82,83]. Based on these results, T-DXd received EMA approval for second-line treatment, while in France reimbursement was initially granted only for third- and later-line treatment. This efficacy was subsequently confirmed in second-line treatment with the DG-04 phase 3 trial, which demonstrated a significant improvement in overall survival and progression-free survival for the T-DXd arm compared with ramucirumab-paclitaxel arm. Patients underwent a new biopsy confirming HER2 positivity after progression on first-line trastuzumab-based treatment [84]. On the basis of these phase III results, early access for TDXd in second-line treatment has been granted in France since February 2026 while reimbursement is under evaluation.

5.2.4. Pembrolizumab

Several data from non-randomized phase II studies have shown that anti-PD-1 monoclonal antibody was effective in pretreated patients for advanced dMMR/MSI adenocarcinoma, regardless of tumor location [85–87]. Based on these data, pembrolizumab received EMA approval in 2022 for advanced dMMR/MSI tumors (stomach, small intestine, biliary tract, endometrium) pretreated with at least one line of chemotherapy. However, in France, immunotherapy is not reimbursed for this indication.

5.3. Third and later-line treatment

The current recommended therapeutic algorithm is summarized in Figure 3b.

5.3.1. Trifluridine/tipiracil

Trifluridine/tipiracil is an oral chemotherapy that showed in the phase 3 TAGS study a significant improvement in overall survival versus supportive care alone (HR=0.69) in patients pretreated with at least two lines of chemotherapy [88]. Trifluridine/tipiracil is approved and reimbursed in France for this indication.

5.3.2. Chemotherapy

Cytotoxic chemotherapy based on taxane or irinotecan, if not previously used, can be discussed as a therapeutic option despite the absence of demonstration of its efficacy in third and later-line.

5.3.3. Recommendations

First-line treatment of HER2-negative metastatic disease

- Addition of anti-PD1 to doublet chemotherapy is recommended in case of PD-L1 positive tumor with nivolumab for CPS $\geq$ 5, pembrolizumab for CPS $\geq$ 10 (EMA approval for CPS $\geq$ 1), and tislelizumab for TAP $\geq$ 5% [recommendation: **grade A**].
- Addition of zolbetuximab to doublet chemotherapy is recommended for tumors with moderate to strong expression of claudin18.2 in $\geq$ 75% of positive tumor cells [recommendation: **grade A**].
- Immune checkpoint inhibitors alone or combined with chemotherapy are recommended for dMMR/MSI tumors [recommendation: **grade C**].
- Docetaxel-triplet first-line chemotherapy based on TFOX regimen is recommended for selected patients (age <70 years and/or ECOG PS 0) with biomarker-negative tumors [recommendation: **grade A**].

First-line treatment of HER2-positive metastatic disease

- First-line doublet chemotherapy with trastuzumab is recommended [recommendation: **grade A**].
- Addition of pembrolizumab to trastuzumab plus doublet chemotherapy is recommended for PD-L1 positive CPS $\geq$ 1 [recommendation: **grade A**].

Second-line treatment

- Ramucirumab plus paclitaxel is recommended [recommendation: **grade A**], while ramucirumab monotherapy is an alternative option for patients with contraindications to paclitaxel [recommendation: **grade B**].
- Chemotherapy based on taxane (paclitaxel or docetaxel) or irinotecan monotherapy [recommendation: **grade A**] or FOLFIRI [expert agreement] is recommended.
- Trastuzumab-deruxtecan is recommended for patients with HER2 positive tumors who have received previous trastuzumab-based chemotherapy [recommendation: **grade A**]. A new biopsy is recommended to verify HER2 positivity status before trastuzumab-deruxtecan [expert agreement].

- Pembrolizumab is recommended for patients with dMMR/MSI tumors not pre-treated with anti-PD1 [recommendation: **grade C**].

Third and later-line treatment

- Trifluridine-tipiracil is recommended [recommendation: **grade A**].
- Alternative options include taxane or irinotecan or FOLFIRI, if not previously administered [expert agreement].
- Trastuzumab-deruxtecan if not received previously is recommended for patients with HER2 positive tumors who have received previous trastuzumab-based chemotherapy [recommendation: **grade B**]. A new biopsy is recommended to verify HER2 positivity status before trastuzumab-deruxtecan [expert agreement].

6. Follow-up

To date, no data published in the literature have shown that systematic follow-up improves patient survival. Nevertheless, follow-up allows for early detection of recurrences, management of symptoms, and prevention of nutritional deficiencies [89,90]. Follow-up should primarily concern patients who may be able to receive a local and/or systemic chemotherapy.

Recommendations

- Dietary support with deficiencies in vitamin B12, iron and minerals should be monitored and supplemented if needed [expert agreement].
- An initial follow-up endoscopy should be performed 3–6 months after endoscopic resection of an early gastric cancer [expert agreement].
- Physical assessment and blood tests every 3–6 months for 5 years after surgical resection can be recommended [expert agreement].
- Imaging assessment (CT-scan of thorax, abdomen and pelvis or other appropriate assessments such as MRI) twice a year for 5 years after surgical resection can be recommended [expert agreement].
- In metastatic disease, imaging assessment (CT-scan of thorax, abdomen and pelvis or other appropriate assessments such as MRI) every 6–12 weeks can be recommended to monitor efficacy of treatment and adapt therapeutic changes [expert agreement].

7. Conclusion

These French intergroup guidelines provide an updated framework for the management of gastric and GEJ adenocarcinoma, covering diagnosis, risk assessment, staging, and therapeutic strategies. They emphasize a multidisciplinary approach, including endoscopic evaluation, imaging, surgical resection with adequate lymphadenectomy, and perioperative chemotherapy as standard of care for locally advanced disease. Radiotherapy has a limited role in gastric cancer since adjuvant or neoadjuvant radiotherapy is generally not recommended after adequate surgery, while palliative radiotherapy may be used in selected cases for symptom control, such as bleeding.

A key recent advance is the addition of durvalumab to perioperative FLOT, which improves clinical outcomes irrespective of PD-L1 expression. In metastatic disease, molecular profiling enables personalized medicine through the use of HER2-directed therapies, claudin18.2-targeted agents, and immune checkpoint inhibitors for biomarker-selected populations, all of which have demonstrated significant improvements in survival. Molecular overlap exists among these biomarkers, and ongoing clinical trials are exploring the potential of combining immunotherapy with targeted therapies to further optimize patient selection and clinical outcomes.

These recommendations can serve as a practical guide beyond France and are broadly applicable across Europe, although national healthcare systems and regulatory approvals may influence accessibility. Notably,

differences exist across European countries regarding PD-L1 thresholds for immunotherapy. Ongoing clinical trials and novel drug development are expected to further refine treatment paradigms, particularly in advanced and biomarker-defined populations. By integrating current evidence and emerging therapies, these guidelines aim to support clinicians in delivering personalized, evidence-based care while anticipating future innovations in gastric cancer management.

Ethics approval statement

Not applicable.

Funding statement

None.

CRediT authorship contribution statement

Aziz Zaanan: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Juliette Palle:** Writing – review & editing, Validation, Data curation. **Florence Renaud:** Writing – review & editing, Validation, Data curation. **Maximilien Barret:** Writing – review & editing, Validation, Data curation. **Meher Ben Abdelghani:** Writing – review & editing, Validation, Data curation. **Bruno Buecher:** Writing – review & editing, Validation, Data curation. **Nicolas Chapelle:** Writing – review & editing, Validation, Data curation. **Olivier Dubreuil:** Writing – review & editing, Validation, Data curation. **Jerome Durand-Labrunie:** Writing – review & editing, Validation, Data curation. **Nadim Fares:** Writing – review & editing, Validation, Data curation. **Johan Gagniere:** Writing – review & editing, Validation, Data curation. **Marine Jary:** Writing – review & editing, Validation, Data curation. **Antoine Mariani:** Writing – review & editing, Validation, Data curation. **Lola-Jade Palmieri:** Writing – review & editing, Validation, Data curation. **Michel Ducreux:** Writing – review & editing, Validation, Supervision, Project administration, Formal analysis, Data curation, Conceptualization. **Olivier Bouché:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. **Aziz Zaanan** reports consulting or advisory role with Amgen, Merck Serono, Sanofi, MSD, Servier, Astellas Pharma, BMS, Pierre Fabre, AstraZeneca, Daiichi Sankyo, BeiGene, AbbVie, Gilead Sciences, and Jazz Pharmaceuticals; has received support for travel or accommodation from Servier, MSD, Pierre Fabre, Amgen, Merck, Jazz Pharmaceuticals, and Astellas Pharmaceuticals; and has received research funding from Amgen. **Florence Renaud** reports consulting or advisory role with Amgen, MSD, Astellas Pharma, BMS, BeiGene/BeOne, and has received research funding from Amgen. **Maximilien Barret** reports consulting or advisory role with Fujifilm, Medtronic, Norgine, Falk Pharma, Sanofi. **Meher Ben Abdelghani** reports consulting or advisory role with AstraZeneca, BMS, Servier, AMGEN, Pierre Fabre, Roche, Merck, Takeda. **Olivier Dubreuil** reports consulting or advisory role with Amgen, BMS, Merck Serono, Sanofi, MSD, Servier, Astellas Pharma, AstraZeneca, Daiichi Sankyo, Novartis and Deciphera, has received support for travel or accommodation from Servier, MSD, Amgen, Merck-Serono, Daiichi Sankyo, Esteve and Novartis. **Nadim Fares** reports consulting or advisory role with Amgen, AstraZeneca, BMS, Incyte, MSD, Servier, Roche; has received support for travel or accommodation from AstraZeneca, BMS, JAZZ, MSD, Roche, Servier. **Marine Jary** reports consulting or advisory role with Amgen, MSD, Servier, BMS,

AstraZeneca, Daiichi Sankyo, and Takeda; has received support for travel or accommodation from Servier, MSD, Pierre Fabre, Amgen, BMS. **Lola-Jade Palmieri** reports consulting or advisory role with Amgen, BMS, Merck Serono, Pierre Fabre, Servier, Takeda; has received support for travel or accommodation from Astra Zeneca, BMS, Merck Serono, Pierre Fabre, Servier, Takeda. **Michel Ducreux** reports consulting or advisory role with Amgen, Astellas, AstraZeneca, Bayer, Beigene, Boehringer, Daiichi Sankyo, GSK, HalioDX, Ipsen, Janssen, Jazz Pharmaceuticals, Lilly, Merck Kga, Lilly, MSD, Pfizer, Pierre Fabre, Roche, Servier, Takeda, Zymeworks, Sandoz. *Given their role as Editor for the European Journal of Cancer, Michel Ducreux had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor.* **Olivier Bouché** reports consulting or advisory role with Amgen, Merck Serono, MSD, Servier, Astellas Pharma, BMS, Pierre Fabre, Gilead Sciences, Takeda and Deciphera; has received support for travel or accommodation from Servier, MSD, Pierre Fabre, Takeda. **All remaining authors have declared no conflicts of interest.**

Acknowledgments

We thank the TNCD review committee: A. Adenis (Montpellier), I. Al Naasan (Chambery), N. Carrere (Toulouse), M. Chauvenet (Pierre Bénite), S. Deguelle (Reims), F. El Hajji (Lille), L. Etchehoury (Bayonne), F.N. Gilly (Pierre Bénite), S. Gaujoux (Paris), B. Guiu (Montpellier), F. Huguet (Paris), T. Lecomte (Tours), C. Louvet (Paris), J.Y. Mabrut (Lyon), L. Maggiori (Paris), S. Manfredi (Dijon), P. Mariani (Paris), J.P. Metges (Brest), L. Mosser (Rodez), G. Piessen (Lille), Y. Ranchoup (Grenoble).

References

- [1] Veziant J, Bouché O, Aparicio T, Barret M, El Hajji F, Lepilliez V, et al. Esophageal cancer - French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (TNCD, SNFGE, FFCF, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, SFP, RENAPE, SNFCP, AFEF, SFR). Dig Liver Dis J Ital Soc Gastroenterol Ital Assoc Study Liver 2023;55:1583–601. <https://doi.org/10.1016/j.dld.2023.07.015>.
- [2] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229–63. <https://doi.org/10.3322/caac.21834>.
- [3] Park JY, Georges D, Alberts CJ, Bray F, Clifford G, Baussano I. Global lifetime estimates of expected and preventable gastric cancers across 185 countries. Nat Med 2025;31:3020–7. <https://doi.org/10.1038/s41591-025-03793-6>.
- [4] Shah SC, McKinley M, Gupta S, Peek RM, Martinez ME, Gomez SL. Population-based analysis of differences in gastric cancer incidence among races and ethnicities in individuals age 50 years and older. Gastroenterology 2020;159:1705–1714.e2. <https://doi.org/10.1053/j.gastro.2020.07.049>.
- [5] Defossez G, Uhry Z, Delafosse P, Dantony E, d'Almeida T, Plouvier S, et al. Cancer incidence and mortality trends in France over 1990–2018 for solid tumors: the sex gap is narrowing. BMC Cancer 2021;21:726. <https://doi.org/10.1186/s12885-021-08261-1>.
- [6] Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet 2020;396:635–48. [https://doi.org/10.1016/S0140-6736\(20\)31288-5](https://doi.org/10.1016/S0140-6736(20)31288-5).
- [7] Brierley J, Giuliani M, O'Sullivan B, Rous B, Eycken E.V. TNM classification of malignant tumours, 9th Edition. John Wiley Sons Ltd 2025.
- [8] Andriulli A, Recchia S, De Angelis C, Mazzucco D, Berti E, Arrigoni A, et al. Endoscopic ultrasonographic evaluation of patients with biopsy negative gastric linitis plastica. Gastrointest Endosc 1990;36:611–5. [https://doi.org/10.1016/S0016-5107\(90\)71180-7](https://doi.org/10.1016/S0016-5107(90)71180-7).
- [9] Bouzian J, Horstmann M. G8 screening and health-care use in patients with cancer. Lancet Healthy Longev 2023;4:e297–8. [https://doi.org/10.1016/S2666-7568\(23\)00101-0](https://doi.org/10.1016/S2666-7568(23)00101-0).
- [10] Kumano S, Murakami T, Kim T, Hori M, Iannaccone R, Nakata S, et al. T staging of gastric cancer: role of multi-detector row CT. Radiology 2005;237:961–6. <https://doi.org/10.1148/radiol.2373041380>.
- [11] Chen C-Y, Hsu J-S, Wu D-C, Kang W-Y, Hsieh J-S, Jaw T-S, et al. Gastric cancer: preoperative local staging with 3D multi-detector row CT—correlation with surgical and histopathologic results. Radiology 2007;242:472–82. <https://doi.org/10.1148/radiol.2422051557>.
- [12] Ramos RF, Scalón FM, Scalón MM, Dias DI. Staging laparoscopy in gastric cancer to detect peritoneal metastases: a systematic review and meta-analysis. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol 2016;42:1315–21. <https://doi.org/10.1016/j.ejso.2016.06.401>.

- [13] Gertsen EC, Brenkman HJF, van Hillegersberg R, van Sandick JW, van Berge Henegouwen MI, Gisbertz SS, et al. 18F-fluorodeoxyglucose-positron emission tomography/computed tomography and laparoscopy for staging of locally advanced gastric cancer: a multicenter prospective dutch cohort study (PLASTIC). *JAMA Surg* 2021;156:e215340. <https://doi.org/10.1001/jamasurg.2021.5340>.
- [14] Luchini C, Bibeau F, Ligtnerberg MJL, Singh N, Nottegar A, Bosse T, et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. *Ann Oncol J Eur Soc Med Oncol* 2019;30:1232–43. <https://doi.org/10.1093/annonc/mdz116>.
- [15] de la Fouchardière C, Cammarota A, Svrcek M, Alsina M, Fleitas-Kannonnikoff T, Lordick Obermannová R, et al. How do I treat dMMR/MSI gastro-oesophageal adenocarcinoma in 2025? A position paper from the EORTC-GITCG gastro-oesophageal task force. *Cancer Treat Rev* 2025;134:102890. <https://doi.org/10.1016/j.ctrv.2025.102890>.
- [16] Bartley AN, Washington MK, Colasacco C, Ventura CB, Ismaila N, Benson AB, 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 J Am Soc Clin Oncol* 2017;35:446–64. <https://doi.org/10.1200/JCO.2016.69.4836>.
- [17] Moehler M, Yoon HH, Wagner D-C, Yang S, Shi J, Zhang Y, et al. Concordance Between the PD-L1 Tumor Area Positivity Score and Combined Positive Score for Gastric or Esophageal Cancers Treated With Tislelizumab. *Mod Pathol J U S Can Acad Pathol Inc* 2025;38:100793. <https://doi.org/10.1016/j.modpat.2025.100793>.
- [18] Fassan M, Kuwata T, Matkowskyj KA, Röcken C, Rüschhoff J, Claudin-18.2 immunohistochemical evaluation in gastric and gastroesophageal junction adenocarcinomas to direct targeted therapy: a practical approach. *Mod Pathol J U S Can Acad Pathol Inc* 2024;37:100589. <https://doi.org/10.1016/j.modpat.2024.100589>.
- [19] Chapelle N, Bouvier A-M, Manfredi S, Drouillard A, Lepage C, Faivre J, et al. Early gastric cancer: trends in incidence, management, and survival in a well-defined French population. *Ann Surg Oncol* 2016;23:3677–83. <https://doi.org/10.1245/s10434-016-5279-z>.
- [20] Dinis-Ribeiro M, Libanio D, Uchima H, Spaander MCW, Bornschein J, Matysiak-Budnik T, et al. Management of epithelial precancerous conditions and early neoplasia of the stomach (MAPS III): European society of gastrointestinal endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG) and European Society of Pathology (ESP) Guideline update 2025. *Endoscopy* 2025; 57:504–54. <https://doi.org/10.1055/a-2529-5025>.
- [21] Ono H, Yao K, Fujishiro M, Oda I, Uedo N, Nimura S, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). *Dig Endosc J Jpn Gastroenterol Endosc Soc* 2021; 33:4–20. <https://doi.org/10.1111/den.13883>.
- [22] Gouzi JL, Huguier M, Fagniez PL, Launois B, Flamant Y, Lacaine F, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg* 1989;209:162–6. <https://doi.org/10.1097/0000658-198902000-00005>.
- [23] Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. *Ital Gastrointest Tumor Study Group Ann Surg* 1999;230: 170–8. <https://doi.org/10.1097/0000658-199908000-00006>.
- [24] Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;340: 908–14. <https://doi.org/10.1056/NEJM199903253401202>.
- [25] Allum W, Lordick F, Alsina M, Andritsch E, Ba-Salamah A, Beishon M, et al. ECCO essential requirements for quality cancer care: oesophageal and gastric cancer. *Crit Rev Oncol Hematol* 2018;122:179–93. <https://doi.org/10.1016/j.critrevonc.2017.12.019>.
- [26] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer J Int Gastric Cancer Assoc Jpn Gastric Cancer Assoc* 2021;24:1–21. <https://doi.org/10.1007/s10120-020-01042-y>.
- [27] Songun I, Putter H, Kranenbarg EM-K, Sasako M, van de Velde CJH. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010;11:439–49. [https://doi.org/10.1016/S1470-2045\(10\)70070-X](https://doi.org/10.1016/S1470-2045(10)70070-X).
- [28] Quan Y, Huang A, Ye M, Xu M, Zhuang B, Zhang P, et al. Comparison of laparoscopic versus open gastrectomy for advanced gastric cancer: an updated meta-analysis. *Gastric Cancer J Int Gastric Cancer Assoc Jpn Gastric Cancer Assoc* 2016;19:939–50. <https://doi.org/10.1007/s10120-015-0516-x>.
- [29] Son S-Y, Hur H, Hyung WJ, Park Y-K, Lee H-J, An JY, et al. Laparoscopic vs Open Distal Gastrectomy for Locally Advanced Gastric Cancer: 5-year Outcomes of the KLASS-02 randomized clinical trial. *JAMA Surg* 2022;157:879–86. <https://doi.org/10.1001/jamasurg.2022.2749>.
- [30] Dat TQ, Thong DQ, Nguyen DT, Hai NV, Phuoc TD, Anh NVT, et al. Laparoscopic vs open distal gastrectomy with D2 lymphadenectomy for clinical T4a gastric cancer: the UMC-UPPERGI-01 randomized clinical trial. *JAMA Surg* 2026;161:9–18. <https://doi.org/10.1001/jamasurg.2025.4929>.
- [31] van der Wielen N, Straatman J, Daams F, Rosati R, Parise P, Weitz J, et al. Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. *Gastric Cancer J Int Gastric Cancer Assoc Jpn Gastric Cancer Assoc* 2021;24:258–71. <https://doi.org/10.1007/s10120-020-01109-w>.
- [32] van der Veen A, Brenkman HJF, Seesing MFJ, Haverkamp L, Luyer MDP, Nieuwenhuijzen GAP, et al. Laparoscopic versus open gastrectomy for gastric cancer (LOGICA): a multicenter randomized clinical trial. *J Clin Oncol J Am Soc Clin Oncol* 2021;39:978–89. <https://doi.org/10.1200/JCO.20.01540>.
- [33] Lu J, Zheng C-H, Xu B-B, Xie J-W, Wang J-B, Lin J-X, et al. Assessment of robotic versus laparoscopic distal gastrectomy for gastric cancer: a randomized controlled trial. *Ann Surg* 2021;273:858–67. <https://doi.org/10.1097/SLA.0000000000004466>.
- [34] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20. <https://doi.org/10.1056/NEJMoa055531>.
- [35] Ychou M, Boige V, Pignon J-P, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol J Am Soc Clin Oncol* 2011;29:1715–21. <https://doi.org/10.1200/JCO.2010.33.0597>.
- [36] Al-Batran S-E, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, 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: 1948–57. [https://doi.org/10.1016/S0140-6736\(18\)32557-1](https://doi.org/10.1016/S0140-6736(18)32557-1).
- [37] Janjigian YY, Al-Batran S-E, Wainberg ZA, Muro K, Molena D, Van Cutsem E, et al. Perioperative durvalumab in gastric and gastroesophageal junction cancer. *N Engl J Med* 2025;393:217–30. <https://doi.org/10.1056/NEJMoa2503701>.
- [38] Tabernero J, Al-Batran S-E, Wainberg Z A, Muro K, Molena D, Cutsem EV, et al. Final overall survival (OS) and the association of pathological outcomes with event-free survival (EFS) in MATTERHORN: A randomised, phase III study of durvalumab (D) plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric / gastroesophageal junction (G / GEJ) adenocarcinoma. *Ann Oncol* 2025;36:S1623–4. <https://doi.org/10.1016/j.annonc.2025.09.096>.
- [39] GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010;303:1729–37. <https://doi.org/10.1001/jama.2010.534>.
- [40] Bang Y-J, Kim Y-W, Yang H-K, Chung HC, Park Y-K, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012;379:315–21. [https://doi.org/10.1016/S0140-6736\(11\)61873-4](https://doi.org/10.1016/S0140-6736(11)61873-4).
- [41] Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; 345:725–30. <https://doi.org/10.1056/NEJMoa010187>.
- [42] Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordmark M, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:616–28. [https://doi.org/10.1016/S1470-2045\(18\)30132-3](https://doi.org/10.1016/S1470-2045(18)30132-3).
- [43] Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol J Am Soc Clin Oncol* 2012;30: 268–73. <https://doi.org/10.1200/JCO.2011.39.1953>.
- [44] Park SH, Lim DH, Sohn TS, Lee J, Zang DY, Kim ST, et al. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial. *Ann Oncol J Eur Soc Med Oncol* 2021;32:368–74. <https://doi.org/10.1016/j.annonc.2020.11.017>.
- [45] Pietrantonio F, Miceli R, Raimondi A, Kim YW, Kang WK, Langley RE, et al. Individual patient data meta-analysis of the value of microsatellite instability as a biomarker in gastric cancer. *J Clin Oncol J Am Soc Clin Oncol* 2019;37:3392–400. <https://doi.org/10.1200/JCO.19.01124>.
- [46] André T, Tougeron D, Piessen G, de la Fouchardière C, Louvet C, Adenis A, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: the GERCOR NEONIPGA phase II study. *J Clin Oncol J Am Soc Clin Oncol* 2023;41:255–65. <https://doi.org/10.1200/JCO.22.00686>.
- [47] Raimondi A, Lonardi S, Murgioni S, Cardellino GG, Tambari S, Strippoli A, 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 J Eur Soc Med Oncol* 2025;36:285–96. <https://doi.org/10.1016/j.annonc.2024.11.016>.
- [48] Lorenzen S, Götze TO, Thuss-Patience P, Biehl M, Homann N, Schenk M, 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 J Am Soc Clin Oncol* 2024;42:410–20. <https://doi.org/10.1200/JCO.23.00975>.
- [49] Marchesi S, Sciertino C, Etessami J, Damonte C, Villa C, Bottelli A, et al. First-line maintenance strategies and later-line options in patients with advanced gastroesophageal adenocarcinoma. *Ther Adv Med Oncol* 2025;17: 17588359251389741. <https://doi.org/10.1177/17588359251389741>.
- [50] Markar SR, Mikhail S, Malietzis G, Athanasiou T, Mariette C, Sasako M, et al. Influence of surgical resection of hepatic metastases from gastric adenocarcinoma on long-term survival: systematic review and pooled analysis. *Ann Surg* 2016;263: 1092–101. <https://doi.org/10.1097/SLA.0000000000001542>.

- [51] Al-Batran S-E, Homann N, Pauligk K, Illerhaus G, Martens UM, Stoeckhmer J, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 trial. *JAMA Oncol* 2017;3:1237–44. <https://doi.org/10.1001/jamaoncol.2017.0515>.
- [52] Al-Batran S-E, Lorenzen S, Riera J, Caca K, Mueller C, Stange DE, et al. Effect of chemotherapy/targeted therapy alone vs. chemotherapy/targeted therapy followed by radical surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction: The IKF-575/RENAISSANCE phase III trial. *LBA4001–LBA4001 J Clin Oncol* 2024;42. https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA4001.
- [53] Bonnot P-E, Piessen G, Kepenekian V, Decullier E, Pocard M, Meunier B, et al. Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for gastric cancer with peritoneal metastases (CYTO-CHIP study): a propensity score analysis. *J Clin Oncol J Am Soc Clin Oncol* 2019;37:2028–40. <https://doi.org/10.1200/JCO.18.01688>.
- [54] Rau B, Lang H, Koenigsrainer A, Gockel I, Rau H-G, Seeliger H, et al. Effect of hyperthermic intraperitoneal chemotherapy on cytoreductive surgery in gastric cancer with synchronous peritoneal metastases: the phase III GASTRIPEC-I trial. *J Clin Oncol J Am Soc Clin Oncol* 2024;42:146–56. <https://doi.org/10.1200/JCO.22.02867>.
- [55] Bang JY, Puri R, Lakhtakia S, Thakkar S, Waxman I, Siddiqui I, et al. Endoscopic or surgical gastroenterostomy for malignant gastric outlet obstruction: a randomised trial. *Gut* 2025;75:24–32. <https://doi.org/10.1136/gutjnl-2025-336339>.
- [56] van de Pavert YL, Kastelijn JB, Besselink MG, Booi DC, Boonstra JJ, Boot J, et al. Endoscopic versus surgical gastroenterostomy for palliation of malignant gastric outlet obstruction (ENDURO): a randomised controlled trial. *Lancet Gastroenterol Hepatol* 2025;10:1065–74. [https://doi.org/10.1016/S2468-1253\(25\)00209-2](https://doi.org/10.1016/S2468-1253(25)00209-2).
- [57] Song IJ, Kim HJ, Lee JA, Park JC, Shin SK, Lee SK, et al. Clinical outcomes of endoscopic hemostasis for bleeding in patients with unresectable advanced gastric cancer. *J Gastric Cancer* 2017;17:374–83. <https://doi.org/10.5230/jgc.2017.17.e42>.
- [58] Mariette C, Bruyère E, Messenger M, Pichot-Delahaye V, Paye F, Dumont F, et al. Palliative resection for advanced gastric and junctional adenocarcinoma: which patients will benefit from surgery? *Ann Surg Oncol* 2013;20:1240–9. <https://doi.org/10.1245/s10434-012-2687-6>.
- [59] Wagner AD, Syn NL, Moehler M, Grothe W, Yong WP, Tai B-C, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2017;(8):CD004064. <https://doi.org/10.1002/14651858.CD004064.pub4>.
- [60] Al-Batran S-E, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol J Am Soc Clin Oncol* 2008;26:1435–42. <https://doi.org/10.1200/JCO.2007.13.9378>.
- [61] Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36–46. <https://doi.org/10.1056/NEJMoa073149>.
- [62] Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol J Am Soc Clin Oncol* 2006;24:4991–7. <https://doi.org/10.1200/JCO.2006.06.8429>.
- [63] Zaanan A, Bouché O, de la Fouchardière C, Le Malicot K, Pernot S, Louvet C, et al. TFOX versus FOLFOX in first-line treatment of patients with advanced HER2-negative gastric or gastro-oesophageal junction adenocarcinoma (PRODIGE 51-FICD-GASTFOX): an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2025;26:732–44. [https://doi.org/10.1016/S1470-2045\(25\)00130-5](https://doi.org/10.1016/S1470-2045(25)00130-5).
- [64] Guimbaud R, Louvet C, Ries P, Ychou M, Maillard E, André T, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. *J Clin Oncol J Am Soc Clin Oncol* 2014;32:3520–6. <https://doi.org/10.1200/JCO.2013.54.1011>.
- [65] Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, 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;398:27–40. [https://doi.org/10.1016/S0140-6736\(21\)00797-2](https://doi.org/10.1016/S0140-6736(21)00797-2).
- [66] Rha SY, Oh D-Y, Yañez P, Bai Y, Ryu M-H, Lee J, 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;24:1181–95. [https://doi.org/10.1016/S1470-2045\(23\)00515-6](https://doi.org/10.1016/S1470-2045(23)00515-6).
- [67] Qiu M-Z, Oh D-Y, Kato K, Arkenau T, Tabernero J, Correa MC, 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. <https://doi.org/10.1136/bmj-2023-078876>.
- [68] Shah MA, Shitara K, Ajani JA, Bang Y-J, Enzinger P, Ilson D, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med* 2023;29:2133–41. <https://doi.org/10.1038/s41591-023-02465-7>.
- [69] Shitara K, Lordick F, Bang Y-J, Enzinger P, Ilson D, Shah MA, 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;401:1655–68. [https://doi.org/10.1016/S0140-6736\(23\)00620-7](https://doi.org/10.1016/S0140-6736(23)00620-7).
- [70] Klempner SJ, Pazo-Cid RA, Lonardi S, Swanson L, Arango MJ, Enzinger P, et al. Consensus guidance for prevention and management of nausea and vomiting in patients treated with zolbetuximab + chemotherapy: a RAND/UCLA modified Delphi panel study. *ESMO Gastrointest Oncol* 2025;7:100131. <https://doi.org/10.1016/j.esmog.2024.100131>.
- [71] Bang Y-J, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki 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;376:687–97. [https://doi.org/10.1016/S0140-6736\(10\)61121-X](https://doi.org/10.1016/S0140-6736(10)61121-X).
- [72] Elimova E, Rha SY, Shitara K, Liu T, Tabernero J, Lee K-W, et al. Zanidatamab + chemotherapy (CT) ± tislelizumab for first-line (1L) HER2-positive (HER2+) locally advanced, unresectable, or metastatic gastroesophageal adenocarcinoma (mGEA): primary analysis from HERIZON-GEA-01. *J Clin Oncol* 2026;44. https://doi.org/10.1200/JCO.2026.44.2_suppl.LBA285.
- [73] Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, 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;402:2197–208. [https://doi.org/10.1016/S0140-6736\(23\)02033-0](https://doi.org/10.1016/S0140-6736(23)02033-0).
- [74] Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, et al. Pembrolizumab in HER2-positive gastric cancer. *N Engl J Med* 2024;391:1360–2. <https://doi.org/10.1056/NEJMc2408121>.
- [75] Kawakami H, Kadowaki S, Makiyama A, Tsuda M, Hirata K, Sugimoto N, et al. Phase II study (NO LIMIT, WJOG13320G) of first-line nivolumab plus low-dose ipilimumab for microsatellite instability-high advanced gastric or esophagogastric junction cancer. *J Clin Oncol J Am Soc Clin Oncol* 2025;43:2184–95. <https://doi.org/10.1200/JCO.24-02463>.
- [76] Ford HER, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15:78–86. [https://doi.org/10.1016/S1470-2045\(13\)70549-7](https://doi.org/10.1016/S1470-2045(13)70549-7).
- [77] Thuss-Patience PC, Kretschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011;47:2306–14. <https://doi.org/10.1016/j.ejca.2011.06.002>.
- [78] Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol J Am Soc Clin Oncol* 2013;31:4438–44. <https://doi.org/10.1200/JCO.2012.48.5805>.
- [79] Lee K-W, Maeng CH, Kim T-Y, Zang DY, Kim YH, Hwang IG, et al. A phase III study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer who failed in first-line therapy (KCSG ST10-01). *Oncologist* 2019;24:18–e24. <https://doi.org/10.1634/theoncologist.2018-0142>.
- [80] Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, 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;383:31–9. [https://doi.org/10.1016/S0140-6736\(13\)61719-5](https://doi.org/10.1016/S0140-6736(13)61719-5).
- [81] Wilke H, Muro K, Van Cutsem E, Oh S-C, Bodoky G, Shimada Y, 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;15:1224–35. [https://doi.org/10.1016/S1470-2045\(14\)70420-6](https://doi.org/10.1016/S1470-2045(14)70420-6).
- [82] Shitara K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Sakai D, et al. Trastuzumab deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med* 2020;382:2419–30. <https://doi.org/10.1056/NEJMoa2004413>.
- [83] Van Cutsem E, di Bartolomeo M, Smyth E, Chau I, Park H, Siena S, 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;24:744–56. [https://doi.org/10.1016/S1470-2045\(23\)00215-2](https://doi.org/10.1016/S1470-2045(23)00215-2).
- [84] Shitara K, Van Cutsem E, Gümiş M, Lonardi S, de la Fouchardière C, Coutzac C, et al. Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer. *N Engl J Med* 2025;393:336–48. <https://doi.org/10.1056/NEJMoa2503119>.
- [85] Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509–20. <https://doi.org/10.1056/NEJMoa1500596>.
- [86] Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409–13. <https://doi.org/10.1126/science.aam6733>.
- [87] Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord J-P, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol J Am Soc Clin Oncol* 2020;38:1–10. <https://doi.org/10.1200/JCO.19.02105>.

- [88] Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau H-T, Prokharau A, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018;19:1437–48. [https://doi.org/10.1016/S1470-2045\(18\)30739-3](https://doi.org/10.1016/S1470-2045(18)30739-3).
- [89] Hu Y, Kim H-I, Hyung WJ, Song KJ, Lee JH, Kim YM, et al. Vitamin B(12) deficiency after gastrectomy for gastric cancer: an analysis of clinical patterns and risk factors. *Ann Surg* 2013;258:970–5. <https://doi.org/10.1097/SLA.0000000000000214>.
- [90] Baiocchi GL, D'Ugo D, Coit D, Hardwick R, Kassab P, Nashimoto A, et al. Follow-up after gastrectomy for cancer: the Charter Scaligero Consensus Conference. *Gastric Cancer J Int Gastric Cancer Assoc Jpn Gastric Cancer Assoc* 2016;19:15–20. <https://doi.org/10.1007/s10120-015-0513-0>.