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Gastric Cancer

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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Gastric Cancer

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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

Gastric cancer is one of the more common malignant diseases. As in other parts of the western world, the age-standardized incidence in Germany, Austria and Switzerland has been steadily decreasing in recent decades. Men are affected twice as often as women. A subgroup of patients has a hereditary risk. One of the acquired risk factors is a Helicobacter pylori infection of the gastric mucosa. Population-based endoscopic screening for the detection of early gastric carcinomas is currently not recommended in Germany.

The patient's prognosis is primarily determined by the stage, but also by histology, general condition and comorbidity. In early and localized stages, the treatment approach is curative; in metastatic stages, it is palliative. The main treatment modalities are surgery and systemic tumor therapy. Despite some progress in the last 10 years, the cancer-specific mortality rate is very high at 70%.

This guideline refers to adenocarcinoma of the stomach. Recommendations on localized tumors of the esophago-gastric junction can be found in Onkopedia Esophageal cancer. The recommendations for the treatment of advanced adenocarcinomas of the esophago-gastric junction and esophagus largely correspond to those for gastric cancer. Recommendations for less common, non-epithelial tumors of the stomach can be found in Onkopedia Gastrointestinal Stromal Tumors (GIST) or Onkopedia Extranodal Marginal Zone Lymphomas (Guideline in German only).

2 Basics

2.1 Definition and basic information

Gastric cancer emerges in the proximal sections of the stomach (subcardial), in the middle third (fundus and corpus) and in the distal stomach (antrum). Subcardial gastric carcinomas often have an anatomic connection to the esophago-gastric junction and are then also referred to as adenocarcinomas of the esophago-gastric junction type III (according to Siewert).

The guideline presented here refers to gastric carcinomas according to the current 8th edition of the TNM/UICC classification. The special features of adenocarcinomas of the esophago-gastric junction type I and type II according to Siewert, which are categorized as esophageal carcinomas according to the current TNM/UICC classification, are only addressed cursorily here, as the clinical algorithms must be differentiated from gastric carcinoma.

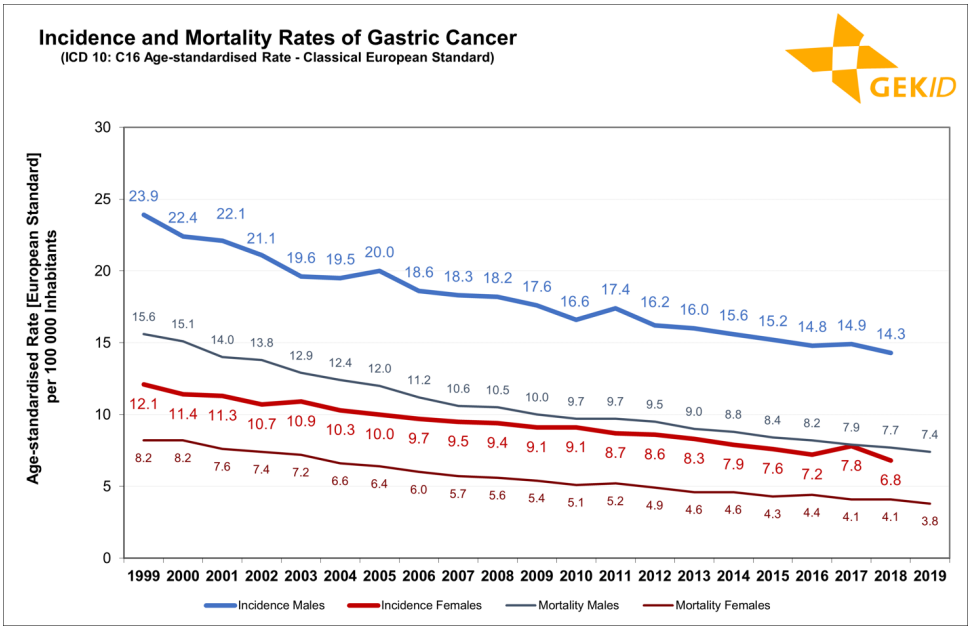
2.2 Epidemiology

Every year, around 9,500 new cases of gastric cancer are diagnosed in men and around 6,000 new cases in women in Germany. This makes gastric cancer the tenth most common cancer in men, accounting for around 3.5% of all malignancies, and the ninth most common malignancy in women, accounting for around 2.4%. In terms of cancer mortality, the relevance of gastric cancer is even higher. It accounts for around 3.5% of all cancer deaths in women and 4.2% in men. The average age of onset is 71 for men and 76 for women, which is higher than for cancer as a whole (70 for men, 69 for women). The average age at death is 74 years (men) and 78 years (women) (cancer overall: 75 and 77 years). It can be assumed that there are around 33,000 patients living in Germany who were diagnosed no more than five years ago and 52,000 patients who were diagnosed in the last 10 years.

The age-standardized incidence rates, as well as the age-standardized mortality rates, have been declining for years for both sexes, see Figure 1. The age-standardized incidence rate for men has fallen by an average of 2.2% per year over the last 16 years - the mortality rate has even fallen by an average of 3.4% per year. The incidence rate for women has fallen by an average of 2.7% per year over the last 16 years - the mortality rate by an average of 3.7% per year. Case numbers and (crude) rates for men are around 60% higher than for women.

The decline in incidence was also confirmed by data from the Dutch cancer registry. Here, the incidence fell from 20.3 to 6.1 per 100,000 between 1989 and 2021, with a simultaneous improvement in relative survival rates [143].

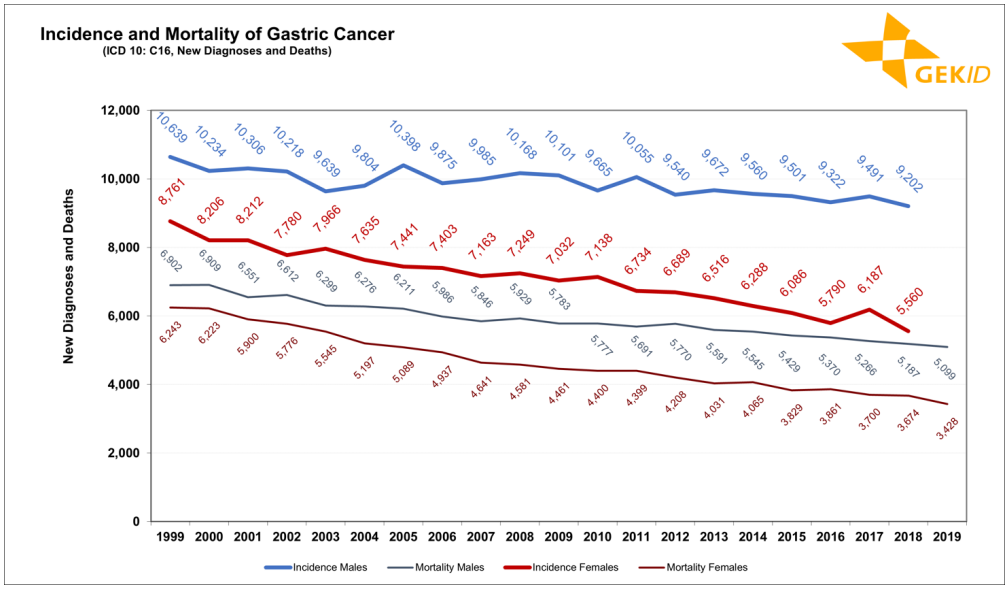
Figure 1: Estimated incidence of gastric cancer (ICD 10: C16) in Germany - age-standardized rates (old European standard) [1]



While the age-standardized new case rates represent a measure of the probability of disease and are largely independent of the population structure, the number of new cases of disease reflects not only the probability of disease but also the age structure and population size. Due to the shift in the age structure towards an older society and the fact that the baby boomers are reaching the age cohorts most likely to develop the disease, the trends in new cases and deaths differ from the trends in rates. This shift is particularly evident in men. Although the number of cases is falling, this is only by an average of 0.2% per year, despite a significant long-term decline in disease rates. The situation is similar for the number of deaths. Here, the number of male patients is falling by an average of 1.2% per year, which is also lower than the decline in mortality rates (3.4%). For women, the decline in the number of new cases (2.1% per

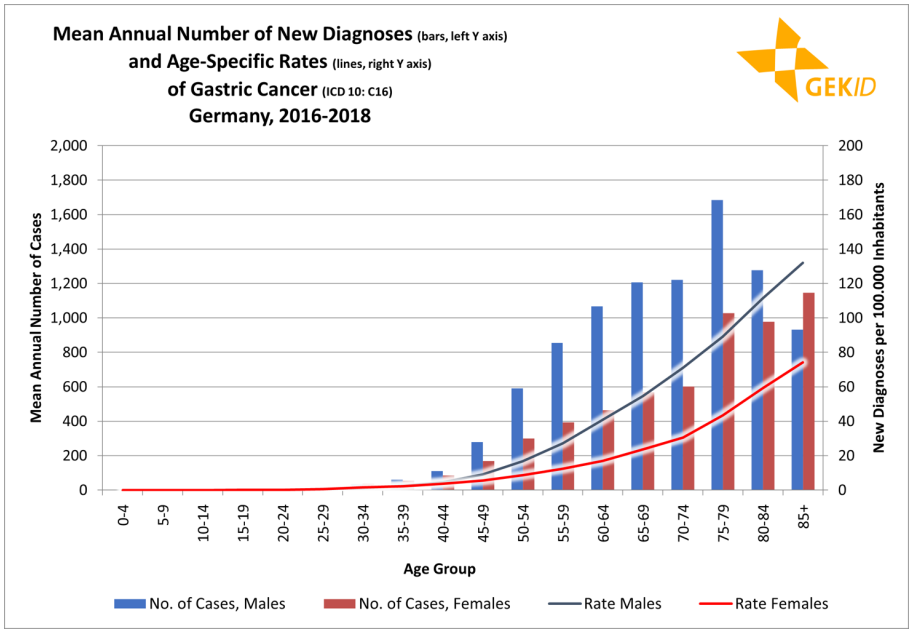
year), and deaths (2.7% per year) is also lower than the corresponding rates. However, the difference is not quite as great (Figure 2).

Figure 2: Estimated incidence of gastric cancer (ICD 10: C16) in Germany - case numbers [1]



Most gastric cancers are diagnosed in men between 75 and 79, see Figure 3 (bar). From the age of 40 until the age of 80, the number of new cases rises steadily. After that, it drops significantly. In women, the number increases almost continuously up to the highest age group. The highest risk of disease - i.e., the number of cases in relation to the underlying population per age group, see Figure 3 (lines) - is found in the highest age group 85 years and older for both sexes. Case numbers and incidence rates for men are higher than for women in all age groups.

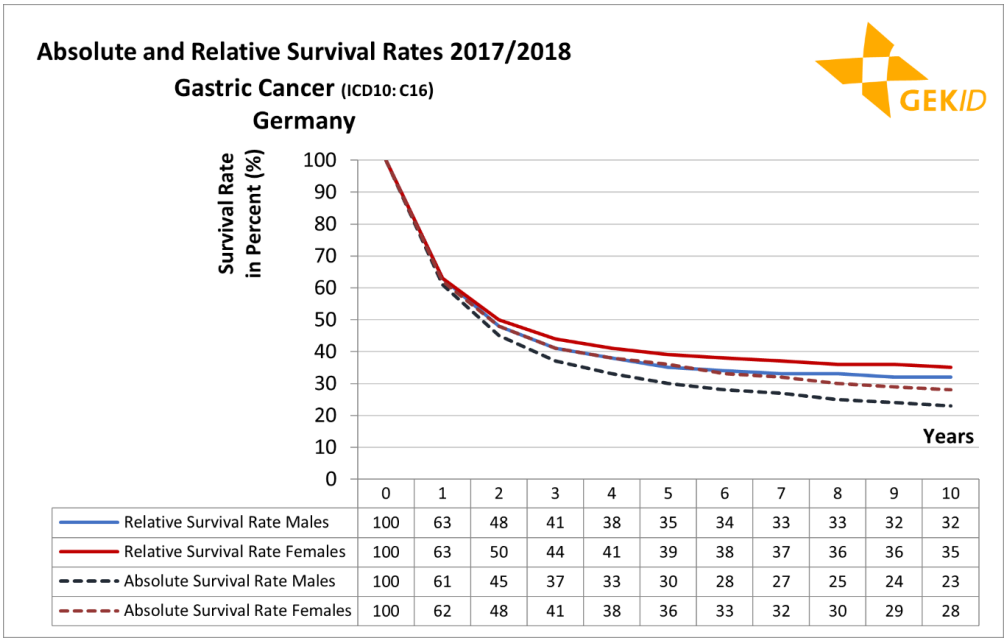
Figure 3: Age distribution of the incidence of gastric cancer (ICD 10: C16) - age-specific case numbers and rates [1]



The prognosis for gastric cancer is relatively unfavorable, especially during the first two years after diagnosis. Around 40% of patients die in the first year after diagnosis. The small difference between the absolute survival rate - i.e., the percentage of patients who survive for a certain time - and the relative survival rate - i.e., the ratio of absolute survival to the expected survival in the general population - shows the excess mortality caused by the cancer. From the fifth year after diagnosis, the gap between the absolute and relative survival rates increases,

while the relative survival rate remains largely constant. This means that after about five years there are hardly any additional cancer-related deaths. Figure 4 shows the absolute and relative survival rates for the first 10 years after diagnosis. There are hardly any differences in survival between the sexes.

Figure 4: Absolute and relative survival rates for gastric cancer in Germany (ICD 10: C16) [1]



	0	1	2	3	4	5	6	7	8	9	10
Relative Survival Rate Males	100	63	48	41	38	35	34	33	33	32	32
Relative Survival Rate Females	100	63	50	44	41	39	38	37	36	36	35
Absolute Survival Rate Males	100	61	45	37	33	30	28	27	25	24	23
Absolute Survival Rate Females	100	62	48	41	38	36	33	32	30	29	28

Based on the current incidence of the disease and the 14th coordinated population projection of the Federal Statistical Office (G2L2W2, moderate development), the number of cases can be expected to increase by around 30% to around 20,000 new cases (2050) over the next 30 years, solely due to the shift in the age structure of the population. In reality, however, the increase is likely to be lower due to falling disease rates.

2.3 Pathogenesis

Gastric cancers - in analogy to carcinomas of the rest of the digestive tract - develop in many cases sequentially in multistage processes via precancerous intermediate stages and histologically defined lesions [2]. Unlike for Laurén's diffuse type, this stepwise process is well characterized for the intestinal type [3]. The clinical observation that gastric cancers are histologically heterogeneous in up to 30%, i.e., have both intestinal and diffuse components, underscores the importance of local factors of cellular microenvironment and genetic or epigenetic heterogeneity. Generally accepted, histologically graspable components of the sequential development of gastric cancer are: Helicobacter pylori infection, atrophic gastritis, intestinal metaplasia, intraepithelial neoplasia (low- and high-grade), and gastric adenoma, which is rare in the western hemisphere.

2.4 Risk factors

The risk of developing gastric carcinoma is associated with the presence of the following risk factors [4]:

- Genetic
  - Hereditary colorectal carcinoma without polyposis (HNPCC, Lynch syndrome) [5]
  - Hereditary diffuse gastric carcinoma (HDGC) with mutations in the cadherin 1- (CDH-1) or catenin-alpha-1 (CTNNA1) gene [6, 7]
  - Peutz-Jeghers syndrome (mutation in the serine-threonine kinase gene [STK11]).

    - First-degree relatives with gastric cancer
    - Male gender (incidence males:females about 2:1)
    - Blood group A
- Acquired
    - Helicobacter (H.) pylori infection of the gastric mucosa
    - Epstein-Barr virus infection of the gastric mucosa
    - Inhalative tobacco use
    - Atrophic gastritis
    - Partial gastrectomy
    - Ménétrier's disease
- Risk factors differ for the various anatomical localizations and histological subtypes. Distal gastric carcinomas are frequently found associated with Helicobacter pylori infection of the gastric mucosa, high-salt and low fruit and vegetable intake. Carcinomas of the intestinal subtype are more frequently associated with an H. pylori infection than carcinomas of the diffuse subtype. The risk of gastric carcinoma is particularly high if there is a genetic predisposition and an H. pylori infection [141] Carcinomas of the esophago-gastric junction are more commonly associated with obesity and gastroesophageal acid reflux.

3 Prevention and early detection

3.1 Prevention

H. pylori eradication with the aim of preventing gastric carcinoma is recommended for people at risk, see also chapter 3.2.2. It is assumed that the timing of treatment is crucial for the effectiveness of H. pylori eradication in preventing gastric cancer. This should take place in adulthood at a time before preneoplastic changes have developed [8]. Data from Japan show a particularly high rate of H. pylori-associated gastric carcinomas in individuals with germline mutations in genes with particular relevance for homologous recombination capacity (ATM, BRCA1, BRCA2 and PALB2), who showed a 40-fold increased risk of developing gastric carcinoma with H. pylori colonization [141]. Results of prospective and controlled intervention studies are not yet available. In a large US population, H. pylori eradication was associated with a significantly lower incidence of gastric cancer after 8 years compared to no treatment. After an observation period of 7 to 10 years, the risk was lower in treated individuals than in the general population. The results show that eradication of H. pylori has the potential to significantly reduce the risk of gastric cancer [139].

There is currently insufficient evidence for chemoprevention of gastric cancer, e.g., with non-steroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors or acetylsalicylic acid [9].

3.2 Early detection

3.2.1 Population

As Germany/Austria/Switzerland are not high-incidence regions for gastric cancer, it seems unlikely that population-based ensocopic screening would be cost-effective. However, a study explicitly examining the cost-effectiveness under the conditions in German-speaking Central Europe has not yet been conducted. Population-based endoscopic screening for the detection of early gastric cancer is currently not recommended in the countries mentioned.

3.2.2 Persons at risk

If more than one first-degree relative has a history of gastric cancer, the risk is increased approximately 10-fold [10]. However, a scientifically sound recommendation for screening endoscopy in individuals with a positive family history cannot be given. There is currently no scientific evidence for the benefit of specific preventive measures in close relatives of patients with gastric cancer [11]. However, it is recommended that H. pylori eradication be performed in first-degree relatives of gastric cancer patients [12].

As individuals with a pathogenic CDH1 germline mutation have a lifetime risk of developing hereditary diffuse gastric carcinoma of 50-80%, a detailed family history should be taken here. Regular endoscopy and prophylactic gastrectomy if signet ring cells are detected, should be performed as standard [131]. Prophylactic gastrectomy should be offered from the age of 20 years [11].

Current knowledge on the penetrance of pathogenic CTNNA1 mutations is still limited, so that a clear recommendation for prophylactic gastrectomy cannot be given at present. At least, close endoscopic surveillance should be advised. Individual consultation of a specialized center is recommended [13, 14].

4 Clinical characteristics

4.1 Symptoms

Early gastric carcinomas are generally asymptomatic. The following symptoms may be observed in locally advanced or metastatic carcinomas [15]:

- Dysphagia
- Dyspepsia
- Recurrent vomiting
- Loss of appetite
- Early feeling of satiety
- Weight loss
- Signs of gastrointestinal bleeding
- Epigastric pain
- Symptoms from metastatically affected organs (such liver capsule pain or ileus/subileus from peritoneal metastases)

Gastric cancer may present with various paraneoplastic syndromes, with cutaneous manifestations being observed more frequently than others [16].

5 Diagnosis

5.2 Diagnostics

5.2.1 Initial diagnosis

Endoscopy is considered the most sensitive and specific diagnostic method. Using high-resolution video-assisted endoscopy, it is possible to detect even discrete changes in color, mucosal

surface, and architecture of the gastric mucosa. Endoscopic detection of early lesions can be improved by chromoendoscopy.

The aims of further diagnostics are to determine the stage of the disease and to guide therapy, see Table 1.

Table 1: Diagnostics and staging of gastric cancer

Investigation	Remark
Physical examination	
Laboratory (blood)	Blood count, liver and kidney function parameters, coagulation
Endoscopy of the upper gastrointestinal tract	Optional use of chromoendoscopy
Endoscopic ultrasound examination (EUS) [1]	For therapy planning for localized disease
Computed tomography of the thorax including the supra-clavicular region, abdomen and pelvis with oral and intravenous contrast medium	For visualization of locoregional and distant tumor spread
Abdominal ultrasound	Complementary to computed tomography
Laparoscopy, if indicated with cytology[2]	In cT2/cT3/cT4 without evidence of other distant metastases, to detect/exclude peritoneal metastasis

Legend:
[1] see chapter 5.2.3.1
[2] Laparoscopy with cytologic examination of the lavage helps to detect clinically occult peritoneal metastasis in locally resectable tumors. The detection of macroscopic peritoneal metastasis has a direct impact on treatment planning [17]. Cytologic evidence of malignant cells in the lavage samples is an unfavorable prognostic factor, but - outside of clinical studies - has no definite impact on treatment recommendations to date. Laparoscopically abnormal findings are more frequently found in T3/T4 classified tumors [18].

5.2.2 Histology and subtypes

The histologic diagnosis of gastric carcinoma should be made from a biopsy, assessed by two experienced pathologists [11].

Biomarker diagnostics from tumor tissue is now standard practice, at least in the presence of stage IV gastric carcinoma. Biomarker diagnostics determined by immunohistochemistry should be performed using 5 tumor-bearing biopsies [51, 132].

Standard diagnostic tests currently include the HER2 status, PD-L1 Combined Positivity Score (CPS) and Tumor Area Positivity (TAP), mismatch repair enzymes (or microsatellite instability) and Claudin 18.2.

In addition to the description of HER2 positivity according to established criteria [51], the precise specification of the proportion of HER2-positive tumor regions [52] and the description of HER2-low status is an option with possible therapeutic consequences in the future. The high rate of discrepancies in around 25% of the findings between different examiners must still be taken into account [138, 142]. The routine determination of Epstein-Barr virus association by means of in-situ hybridization (EBER-FISH) is under discussion, as it occurs very rarely [22].

5.2.2.1 Laurén classification

Histologically, gastric cancer is characterized by a strong heterogeneity, as several different histological features may be present in one tumor. Over the past decades, histologic classification has been based on the Laurén classification [19]:

- Intestinal type, approximately 54%

- Diffuse type, approx. 32
- Indeterminant, approx. 15%

The diffuse subtype is found more often in women and people of younger age, while the intestinal type is more common in men and people of older age and is associated with intestinal metaplasia and H. pylori infection [20].

5.2.2.2 World Health Organization (WHO) classification

The World Health Organization (WHO) classification distinguishes four definitive types of gastric cancer [21]:

- Tubular
- Papillary
- Mucinous
- Poorly cohesive (including signet ring cell carcinoma).

The classification is based on the predominant histologic pattern of the carcinoma, which often coexists with less dominant features or other histologic patterns.

5.2.2.3 The Cancer Genome Atlas (TCGA) classification

Molecular genetic studies divide gastric cancer into molecular subtypes based on studies of the genome, transcriptome, epigenome and proteome. The molecular genetic heterogeneity of gastric carcinoma is the subject of extensive genome-wide sequencing studies [133]. The best-known molecular subtyping according to TCGA distinguishes four subtypes [22].

- Chromosomally unstable - CIN
- Epstein-Barr virus-associated - EBV
- Microsatellite unstable - MSI
- Genomically stable - GS

5.2.3 Stages and staging

5.2.3.1 TNM staging

The classification of the extent of the primary tumor and metastasis is based on the UICC/AJCC TNM criteria [19, 21, 23]. The 8th edition has been used in Europe since 2017 [21]. The TNM criteria are summarized in Table 2 and the staging in Table 3.

Table 2: UICC-TNM classification of gastric cancer [21]

Classification	Tumor
T	**Primary tumor**
T1	Superficially invading tumor
T1a	Tumor invading lamina propria or muscularis mucosae
T1b	Tumor invading submucosa
T2	Tumor invading muscularis propria
T3	Tumor invading subserosa without invasion of visceral peritoneum
T4a	Tumor penetrating subserosa (visceral peritoneum)
T4b	Tumor invading adjacent structures
N	**Regional lymph nodes**
N0	No regional lymph node metastases
N1	Metastases in 1-2 lymph nodes
N2	Metastases in 3-6 lymph nodes
N3a	Metastases in 7-15 lymph nodes
N3b	Metastases in 16 or more lymph nodes
M	**Distant metastases**
M0	No distant metastases
M1	Distant metastases or positive peritoneal cytology

Table 3: Classification of tumor stages [21]

UICC stage	Primary tumor	Lymph nodes	Distant metastases
0	Tis	N0	M0
IA	T1a T1b	N0 N0	M0 M0
IB	T2 T1	N0 N1	M0 M0
IIA	T3 T2 T1	N0 N1 N2	M0 M0 M0
IIB	T4a T3 T2 T1	N0 N1 N2 N3	M0 M0 M0 M0
IIIA	T4a T3 T2	N1 N2 N3	M0 M0 M0
IIIB	T4b T4a T3	N0/1 N2 N3	M0 M0 M0
IIIC	T4b T4a	N2/3 N3	M0 M0
IV	Any T	Any N	M1

Endosonography (EUS) is particularly suitable for determining the clinical T category, as it can visualize the different layers of the gastric wall better than other examination techniques. EUS should therefore be part of primary staging in a patient with a curative therapeutic approach.

The following characteristics serve to identify malignant lymph nodes on CT slice imaging [24]:

- Diameter ≥ 6-8 mm (shorter axis) in perigastric lymph nodes
- Round shape
- Central necrosis
- Loss of the fat hilus
- Heterogeneous or enhanced contrast agent uptake

The sensitivity of CT for lymph node staging is variably estimated at 62.5-91.9% in systematic reviews [25].

EUS improves the accurate determination of the T and N categories and can help determine the proximal and distal margins of the tumor. EUS is less accurate for tumors of the antrum. EUS complements CT in diagnosing malignant lymph nodes.

Signs of malignancy on EUS include [26]:

- Hypoechoic
- Round shape
- Blurred demarcation from the surrounding area
- Size in the longest diameter > 1cm

6 Therapy

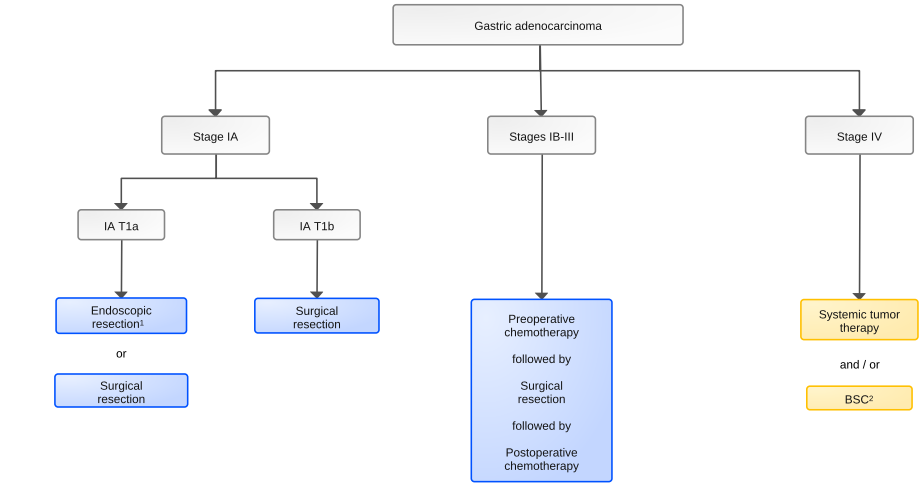
6.1 Treatment structure

Multidisciplinary planning is required for any initial treatment recommendation. It should be developed in a qualified multidisciplinary tumor board.

The core members of the multidisciplinary board include the following disciplines: visceral surgery, medical oncology, radiation oncology, gastroenterology, radiology and pathology. In addition to determining the best possible standard therapy, the possible inclusion in clinical trials should be part of the discussion in the tumor board.

Therapy is stage-adapted. A treatment algorithm for first-line therapy is shown in Figure 5.

Figure 5: Algorithm for primary therapy of gastric cancer



Legend:
curative intended therapy; non-curative intended therapy;
[1] see Table 4
[2] Best supportive care

6.1.1 Stage IA - T1a (early carcinoma)

Since the probability of lymph node metastasis in mucosal gastric cancer (T1a) is very low, endoscopic resection (ER) may be sufficient [27]. If histopathologic workup after endoscopic resection reveals that tumor infiltration extends into the submucosa (T1b), surgical resection with systematic lymphadenectomy should be performed, as lymph node metastases may already be present in up to 30% of cases.

Gastric cancers classified as pT1a cN0 cM0 should be treated with endoscopic resection, considering the adapted Japanese criteria, if the following criteria are met [11, 28], see Table 4.

Table 4: Criteria for endoscopic resection in stage IA T1a [11, 107]

• Lesions ≤ 2 cm in elevated types • Lesions ≤ 1 cm in flat types • Histological degree of differentiation good or intermediate (G1/G2) • No macroscopic ulceration • Invasion limited to the mucosa • No residual tumor after endoscopic resection

Early gastric cancers with a maximum of one "extended criterion" can also be curatively resected endoscopically [11]. Endoscopic submucosal dissection (ESD) should be used for resection. If more than one extended criterion is present, oncologic surgical resection should be performed. The extended criteria are defined as:

- Differentiated mucosal carcinoma (G1/G2) without ulceration and size > 2cm
- Differentiated mucosal carcinoma (G1/G2) with ulceration and size < 3cm
- Well-differentiated carcinomas (G1/G2) with submucosal invasion < 500µm and size < 3cm
- Undifferentiated mucosal carcinoma (G3/G4) < 2cm diameter (if there is no histological evidence of tumor cells at a distance ≤ 1cm [11])
- ER of early gastric cancer is performed as an en-bloc resection. It allows complete histological assessment of the lateral and basal margins. The recommended endoscopic control intervals are 3 months in the first and 6 months in the second year of follow-up. Thereafter, controls should be performed annually. Local recurrences after ER of early

gastric cancer can be treated endoscopically if relapse is confined to the mucosal (rT1a cN0 cM0). A (limited) surgical approach is an alternative.

6.1.2 Stage IA - T1b

For stage IA gastric cancer with infiltration of the submucosa, the risk of lymph node metastases is 25-28%. The 5-year survival rate is 70.8% for all stage IA in the SEER database [29], and the cancer-specific survival rate at 10 years is 93% in the Italian IRGGC analysis. Therapy of choice in stage IA (T1 N0 M0) is radical surgical resection (subtotal, total, or transhiatal extended gastrectomy). Limited resection can be recommended only in exceptional cases due to the imprecise accuracy of pretherapeutic staging.

A benefit from perioperative or adjuvant chemotherapy has not been established for stage IA patients.

6.1.3 Stage IB - III

In stage IB - III, surgical treatment should consist of radical resection (subtotal, total, or transhiatal extended gastrectomy) in combination with D2- lymphadenectomy. Subtotal gastrectomy can be performed if safe free tumor margins can be achieved. The previously recommended tumor-free margins of 5 and 8 cm for intestinal and diffuse tumor growth types, respectively, are no longer accepted. The scientific evidence for definitive recommendations is low. A negative oral margin in the intraoperative frozen section is crucial.

Perioperative chemotherapy with a platinum derivative, a fluoropyrimidine, and an anthracycline significantly prolonged overall survival in patients with resectable gastric cancer in the MAGIC trial [30]. In the French FNCLCC / FFCD multicenter study, perioperative chemotherapy with a platinum derivative and a fluoropyrimidine without anthracycline showed a comparable effect size on improving survival [31]. Currently, neither chemotherapy regimen is the first choice.

Treatment according to the FLOT regimen (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) further improved progression-free survival (hazard ratio, HR 0.75) and overall survival (HR 0.77) in patients with stage ≥ cT2 and/or cN+ compared with therapy analogous to MAGIC; see also chapter 6.2.3.1 The relatively higher efficacy of FLOT was shown to be consistent across relevant subgroup analyses such as age, histology, and tumor location. The rate of perioperative complications was comparable [32].

Adjuvant chemotherapy can be considered for patients with gastric cancer ≥ stage IB who underwent resection without prior chemotherapy (e.g., due to incorrect tumor staging prior to surgery), see chapter 6.2.3.1.

In HER2-positive tumors, a benefit from combining perioperative chemotherapy with a HER2 antibody in the perioperative setting with regard to overall survival has not yet been clearly proven. The AIO-PETRARCA phase 2 study showed a higher histopathologic remission rate and a trend towards better progression-free and overall survival when FLOT chemotherapy was combined with trastuzumab + pertuzumab [121]. The multinational EORTC1203-INNOVATION study shows very promising response rates, especially for the combination of FLOT + trastuzumab, with good feasibility of the regimen, while FLOT + trastuzumab + pertuzumab did not prove additional benefit due to increased toxicity [144]. According to current data, neither trastuzumab alone nor trastuzumab + pertuzumab led to improved survival [144]. After discussion in the multidisciplinary tumor board, primary systemic therapy with FLOT plus trastuzumab can be considered in cases of questionable R0 resectability in locally advanced HER2-positive

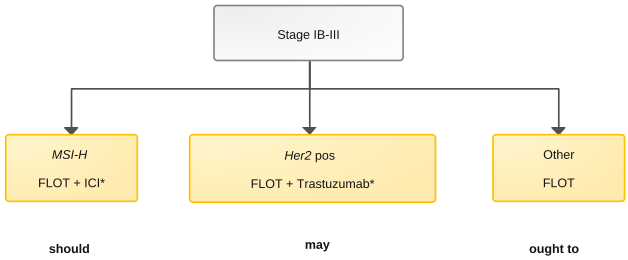
carcinomas of the stomach or esophago-gastric junction in order to achieve resectability (so-called conversion chemotherapy).

In microsatellite-instable localized gastric adenocarcinomas, retrospective data analyses cast doubt on the efficacy of perioperative chemotherapy [35]. Current data from the DANTE study show that complete and subtotal tumor remissions can also be achieved with FLOT chemotherapy in gastric carcinomas of the MSI subtype. However, the response is significantly higher with the chemotherapy/immunotherapy combination and there is a significant risk of non-response and progression with chemotherapy alone [35, 36]. The best approach for resectable MSI-high gastric carcinomas is currently the subject of ongoing studies. A clear recommendation cannot be given at present. Several studies show that the addition of an immune checkpoint inhibitor to neoadjuvant chemotherapy in cases of deficient DNA mismatch repair/microsatellite instability leads to significantly better remission rates [34, 136]. In addition, in exploratory subgroup analyses, event-free and overall survival are also significantly improved when perioperative chemotherapy is supplemented with an immune checkpoint inhibitor in MSI-high gastric adenocarcinomas [140]. The FFCD-NEONIPIGA phase 2 study shows a high histopathologic remission rate after 12 weeks of treatment with nivolumab + ipilimumab without chemotherapy in resectable MSI cancers [122]. The same observation was reported from the GONO Infinity study on a small group of patients treated neoadjuvantly with durvalumab + tremelimumab [146]. These data require validation in larger and independent cohorts; nevertheless, preoperative immunotherapy - as of today most likely in combination with FLOT chemotherapy as tested in the randomized and controlled trials Dante, Keynote-585 and Matterhorn with regard to safety and response rate - can be considered if MSI-high status is confirmed, regardless of the approval status of the drugs. This applies in particular to locally advanced tumors (T3/T4 N+) with borderline R0 resectability. Preferably, patients should be treated in studies that include preoperative/perioperative immunotherapy, as a considerable increase in knowledge is still required in the field of the best perioperative management of MSI-high gastric cancer.

To date, there is no indication for perioperative immunotherapy for microsatellite-stable tumors outside of clinical trials. Adjuvant immunotherapy proved to be insufficiently effective in the EORTC1707 VESTIGE trial (nivolumab and ipilimumab) and in the Asian ATTRACTION-5 trial (nivolumab and chemotherapy) [147, 148]. The same applies to immunotherapy with the checkpoint inhibitor pembrolizumab in addition to perioperative chemotherapy in the KN-585 trial [140].

Nowadays, there is no longer a reliable indication for pre- or postoperative radiotherapy, regardless of the underlying tumor subtype. According to the publication of the ESOPEC study and TOPGEAR study, this applies to subcardiac gastric carcinomas and adenocarcinomas of the esophago-gastric junction [149, 150]. Only after R1 resection may adjuvant radiochemotherapy be considered, see chapter 6.2.2.1.

Figure 6: Perioperative systemic therapy for gastric adenocarcinoma in stages IB-III



Legend:
ICI: PD-1/PD-L1 immune checkpoint inhibitor, FLOT: 5-fluorouracil, folinic acid, oxaliplatin, docetaxel; MSI-H: high microsatellite instability;
**off-label; recommended for borderline resectable or locally irresectable local tumor spread in the sense of conversion therapy; otherwise prior clarification with health insurance provider recommended (no survival benefit yet confirmed in studies).*

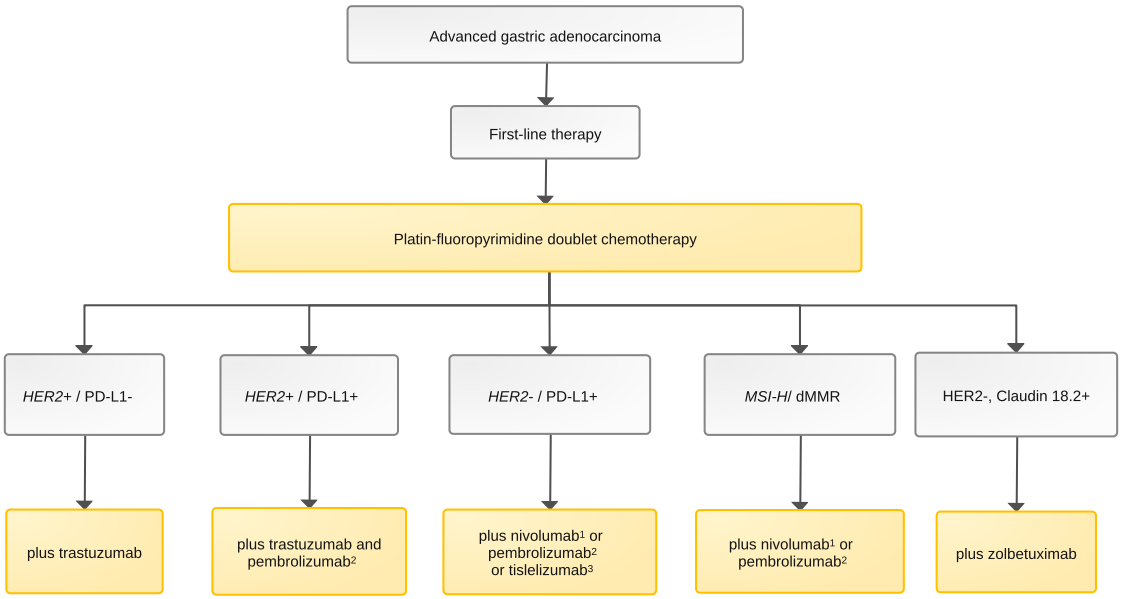
6.1.4 Stage IV

In stage IV, the aim of therapy is usually non-curative. The first priority is systemic drug therapy, supplemented in individual cases by local therapeutic measures. Active symptom control and supportive measures such as nutritional counseling, psychosocial support, and palliative care are an integral part of treatment. The prognosis of patients with locally advanced and irresectable or metastatic (pooled here as "advanced") gastric cancer is unfavorable. Studies evaluating the benefit from chemotherapy have shown a median survival of less than one year [35]. However, there is evidence that chemotherapy can prolong the survival of patients with advanced gastric cancer compared with best supportive care alone and maintain quality of life for longer [36]. Longer-term survival rates have improved significantly with the introduction of HER2- and Claudin18.2-targeted therapies and with the introduction of immune checkpoint inhibitors.

6.1.4.1 Systemic tumor therapy - stage IV

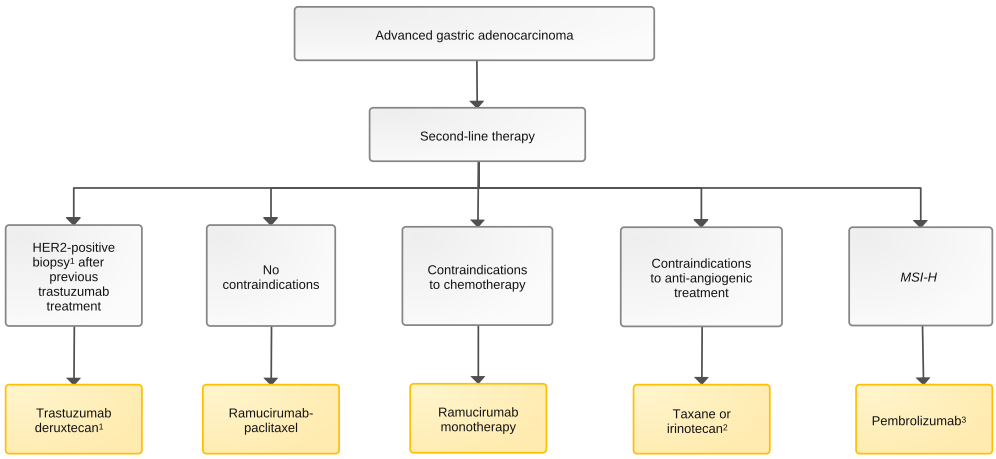
The currently recommended algorithms for systemic tumor therapy in patients with advanced gastric adenocarcinoma are shown in Figure 7, Figure 8, and Figure 9.

Figure 7: Algorithm for first-line treatment of advanced gastric cancer



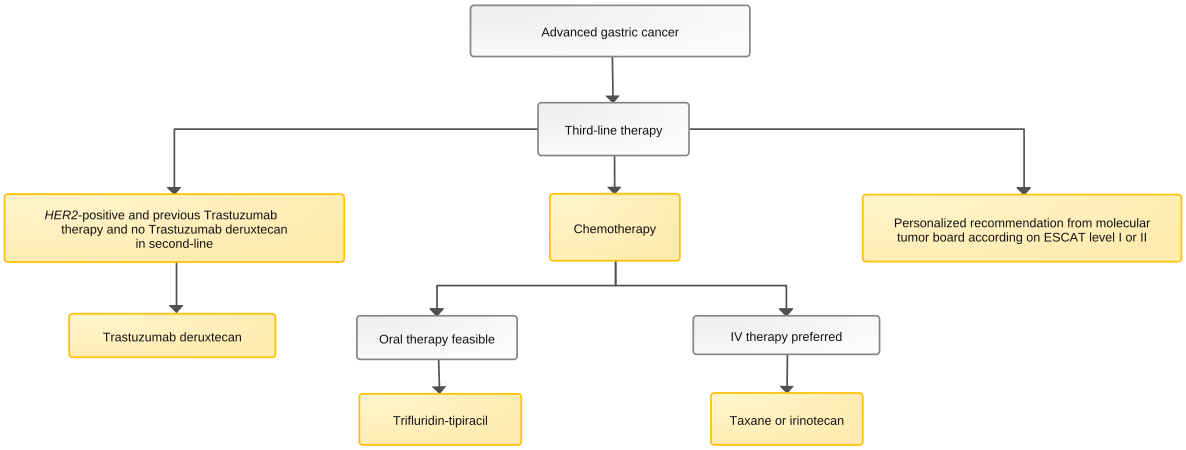
Legend:
[1] Nivolumab approved in Europe for PD-L1 CPS ≥ 5 according to Checkmate-649 study;
[2] Pembrolizumab approved in Europe for adenocarcinoma of the esophagus in PD-L1 CPS ≥ 10 according to Keynote 590 study and for HER2 negative and HER2 positive adenocarcinoma of the stomach and esophago-gastric junction in PD-L1 CPS ≥ 1 according to Keynote 859 study and Keynote 811 study;
[3] Tislelizumab approved in Europe for adenocarcinoma of the stomach and esophago-gastric junction with PD-L1 TAP ≥ 5%.

Figure 8: Algorithm for second-line treatment of advanced gastric cancer



Legend:
[1] Since many tumors lose their HER2 overexpression after trastuzumab failure, a re-examination of the current HER2 status based on a fresh biopsy is recommended before T-DXd therapy in the second line.
[2] 5-FU/folinic acid irinotecan is also used in some cases due to higher response rates than with irinotecan monotherapy.
[3] Pembrolizumab in the second-line therapy only if no PD-1/PD-L1 inhibitor was administered first line

Figure 9: Algorithm for third-line treatment of advanced gastric cancer



Legend:
According to the Destiny-Gastric01 study, re-testing of the HER2 status is not mandatory for third-line T-DXd therapy

6.1.4.1.1 First-line chemotherapy, targeted therapy and immunotherapy

6.1.4.1.1.1 Chemotherapy

The standard of care for first-line chemotherapy of advanced gastric cancer is a platinum-fluoropyrimidine doublet. Oxaliplatin and cisplatin are comparably effective, with a more favorable side effect profile for oxaliplatin. This may contribute to a trend toward better efficacy, especially in patients > 65 years [37, 23]. Fluoropyrimidines can be administered as infusion (5-FU) or orally (capecitabine or S-1). Oral fluoropyrimidines are comparably effective to infused 5-FU [38, 41]. Capecitabine is approved in combination with a platinum derivative and has been studied with both cis- and oxaliplatin in European patients. S-1 is established as a standard of care in Japan and approved in Europe for palliative first-line therapy in combination with cisplatin. Infused 5-FU should be preferred over oral medications in patients with dysphagia or other feeding problems. In elderly or frail patients, results of the phase III GO-2 trial support a dose-reduced application of oxaliplatin-fluoropyrimidine chemotherapy (to 80% or 60% of the standard dose from the beginning), resulting in fewer side effects with comparable efficacy [42].

The addition of docetaxel to a platinum-fluoropyrimidine combination (three-week DCF regimen) improved the radiologic response rate and prolonged overall survival in a historical phase III trial, but also resulted in significantly increased side effects [43]. Other phase II studies investigated modified docetaxel-platinum-fluoropyrimidine triplets. Some of these showed reduced toxicity compared to DCF [46, 49]. In the phase III JCOG1013 trial, patients with advanced gastric cancer received either cisplatin plus S-1 or cisplatin plus S1 and docetaxel. There were no differences in radiologic response, progression-free and overall survival [48] However, the subgroup of patients who had already received adjuvant fluoropyrimidine-based chemotherapy after gastrectomy benefited significantly from the addition of the taxane in the palliative setting. The authors also discuss that 79% of patients had received second-line therapy after the study, which may have an impact on overall survival. A recently presented but not yet fully published French investigator-initiated phase III study showed a significantly longer progression-free survival and a significantly longer overall survival for a platinum-fluoropyrimidine-docetaxel triplet (modified FLOT, called T-FOX) compared to the doublet FOLFOX. The median overall survival was improved from 12 to 15 months (HR 0.76 95% CI 0.62-0.93; p = 0.008) [145]. It should be noted that all patients were docetaxel-naïve and that these effects

were not observed in patients over the age of 65, in patients with an ECOG performance status > 0 and in Laurén intestinal-type carcinomas. The toxicity rate was found to be increased in numerous categories (hematologic, gastrointestinal, neurologic) with mFLOT/T-FOX). Nevertheless, the time to deterioration of quality of life was significantly prolonged in the mFLOT/T-FOX group. With increased toxicity and uncertain effects on overall survival, it is therefore not possible to make a general recommendation for first-line therapy with docetaxel-platinum-fluoropyrimidine. Modified FLOT/T-FOX triplet chemotherapy is an individually usable regimen for patients with high remission pressure, no docetaxel pretreatment and no option of biomarker-supported targeted or immunotherapy. The standard remains a platinum-fluoropyrimidine doublet.

Irinotecan-5-FU has been compared with cisplatin-5-FU and with epirubicin-cisplatin-capecitabine in randomized phase III trials and showed comparable survival with controllable side effects [49, 50]. Irinotecan-5-FU can therefore be considered a treatment alternative to platinum-fluoropyrimidine doublets according to scientific evidence, however, irinotecan has no approval in Europe for gastric cancer.

6.1.4.1.1.2 HER2-positive gastric carcinoma

HER2 positivity is defined in gastric cancer as the presence of protein expression with immunohistochemistry score [IHC] of 3+ or IHC 2+ and concomitant gene amplification on in situ hybridization [ISH], HER2/CEP17 ratio ≥ 2.0. HER2 diagnosis should be quality-controlled [51, 52]. Trastuzumab should be added to chemotherapy in patients with HER2-positive advanced gastric cancer [36, 53]. The recommendation is based on data from the phase III ToGA trial, showing a higher response rate and prolonged survival for trastuzumab-cisplatin-fluoropyrimidine chemotherapy versus chemotherapy alone using the above selection criteria; the additional trastuzumab side effects are minor and controllable [53]. Combinations of trastuzumab and oxaliplatin plus fluoropyrimidine show comparable results to the historical cisplatin-containing ToGA regimen [54, 56].

Based on the randomized phase III Keynote-811 trial [137], the EMA approved the combination of pembrolizumab plus trastuzumab and chemotherapy for first-line treatment for HER2-positive advanced gastric or esophagogastric (GEJ) adenocarcinoma with PD-L1 expression of CPS ≥ 1 in September 2023 [134] (Figure 7). 698 patients with HER-2 positive advanced carcinoma of the stomach or esophago-gastric junction were randomized between platinum-fluoropyrimidine-trastuzumab plus pembrolizumab or placebo. In the 85% of patients whose tumors showed PD-L1 expression (CPS ≥ 1), progression-free survival was significantly prolonged in the pembrolizumab arm (HR 0.70; 95% CI 0.58-0.85). Overall survival was prolonged from a median of 15.7 to 20.1 months (HR 0.79; 95% CI 0.66-0.95) [137]. Patients with PD-L1-negative tumors did not benefit from the addition of pembrolizumab. In HER2- and PD-L1-positive tumors, pembrolizumab should therefore now be added to the chemo-trastuzumab combination (Figure 7).

6.1.4.1.1.3 Immunotherapy

The phase III CheckMate 649 trial evaluated the addition of nivolumab to chemotherapy (capecitabine-oxaliplatin or 5-FU/folinic acid-oxaliplatin) in patients with previously untreated gastric, esophago-gastric junction, or esophageal adenocarcinoma [57]. The study included patients regardless of tumor PD-L1 status; the dual primary endpoints were overall survival and progression-free survival. Approximately 60% of the study population had tumors with a PD-L1 CPS ≥ 5. Nivolumab plus chemotherapy yielded a significant improvement over chemotherapy alone in overall survival (14.4 vs 11.1 months, HR 0.71 [98.4% CI 0.59-0.86]; $p < 0.0001$) and progression-free survival (7.7 vs. 6.0 months, HR 0.68 [98% CI 0.56-0.81]; $p < 0.0001$) in patients with a PD-L1 CPS ≥ 5. Long-term data confirm these results [135].

The Asian phase II/III trial ATTRACTION-04 also showed a significant improvement in progression-free survival associated with the addition of nivolumab to first-line chemotherapy [58].

The multinational randomized phase III Keynote-859 study included 1589 patients with advanced incurable gastric cancer. Patients received either platinum-fluoropyrimidine and pembrolizumab or the same chemotherapy and placebo every 3 weeks intravenously. Overall survival was prolonged in favor of the pembrolizumab group (HR 0.78 [95% CI 0.70-0.87], p < 0.0001). The effect was particularly pronounced in the subgroup with a PD-L1 CPS ≥ 10 (HR 0.64). In patients with PD-L1 CPS ≥ 1, the risk of death was reduced by 26% (HR 74 [95% CI 0.65 - 0.85], p < 0.0001) [123].

The results thus complement the positive study data from the phase III Keynote-590 study, which led to EU approval of pembrolizumab in combination with platinum-fluoropyrimidine chemotherapy for adenocarcinoma of the esophagus and a CPS ≥ 10 [124]. This was followed in January 2024 by the EMA approval of pembrolizumab in combination with first-line platinum-fluoropyrimidine chemotherapy for PD-L1 CPS ≥ 1.

In the phase III Rationale 305 study, tislelizumab prolonged overall survival in combination with platinum-fluoropyrimidine or platinum-investigator choice chemotherapy in patients with a positive PD-L1 score (TAP ≥ 5%). TAP stands for Tumor Area Proportion and is given as a percentage of the PD-L1-positive staining tumor area) [126].

Patients with carcinomas with weak PD-L1 expression benefit only marginally from the addition of an immune checkpoint inhibitor to first-line chemotherapy. A combined analysis of the studies CM-649, KN-859 and Rationale-305, which are relevant for European approval, showed marginal efficacy: PD-L1 CPS 1-9, median survival 12.4 vs 11.9 months, hazard ratio 0.84, p=0.002; PD-L1 CPS 1-4, median survival 12.1 vs 12.0 months, hazard ratio 0.87, p=0.018; PD-L1 CPS 5-9, median survival 13.1 vs 12.2 months, hazard ratio 0.87, p=0.18 [125].

6.1.4.1.1.4 Microsatellite-instable carcinomas

Due to the convincing efficacy of PD-1/PD-L1 inhibitors in carcinomas with DNA mismatch repair deficiency (microsatellite unstable type), all patients with MSI-high diagnosed gastric carcinomas or adenocarcinomas of the esophago-gastric junction should now receive one of the approved PD-1 immune checkpoint inhibitors first-line. The subgroup analyses are convincingly positive for the administration of an immune checkpoint inhibitor plus chemotherapy in all pivotal studies (CheckMate 649, Keynote-859) and also in the studies that could not be used for approval (e.g., Keynote-062). Whether the addition of chemotherapy can be dispensed in this situation is uncertain, according to current data, and should therefore be investigated in studies.

6.1.4.1.1.5 Claudin 18.2

In 2023, data from the multinational phase III Spotlight study were presented. These show that in patients with advanced irresectable gastric cancer and claudin18.2 expression in ≥ 75% of tumor cells, zolbetuximab, a chimeric monoclonal IgG1 antibody directed against claudin18.2, in combination with FOLFOX chemotherapy prolongs overall survival (median 18.23 vs. 15.54 months, HR 0.750, p = 0.0053). The main side effects of zolbetuximab are nausea and vomiting, especially during the first applications [127]. The results of the Spotlight study are largely confirmed by the multinational phase III GLOW study, in which the chemotherapy doublet was used as a control therapy or combination partner for zolbetuximab [128]. The aggregated data from Spotlight and Glow show an improvement in progression-free survival (median 9.2 versus 8.2 months, hazard ratio 0.71 (95% CI, 0.61-0.83) and an improvement in overall survival (median 16.4 versus 13.4 months, hazard ratio 0.77 (95% CI, 0.67-0.89) [128].

Zolbetuximab was approved in September 2024 in the following indication: in combination with chemotherapy containing a fluoropyrimidine and a platinum analog for the first-line treatment of adult patients with locally advanced, unresectable or metastatic HER2-negative adenocarcinoma of the stomach or esophago-gastric junction whose tumors are Claudin18.2-positive.

Due to the high emetogenicity of zolbetuximab, special attention should be paid to consistent anti-emetic prophylaxis and patient care [152, 153].

6.1.4.1.2 Second and third-line therapy

6.1.4.1.2.1 Chemotherapy and anti-angiogenic therapy

Figures 8 and 9 show the algorithms for second- and third-line therapy for patients with advanced gastric cancer. The evidence-based chemotherapy options in this setting include paclitaxel, docetaxel, and irinotecan, which have comparable efficacy with different specific toxicities [59, 62]. Irinotecan may be preferred in patients with preexisting neuropathy, however, it has no EU approval for this indication. 5-FU/folinic acid plus irinotecan (FOLFIRI) is also occasionally used, but the scientific evidence for this regimen in second- and third-line treatment is limited [63]. Ramucirumab plus paclitaxel is the recommended standard for second-line therapy, and is approved in the EU. The addition of the anti-vascular endothelial growth factor receptor-2 (VEGFR-2) antibody ramucirumab to paclitaxel increases tumor response rates and prolongs progression-free and overall survival according to the results of the phase III RAINBOW trial [64]. In the phase III REGARD trial, ramucirumab monotherapy had shown prolonged survival compared to placebo, albeit with a low radiologic response rate [65].

6.1.4.1.2.2 Immunotherapy in second- and third-line treatment

In the phase III Keynote-061 trial, pembrolizumab monotherapy did not show prolonged overall survival compared with chemotherapy [64]. However, an exploratory subgroup analysis recognized a clear benefit for anti-PD-1 immunotherapy in patients with MSI-H gastric cancer [67]. Therefore, PD-1 inhibition is recommended in advanced MSI-H carcinomas at the latest in second-line treatment. Pembrolizumab has European approval for this indication based on the Keynote-061 and Keynote-158 trials [68]. Other biomarkers, particularly EBV and tumor mutation burden, are also discussed as predictive factors for PD-1 immune checkpoint inhibitor efficacy [69, 71]. However, the evidence to date is not sufficient to support a positive recommendation for immunotherapy based upon the presence of these biomarkers.

6.1.4.1.2.3 HER2-targeted therapy

Studies investigating trastuzumab, lapatinib or trastuzumab emtansine for second-line treatment in patients with HER2-positive carcinomas were negative [72, 75]. Therefore, these drugs should not be used in gastric cancer outside of clinical trials. A randomized phase II trial showed an improvement in tumor response rate and overall survival for the antibody-drug conjugate trastuzumab-deruxtecan (T-DXd) compared with standard chemotherapy in patients with pretreated HER2-positive advanced gastric cancer [76].

Prerequisits for inclusion in the Destiny-GC-01 study were at least two prior lines of therapy, prior treatment with a platinum derivative and a fluoropyrimidine and trastuzumab, and previously confirmed HER2 positivity. The study recruited exclusively East Asian patients. The results of Destiny-GC-01 were largely confirmed in the single-arm phase II Destiny-GC-02 trial, which included non-Asian patients in second-line therapy. Mandatory was platinum-fluoropyrimidine-trastuzumab pretreatment and confirmed HER2 positivity of the tumor in a recent re-biopsy before initiating T-DXd therapy [129].

The EU approval includes the following indication of T-DXd: monotherapy for the treatment of adult patients with advanced HER2-positive adenocarcinoma of the stomach or esophago-gastric junction who have received a prior trastuzumab-based regimen.

We recommend, according to the classically established HER2 diagnostic criteria, to check the HER2 status prior to therapy with T-DXd, especially if use in second-line therapy is planned,

where a valid alternative with paclitaxel-ramucirumab is available. This recommendation is based on the inclusion criteria of the Destiny-GC-02 trial and the knowledge that loss of HER2 status occurs in approximately 30% of gastric cancers after first-line therapy with trastuzumab [72].

Clinical data indicate the efficacy of T-DXd with low HER2 expression [130]. However, this is not yet sufficient to recommend its use.

6.1.4.1.2.4 Third-line therapy

For the treatment of patients with advanced gastric cancer in the third-line and beyond, the best evidence is available for trifluridine-tipiracil (FTD/TPI) based on the phase III TAGS trial. Median overall survival with FTD/TPI versus placebo was significantly improved in the overall patient cohort, in the third-line cohort, and in the fourth-line cohort [77, 79]. Therefore, if oral therapy is feasible, trifluridine-tipiracil (FTD/TPI) should be used; alternatively, if intravenous therapy is preferred, irinotecan or a taxane can be given, if not already used in a previous line of therapy. As shown above, T-DXd is a very effective third-line therapy for HER2-positive carcinoma after trastuzumab pretreatment. Nivolumab also proved to be effective; however, the data from the ATTRACTION-03 trial were obtained exclusively in Asian patients [80], so that nivolumab in the third line of treatment in patients with advanced gastric cancer does not have EMA approval and therefore cannot be recommended.

Following the recommendation of a molecular tumor board, a yet unapproved therapeutic option may also be preferred in select cases, especially if the recommendation can be based on an ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) level I or II [81].

6.1.4.1.3 Surgery for metastatic gastric carcinoma

The randomized phase III REGATTA trial showed that gastrectomy in addition to chemotherapy for metastatic disease does not provide a survival benefit compared to chemotherapy alone [84]. International data collections indicate that surgical therapy for oligometastatic disease is increasingly perceived as a treatment option [83, 85]. The AIO-FLOT3 phase II trial reported results on the feasibility of resection in stage IV gastric cancer and survival times in highly selected patients with oligometastatic disease that was without primary progression under FLOT chemotherapy [86]. The randomized phase III RENAISSANCE trial did not show a survival benefit for surgical resection of primary tumor and metastases in patients with stage IV gastric cancer [151].

In a Delphi procedure, a definition of oligometastasis was determined in a European expert group (OMEC). According to this definition, the following phenotypes can be considered oligometastatic: 1-2 metastases in either the liver, lungs, retroperitoneal lymph nodes, adrenal glands, soft tissue or bone [85]. In selected patients with oligometastasis, after consensus in the tumor board, the concept of primary systemic tumor therapy and, in case of response, subsequent resection of the primary tumor with resection or ablation of metastases can be considered, provided that all tumor manifestations can be completely removed.

Currently available data do not permit a recommendation for radical tumor resection in stage IV. Any decisions are individual treatment attempts with unclear survival benefit. Possible complications of surgery and the resulting shortening of life must be taken into account and should not be excluded from consultation. Other local ablative procedures (stereotactic radiotherapy, radiofrequency ablation, etc.) have not yet been evaluated in this setting and therefore cannot be assessed.

6.1.4.1.4 Supportive care and nutrition

It is recommended that nutritional and symptom screening with appropriate tools be performed regularly in all patients with advanced gastric cancer, and appropriate supportive therapies be derived. A study from China showed that early integration of supportive-palliative care is effective and suggests a survival benefit in patients with advanced gastric cancer [87].

Weight loss is a multifactorial phenomenon and may be due to digestive tract obstruction, malabsorption, or hypermetabolism. Clinical data show that a weight loss of ≥ 10% before chemotherapy or ≥ 3% during the first cycle of chemotherapy is associated with poorer survival [88]. Also, a change in body composition with impaired muscular capacity was shown to be prognostically unfavorable in patients with advanced gastric cancer [79]. The modified Glasgow Prognostic Score (serum CRP and albumin) can be used to assess the extent of sarcopenia and the prognosis of patients with advanced gastric cancer [90].

From this, it can be concluded that screening for nutritional status should be performed in all patients with advanced gastric cancer (for example, using Nutritional Risk Screening, NRS) [91] and expert nutritional counseling and co-supervision should be offered, if nutritional deficiency is evident.

Dysphagia in proximal gastric cancer can be improved with radiotherapy or stent insertion [92]. Single-dose brachytherapy is the preferred option at some centers and results in longer-lasting symptom control and fewer complications than stent insertion. Stenting is needed for severe dysphagia and especially in patients with limited life expectancy, as the effects of the stent are immediate, whereas radiotherapy improves dysphagic symptoms only after approximately 4-6 weeks [93]. If radiotherapy or a stent are not an option, enteral nutrition via naso-gastric, naso-jejunal, or percutaneously placed feeding tubes may provide relief [94]. The indication for parenteral nutrition follows generally accepted guidelines.

6.2 Treatment modalities

6.2.1 Resection

6.2.1.1 Endoscopic resection

Endoscopic resection (ER) is a minimally invasive procedure for resection of early carcinomas. The criteria for ER are described above (chapter 6.1.1). Methods include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR of early gastric carcinoma is performed as an en-bloc resection. It allows complete histologic assessment of the lateral and basal margins. The recommended endoscopic control intervals are 3 months in the first year and 6 months in the second year. Thereafter, controls should be performed annually. Local recurrences after ER of early gastric carcinoma can be treated endoscopically, if relapse is confined to the mucosa (rT1a cN0 cM0). A (limited) surgical approach is an alternative, see Table 4.

6.2.1.1.1 Gastrectomy and lymphadenectomy

Surgery of the primary tumor is essential for curative therapy. The goal of surgery is to achieve an R0 situation.

Regarding lymphadenectomy, a consensus has been reached in the Western world that patients with normal surgical risks should undergo D2 lymphadenectomy. D1 resection includes removal of the perigastric lymph nodes; D2 lymphadenectomy includes additional removal the

lymph nodes along the A. gastrica sinistra artery, A. hepatica communis artery, splenic artery, and coeliac axis [95]. Long-term results of a randomized trial from the Netherlands showed a lower local recurrence rate and better cancer-specific survival after D2 versus D1 lymphadenectomy [96]. The current UICC/AJCC TNM (8th edition) classification recommends removal and examination of at least 15 lymph nodes for reliable staging [21]. In the current German S3 guideline on gastric cancer, removal of at least 25 lymph nodes is considered adequate [11].

Surgery should be performed at a certified high-volume center with adequate surgical expertise and perioperative care [11]. Numerous studies demonstrate better short-term and long-term survival for patients treated at centers with proven expertise [98, 100]. Perioperative morbidity and mortality should not exceed 15% and 3%, respectively [101]. The concept of "enhanced recovery" is presented in the Enhanced Recovery After Surgery (ERAS®) Society Guidelines and encompasses all aspects of optimized perioperative care [102].

In patients after gastrectomy, lifelong substitution of vitamin B12 is required. After Roux-Y reconstruction, pancreatic enzyme substitution is indicated.

6.2.2 Radiotherapy

6.2.2.1 Adjuvant radiochemotherapy

The North American Intergroup-0116 trial showed that adjuvant therapy with 5- FU/folinic acid plus conventionally fractionated radiotherapy (45 Gy in 25 fractions) improved overall survival compared with surgery alone (50% vs. 41% 3-year survival [66, 103]). This therapy was therefore recommended as a standard of care in North America. It did not find acceptance in Germany and Europe because of inadequate surgical quality within the INT-0116 trial. This reluctance is justified by the randomized controlled phase III CRITICS trial, which suggested that adjuvant radiochemotherapy reduces the local recurrence rate after D1 lymphadenectomy, but shows no benefit after D2 lymphadenectomy [104].

The results of the Dutch-Scandinavian CRITICS trial show that adjuvant radiochemotherapy after neoadjuvant chemotherapy and quality-assured surgery does not confer a survival benefit [105]. The ARTIST-2 trial conducted in Korea also failed to find value for adjuvant radiochemotherapy compared with adjuvant chemotherapy with a platinum-fluoropyrimidine doublet in adequately (D2 lymphadenectomy) and curatively (R0) resected patients with gastric cancer and positive nodal tumor status [106].

The multinational TOPGEAR trial investigated whether preoperative radiochemotherapy plus perioperative chemotherapy improves the survival of patients with resectable gastric carcinoma or carcinoma of the esophago-gastric junction compared to perioperative chemotherapy without preoperative radiochemotherapy. The study did not meet its primary endpoint. The median overall survival time was 46 months with preoperative radiochemotherapy and 49 months with perioperative chemotherapy (hazard ratio for death 1.05; 95% confidence interval 0.83 to 1.31), and the median progression-free survival time was 31 months and 32 months, respectively [150].

In patients with R1 resection, retrospective studies suggest that adjuvant radiochemotherapy may improve prognosis [100, 107]. Therefore, in individual cases, after weighing the benefits against the potential risks and burden, adjuvant radiochemotherapy may be considered in case of R1 status.

6.2.3 Systemic tumor therapy

6.2.3.1 Anticancer agents

6.2.3.1.1 Capecitabine

Capecitabine is an oral fluoropyrimidine that is metabolized to 5-FU. In comparative clinical studies, it was at least as effective as intravenous 5-FU plus folinic acid. It can be used in palliative therapy instead of 5-fluorouracil. In combination with platinum derivatives, remission rates of up to 45% were achieved. Severe side effects (grade 3 / 4) occurring in more than 5% of patients in pivotal studies are diarrhea and hand-foot syndrome. Patients with functionally relevant polymorphisms of the genes of 5-FU degradation have an increased risk for severe side effects.

6.2.3.1.2 Cisplatin

In combination with other cytostatic drugs, cisplatin is part of the standard drug regimen in perioperative and palliative therapy. In palliative therapy, cisplatin in combination with fluoropyrimidines achieves remission rates of up to 30%. Specific severe side effects (grade 3/4) are nausea and vomiting, nephrotoxicity, polyneuropathy, ototoxicity, hematotoxicity, electrolyte shifts and diarrhea.

6.2.3.1.3 Docetaxel

Docetaxel belongs to the taxanes. Docetaxel is an effective combination partner of fluoropyrimidines and platinum derivatives in perioperative and palliative therapy, and is part of the FLOT regimen [32, 45, 111]. Severe grade 3/4 adverse effects include infections, nail changes, stomatitis and diarrhea, while grade 2 side effects include alopecia. Polyneuropathy, which may be irreversible, is particularly harmful. Common side effects such as nausea/vomiting and allergic reactions can be prevented by adequate supportive therapy, see Onkopedia Antiemesis.

6.2.3.1.4 5-Fluorouracil

5-Fluorouracil is used in almost all forms of drug-based tumor therapy for patients with gastric carcinoma. Its efficacy is increased by combining it with folinic acid. Severe side effects are diarrhea and stomatitis. Patients with functionally relevant polymorphisms of the 5-FU degradation genes have an increased risk of severe side effects. Since 2020, the European Medicine Agency has recommended that patients should be tested for the deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD) before initiation of therapy in order to prevent severe side effects caused by 5-fluorouracil or capecitabine or tegafur (https://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine).

6.2.3.1.5 Irinotecan

Irinotecan is a topoisomerase I inhibitor. In combination with fluoropyrimidines, remission rates are up to 40%. FOLFIRI is at least as effective as cisplatin-fluoropyrimidine-based therapies in terms of progression-free survival and overall survival. Serious adverse events (grade 3/4), which occurred in more than 5% of patients in pivotal trials, include diarrhea, nausea/vomiting, neutropenia, and neutropenic fever. The substance can be applied as monotherapy weekly, bi-weekly or tri-weekly.

6.2.3.1.6 Oxaliplatin

This platinum derivative is effective in combination with fluoropyrimidines (5-FU/folinic acid, capecitabine). In first-line therapy for stage IV gastric cancer, remission rates of around 45% are achieved. Severe side effects (grade 3/4), which occurred in more than 5% of patients in pivotal trials, include nausea/vomiting, diarrhea, mucositis, and polyneuropathy. Oxaliplatin is part of the FLOT regimen recommended perioperatively.

6.2.3.1.7 Paclitaxel

Paclitaxel is another taxane. It is effective as monotherapy in second-line palliative therapy. Severe side effects (grade 3/4) include infections, stomatitis and diarrhea, and allergic reactions to the solvent cremophor; grade 2 distressing side effects include alopecia. Particularly burdensome is a partly irreversible polyneuropathy. Common side effects such as allergic reactions can be partially prevented by adequate supportive therapy.

6.2.3.1.8 Ramucirumab

Ramucirumab is a VEGF receptor2 antibody that inhibits neoangiogenesis. In combination with paclitaxel, ramucirumab leads to a prolongation of progression-free survival (HR 0.64; median 1.5 months), prolongation of overall survival (HR 0.81; median 2.2 months), and an increase in remission rate compared to paclitaxel monotherapy. In patients ineligible for paclitaxel therapy, ramucirumab monotherapy versus placebo also results in prolonged progression-free survival (HR 0.48; median 0.8 months) and overall survival (HR 0.78; median 1.4 months). The only side effect of CTCAE grade 3/4 that occurred in more than 5% of patients on ramucirumab monotherapy was arterial hypertension. More common side effects in combination therapy were fatigue (12%), neuropathy (8%), and abdominal pain (6%).

6.2.3.1.9 Tegafur/S-1

An orally bioavailable fluoropyrimidine consisting of tegafur in combination with two modulators of 5-fluorouracil (5-FU) activity, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate, in a molar ratio of 1: 0.4: 1 is S-1. Tegafur is a prodrug of 5-fluorouracil, an antimetabolite that inhibits thymidylate synthase, DNA synthesis, and cell division and competes with uridine triphosphate, inhibiting RNA and protein synthesis. CDHP is a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), which is responsible for the rapid degradation of 5-FU to inactive metabolites. Potassium oxonate localizes preferentially in the intestine and inhibits the enzyme orotate phosphoribosyl transferase (OPRT), thereby reducing the activation of 5-FU in the intestine and the gastrointestinal toxicity associated with 5-FU.

Since 2020, all fluoropyrimidines have been subject to the recommendation of the European Medicine Agency that patients be tested for deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD) prior to initiation of therapy to prevent severe side effects caused by 5-fluorouracil or capecitabine or tegafur (https://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine).

6.2.3.1.10 Trastuzumab

Trastuzumab is the first monoclonal antibody that specifically interferes with the HER2/neu receptor and has been approved for the treatment of patients with HER2 overexpression or gene amplification. It is effective in the palliative setting. In HER2-positive gastric cancer, trastuzumab in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone results in prolonged overall survival (HR 0.74; median 2.7 months). Severe adverse events (grade 3/4) are rare.

6.2.3.1.11 Trastuzumab deruxtecan (T-DXd)

Trastuzumab deruxtecan is an antibody-drug conjugate containing a humanized anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently bound to DXd, an exatecan derivative and topoisomerase I inhibitor, via a tetrapeptide-based cleavable linker. Approximately 8 DXd molecules are bound to each antibody molecule. T-DXd is used as monotherapy to treat adult patients with advanced HER2-positive adenocarcinoma of the stomach or esophago-gastric junction who have received a prior trastuzumab-based therapeutic regimen. Patients treated with T-DXd must have a documented HER2-positive tumor status, defined either immunohistochemically (IHC) by a score of 3+ or by a gene copy number ratio relative to CEP17 of ≥ 2 measured by in situ hybridization (ISH).

The recommended dose of T-DXd in gastric cancer (different from breast cancer) is 6.4 mg/kg and is given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The initial dose is to be given as a 90-minute intravenous infusion. If the preceding infusion was well tolerated, subsequent T-DXd may be given as a 30-minute infusion. If the patient exhibits infusion-related symptoms, the infusion rate of T-DXd must be decreased or the infusion must be discontinued. If severe reactions to the infusion occur, T-DXd must be permanently discontinued. Special attention should be paid to the possible occurrence of pulmonary toxicity in the form of interstitial lung disease or pneumonitis. It should also be noted that trastuzumab deruxtecan has moderate to high acute and delayed emetogenic potential. We therefore recommend the prophylactic use of 3 antiemetics (dexamethasone, 5-HT3 antagonist, NK-1 antagonist).

6.2.3.1.12 Trifluridine/Tipiracil (FTD/TPI; TAS-102)

The fixed drug combination FTD-TPI consists of the nucleoside thymidine analogue trifluridine (FTD) and the thymidine phosphorylase inhibitor tipiracil (TPI). The molar ratio of trifluridine/tipiracil is 1:0.5 (exact mass ratio: 1:0.471). TF is phosphorylated intracellularly by the enzyme thymidine kinase to monophosphate (TF-MP) and subsequently by the enzyme thymidylate kinase to di- (TF-DP) and triphosphate (TF-TP). TF-TP is incorporated into the DNA as a defective component. This incorporation results in long-lasting DNA damage and DNA strand breaks. TF-MP, in turn, binds covalently to thyrosine-146 in the active site of the enzyme thymidilate synthetase (TS, also thymidilate synthase) and inhibits its activity. TS is responsible for the conversion of uracil nucleotides to the thymidine nucleotides and is thus vital for DNA synthesis by

maintaining sufficient amounts of thymidine. FTD-TPI proved superior to placebo in the third line of treatment of metastatic gastric cancer, prolonging overall survival (HR 0.69; $p < 0.001$) and was satisfactorily tolerated: Grade ≥ 3 adverse events occurred in 267 (80%) patients in the trifluridine/tipiracil group and in 97 (58%) in the placebo group.

6.2.3.1.13 Nivolumab

Nivolumab is an immune checkpoint inhibitor. It is a fully human monoclonal antibody of the immunoglobulin G4 (IgG4) class that binds to the PD-1 receptor on T cells and prevents interaction with the PD1 receptor ligand that binds here. In this way, the cellular immune system is indirectly stimulated by suppressing the inhibitory influence of the PD1 ligand/PD1 receptor interaction. Nivolumab is indicated in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of HER2-negative advanced or metastatic adenocarcinomas of the stomach, esophago-gastric junction, or esophagus in adults whose tumors express PD-L1 (combined positive score [CPS] ≥ 5). The recommended dose is 360 mg nivolumab intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy every 3 weeks or 240 mg nivolumab intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy every 2 weeks. Treatment with nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

6.2.3.1.14 Pembrolizumab

Pembrolizumab is an immune checkpoint inhibitor. It is a fully human monoclonal antibody of the immunoglobulin G4 (IgG4) class that binds to the PD-1 receptor on T cells and prevents interaction with the PD1 receptor ligand that actually binds here. In this way, the cellular immune system is indirectly stimulated by suppressing the inhibitory influence of the PD1 ligand/PD1 receptor interaction. Pembrolizumab is indicated in combination with platinum- and fluoropyrimidine-based chemotherapy for first-line treatment of locally advanced unresectable or metastatic HER2-negative adenocarcinoma of the stomach and the esophago-gastric junction in adults with PD-L1-expressing tumors (CPS ≥ 10). Pembrolizumab is also indicated as monotherapy for the treatment of gastric cancer with MSI-H or with a deficient DNA mismatch-repair (dMMR) in adults after at least one prior systemic therapy.

6.2.3.1.15 Tislelizumab

Tislelizumab is a drug from the group of monoclonal antibodies for the treatment of adult patients with esophageal cancer (squamous cell carcinoma of the esophagus), lung cancer (non-small cell lung carcinoma) and gastric cancer or tumors of the gastroesophageal junction. As a PD-1 inhibitor, tislelizumab is one of the immune checkpoint inhibitors. The active substance is a humanized monoclonal IgG4 antibody modified in the Fc part and was developed with the aim of minimizing binding to Fcγ receptors on macrophages and increasing the functional activity of T cells, which was demonstrated in cell-based in vitro tests. Tislelizumab is indicated in combination with platinum- plus fluoropyrimidine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2-negative adenocarcinoma of the stomach and esophago-gastric junction in adults with PD-L1-expressing tumors (TAP ≥ 5%).

6.2.3.1.16 Zolbetuximab

Zolbetuximab is a monoclonal antibody that is approved in combination with 5-fluorouracil- plus platinum-containing chemotherapy for the first-line treatment of adult patients with locally advanced, unresectable or metastatic HER-2-negative adenocarcinoma of the stomach or esophago-gastric junction. Patients with a Claudin-18.2-positive tumor (≥75% of tumor cells stain positive with an ICH score of 2+ or 3+) are eligible for treatment with zolbetuximab. Claudin-18.2 is a transmembrane protein that is expressed in around 38% of patients with the aforementioned types of cancer. Zolbetuximab is administered as an intravenous infusion. Before the infusion, antiemetic premedication in accordance with the recommendations for highly emetogenic chemotherapy is recommended:

- Antiemesis for zolbetuximab-treated patients should follow the guidelines recommendations for highly emetogenic substances [152, 153].
- The focus of prophylaxis and management is on the first two doses, as nausea and vomiting occurred most frequently here, according to study results. Patients should be made aware of the efficacy of zolbetuximab and it should be emphasized that nausea and vomiting occur less frequently from the second cycle onwards.
- It is particularly important to actively ask patients about side effects during and after the first administration. Nursing staff play an important role in the monitoring and management of side effects.

6.3 Special settings

6.3.1 Peritoneal metastasis

Several smaller randomized trials from Asia suggest a survival benefit for adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with curatively resected gastric cancer at high risk of recurrence [109, 110]. The ongoing randomized GASTRICHIP trial is attempting to clarify the efficacy of this approach in a European patient population [111]. For patients with peritoneal metastasis, there are also smaller randomized studies from Asia that suggest an advantage for cytoreductive surgery and HIPEC [112]. A larger multicenter case series from France showed a median survival for surgery plus HIPEC of 9.2 months, with a 5-year survival of 13% for all patients and 23% for patients with complete cytoreduction [113]. In Germany, the approach of peritonectomy plus HIPEC plus perioperative chemotherapy was compared with peritonectomy without HIPEC plus perioperative chemotherapy in the multicenter prospective randomized GASTRIPEC trial. The trial had to be closed prematurely after 105 patients due to slow recruitment and showed no survival benefit [114].

Based on current knowledge, adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) and peritonectomy are not standard therapies in this indication.

6.3.2 Signet ring cell carcinoma in locally advanced stages

Gastric signet ring cell carcinomas are associated with a poorer prognosis. This is at least partly due to a late diagnosis with presence of higher tumor stages at initial diagnosis [115]. Retrospective case series suggest that signet ring carcinomas respond less well to chemotherapy and radiochemotherapy [116, 117]. A retrospective study from a French national registry, albeit without a central histopathologic review of the tumor samples, suggests a worse prognosis for patients with signet ring carcinomas who receive perioperative chemotherapy in addition to resection [118]. However, the evidence from these studies is insufficient to make specific treatment recommendations. A French study [PRODIGE 19 - FFCD1103 - DCI002 (NCT01717924)]

addressed the issue of perioperative chemotherapy for resectable signet ring carcinoma of the stomach and compared this standard with adjuvant chemotherapy alone [119]. An evaluation published as an abstract yielded the result of sufficient efficacy of perioperative chemotherapy in patients with signet ring carcinoma [120]. In the German FLOT-4 study, the remission rate was the same under FLOT and ECF/ECX, but in a subgroup analysis, overall survival in the FLOT arm was also significantly prolonged in patients with signet-ring cell carcinoma [32]. Therefore, based on current knowledge, the same perioperative treatment recommendations apply to patients with locally advanced signet-ring cell carcinoma as to patients with non-signet-ring cell carcinoma.

7 Rehabilitation

Gastric carcinoma and the treatments, both surgical and medicinal, can lead to considerable secondary disorders such as weight loss, tumor cachexia, maldigestion and neuropathy. In addition, patients are often psychologically stressed and suffer from fatigue syndrome. Targeted rehabilitative measures are therefore necessary. When selecting the rehabilitation facility, the approval of the clinic for gastric carcinoma patients by the health insurance (pension insurance, health insurance) is a prerequisite; in addition, the patient's right of wish and choice according to §9 SGB IX should be taken into account. During rehabilitation, comprehensive nutritional advice should be given, patients should be included in the training kitchen, and there should be the possibility of administering all scientifically recognized diets, from normal whole foods to complete parenteral nutrition. All patients should be offered psycho-oncological care. Rehabilitation facilities should be able to continue ongoing drug therapies, including chemotherapy and immunotherapy, in accordance with the pre-treatment centers. Patients who have not yet reached the statutory retirement age should be informed about benefits for participation in working life as part of medical-occupational rehabilitation (German MBOR). Social-medical issues and any further care that the patient may require should be clarified during rehabilitation.

8 Monitoring and follow-up

8.1 Monitoring

During ongoing chemotherapy, patients’ general condition and vital body functions should generally be checked once a week, or more frequently if indicated [11]. Imaging follow-up examinations, preferably by computed tomography, are indicated every 6-12 weeks in order to timely detect an unfavorable course of the disease in time and not to expose patients to ineffective therapies for an unnecessarily long time, or to maintain the chance of more effective therapies.

8.2 Follow-up

There are no prospective data on the basis of which a specific follow-up regimen can be recommended. The German S3 guideline recommends to offer patients a structured follow-up after curative therapy, which includes clinical control, endoscopic and imaging control. The intervals should be at least semiannual for the first two years and then at least annual until the 5th year. In past and ongoing studies, the scheme shown in Table 5 has been established.

Table 5: Structured monitoring and follow-up in patients after curative therapy of gastric cancer

Procedure	Months post surgery (optional procedures in parenthesis)													
	(3)	6	(9)	12	(15)	18	(21)	24	(30)	36	(42)	48	54	60
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Blood count and routine clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy [1]	X		X		X		X		X		X	X	X	X
Imaging: Abdominal ultrasound or if necessary CT thorax/ abdomen/ pelvis	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Legend:
[1] optional in the absence of symptoms, recommended promptly in the presence of signs and symptoms suspicious of tumor recurrence, postoperative complications, or other endoscopically detectable pathology

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.