Gastric Cancer: Advanced/ Metastatic Disease

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Gastrointestinal Cancers

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Learning Objectives

By the end of the chapter, the reader will:

- Be able to choose the correct treatment algorithm for inoperable locally advanced and metastatic gastric cancer
- Have learned the basic concepts of molecular classification of gastric cancer
- Have reached in-depth knowledge of inoperable locally advanced and metastatic stomach cancer treatment
- Be able to put acquired knowledge into daily clinical practice

36.1 Introduction

Gastric cancer (GC) is the fifth most common tumor and the second leading cause of cancer-related death worldwide. Nowadays, we know that gastric cancers can be divided into two different clinical entities, gastroesophageal junction and stomach (body/antrum) tumors, that showed different features from epidemiologic, biologic, genetic, and clinical points of view.

In this chapter, only relevant aspects for the evaluation and treatment of unresectable locally advanced and metastatic disease are reported. For a complete description of the general features of gastric cancer, see the previous chapter.

36.2 Epidemiology

Gastric cancer shows significant global differences in incidence worldwide. Indeed, the highest rates are recorded in Eastern Asia, South America, and Eastern Europe while the lowest in North America and Western Europe. In particular, in Europe, the highest rates are reported in Portugal in addition to the eastern countries, while the lower incidence is described in Denmark [1]. According to this global view, a gradual decline of the incidence of GC has been observed in Western Europe and North America in the last decades due to the improvement of life conditions and due to an epidemiologic shift that lead to the decrease of distal gastric cancer and the increase of the junctional disease [2]:

- Globally, gastric cancer had an estimated unadjusted incidence of around 18 and 9/100,000/year for men and women, respectively.
- Gastric cancer is frequently diagnosed in men with an age between 60 and 80 years.
- More than 60% of patients are older than 65 years, with an age-related increase of the risk (from 15 new diagnosis/100,000/year in under 30 years patients to 140/100,000/year in over 75 years old patients)
- 90% of gastric cancer are sporadic, while only 1–3% are hereditary.

36.3 Clinical Features

Gastric cancers are usually asymptomatic in the early stage, and they may cause specific and faded symptoms afterward, leading to a late diagnosis.

Weight loss, anorexia, dysphagia, and heartburn are the most common signs and symptoms at the diagnosis. Specific symptoms may arise in more advanced stage due to the growth of tumor that could lead to significant stenosis or hemorrhages. Dysphagia and vomit may appear in case of a stenosis located at the gastroesophageal junction or if a prominent stenosis is located at the antrum. Hematemesis, melena, or sign and symptoms of chronic anemia (malaise, fatigue, or exertional dyspnea) are the most common clinical manifestation of active bleeding.

During the natural history of these tumors, lymphonodal involvement is frequent and represents an early step in metastatic spread. The most common signs of superficial lymphonodal involvement are Troisier's sign due to the left supraclavicular lymphadenopathy (Virchow's lymph node), Sister Joseph's nodule at the navel, and Irish's sign, which is a left axillar lymphadenopathy.

The liver, peritoneum, retroperitoneal lymph nodes, and lung are the most common sites of metastasis. Bones and brain metastasis are less common but possible. Liver involvement is predominant through celiac vessels and can lead to hepatomegaly and jaundice, while dyspnea can appear in case of diffuse lung involvement, pleural effusion, or profuse ascites. Bone pain and neurologic signs and symptoms can appear in case of bone and brain involvement, respectively. Peritoneal involvement is frequent in case of GC with a signet-ring cell component or in case of undifferentiated or diffuse-type tumors (according to Lauren classification). It spreads through lymphatic vessels on the gastric wall and cause different entity of peritoneal carcinomatosis with ascites, secondary ovary involvement (Krukenberg tumor), or nodules in the pouch of Douglas, also known as a sign of Blumer's shelf.

As other tumors, also in metastatic gastric cancer, some paraneoplastic syndromes can occur, such as acanthosis nigricans, diffuse intravascular coagulation, venous thrombosis (Trousseau syndrome), and many others, due to the secretion of different active substances (cytokines, hormones, etc.) by the tumor.

36.4 Pathological Features

36.4.1 Microscopic Aspects and Immunohistochemical

In case of locally advanced, recurrent, or metastatic GC, pathological report should include not only the classical microscopic parameters, such as the histological subtypes and Lauren's classification, but also the evaluation of human epidermal growth factor receptor 2 (HER2) status.

Still today, HER2 determination represents the only validated biomarker in GC, able to influence the treatment choices. HER2 positivity is determined by quantification of the HER2 cell surface receptors by immunohistochemistry (IHC) and/or by measuring the number of HER2 gene copy numbers using fluorescence in situ hybridization (FISH). Determination of HER2 status via IHC is distinct for gastric and breast cancer, because an incomplete basolateral or lateral staining alone in gastric cancer is considered positive in addition to complete membrane staining. This difference results in tumor heterogeneity and potential inaccuracy determination of the HER2 positivity, and multiple biopsies of different sites of neoplastic lesion are recommended to overcome this risk (at least five to six biopsies are usually required).

In GC, HER2 positivity is defined by 3+ scoring on IHC or 2+ on IHC with a FISH amplification (HER2/CEP 17 ratio ≥ 2.0), according to an IHC scoring criteria specific for HER2 overexpression in gastric cancer. HER2 status is considered negative in case of results 0 or 1+ by IHC [3]. Another relevant issue in this field is that the IHC staining pattern that determines the highest level of HER2 expression by IHC (IHC 3+) depends on whether a surgical specimen or biopsy is tested. As a matter of fact, basolateral or lateral membranous reactivity in ≥10% of tumor cells represents an IHC 3+ staining pattern in a surgical specimen, while an IHC 3+ staining pattern on a tumor biopsy is determined by tumor cell clusters with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cell stained (Fig. 36.1). Tumors with equivocal IHC scores (2+) should be tested further using FISH or other in situ methods (ISH (immunofluorescence in situ hybridization)) in order to evaluate gene amplification(Fig. 36.2).

Even if different trials have investigated the role of mesenchymal-epithelial transition factor (c-Met) in gastric cancer, the results are still controversial, and there is

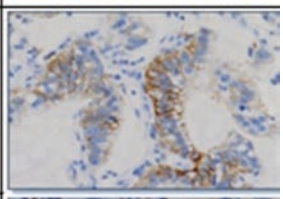
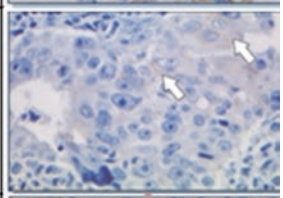
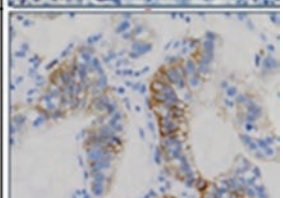
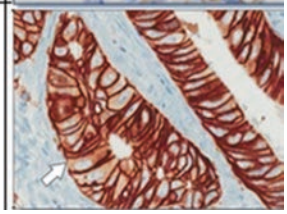
Score	Staining pattern (biopsy)	Staining pattern (resection)	Classification	IHC
0	No reactivity or no membranous reactivity in any tumor cell	No reactivity or membranous reactivity in < 10% of cells	Negative	
1+	Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	Faint/barely perceptible membranous reactivity in >10% of cells; cells are reactive only in part of their membrane	Negative	
2+	Tumor cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of Tumor cells stained	Weak o moderate complete or basolateral membranous reactivity in > 10% of tumor cells	Equivocal	
3+	Tumor cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	Moderate to strong complete or basolateral membranous reactivity in > 10% of tumor cells	Positive	

Fig. 36.1 HER2 scoring system in gastric cancer

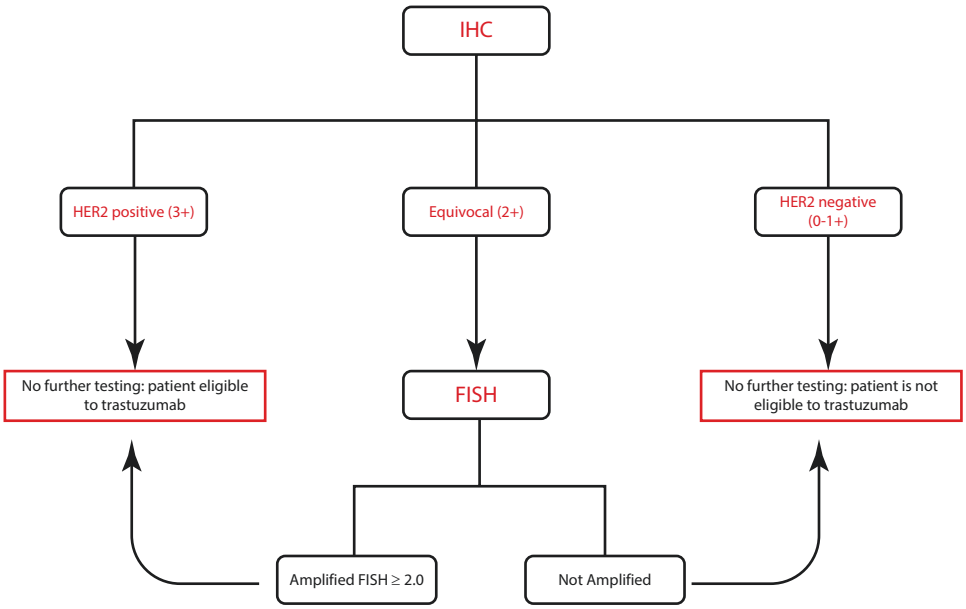


Fig. 36.2 Algorithm of HER2 status determination by IHC and FISH

not yet a validated method to assess Met amplification and overexpression. Furthermore, Met evaluation is not recommended in daily clinical practice.

With the development of immunotherapy, further biomarkers have been investigated and validated during the last years. Microsatellite instability (MSI) evaluates the genetic mutability condition. In case of impaired DNA mismatch repair (MMR), the normal function of these mechanisms leads to a genetic hypermutability and a kind of mutation accumulation that result in a high neoantigen production and a consequent sensitivity to immunotherapeutic agents. This condition is called "high microsatellite instability" (MSI-H). MMR status can also be determined by the immunohistochemical analysis of some protein expression (such as MLH1, PMS2, MSH2, MSH6).

Another possible predictive factor for immunotherapy is the programmed death-ligand 1 (PD-L1).

PD-L1 is a transmembrane protein involved in the suppressing signaling of the immune response and in the "self-tolerance," acting as an inhibition factor (coinhibitor) for T-cell activity. It is a part of those regulators that constitute the so-called immune checkpoints. The "immune checkpoint inhibitors" are the drugs mainly use as immunotherapy against cancer, thanks to their blocking action on these receptors or their ligands. A high PD-L1 expression, assessed via IHC, is considered a positive predictive factor for immunotherapy across many tumor types. Its evaluation may be carried out according to tumor proportion score (TPS) or, more effectively, according to combined positive score (CPS) analysis of not only the viable tumor cells but also the other PD-L1 staining cells in the microenvironment (lymphocytes and macrophages).

In addition to these biomarkers, also the Epstein-Barr virus (EBV) status may be a useful tool for treatment selection. Its evaluation can be done by ICH or by Epstein-Barr encoding region (EBER) in situ hybridization, even if its role is still debated and far from being already validated for GC.

36.5 Molecular Biology and Main Therapeutic Targets in Advanced Gastric Cancer

For many years, GC was considered as a single disease: however, we know that it should be considered as a collection of very different molecular entities, each characterized by different clinical and molecular features. A first attempt to define GC heterogeneity was performed by Lauren P [4], who identified two types of GC on histological bases: the first one called "intestinal," because it displayed feature characteristic of the intestinal mucosa (in fact, it arises from intestinal metaplasia), and the other one called "diffuse," because the cancer cells, often poorly cohesive, diffusely infiltrated the gastric wall. On the other side, the World Health Organization (WHO) Classification of Tumors of the Digestive System (2019) classifies GC, according to their histological appearance, in "tubular adenocarcinomas," "papillary adenocarcinomas," "mucinous adenocarcinomas," and "signet-ring cell adenocarcinomas," the latter one resembling those that are classified as "diffuse-type" in the Lauren classification. Moreover, in addition to classic histological features, we can now classify these neoplasms also by their molecular profile. In particular, many studies

have shown that gastric cancer can be driven by different genetic and/or epigenetic abnormalities: these findings led us to create robust molecular classifications that could become important especially in metastatic setting in order to develop novel target therapies.

36.5.1 Molecular Classifications

One of the first molecular GC classifications was by Patrick Tan et al. [5]: they classified GC into two distinct intrinsic subgroups – G-INT (genomic intestinal) and G-DIF (genomic diffuse). The authors used a panel of 37 GC cell lines and identified a "gene expression signature" of 171 genes that is able to distinguish between these two intrinsic subtypes, the first one called "G-INT" because more related to Lauren's intestinal subtype and the other one "G-DIF" because more related to diffuse subtype. The classification was then validated in a clinical cohort of 270 GC patients, showing that these two intrinsic classes really exist. Moreover, useful predictive information came out from in vitro experiments on 28 cell lines, with relevant implications for patient's care: G-INT cell lines were found to be more sensitive to 5-fluorouralcil and oxaliplatin, while G-DIF resulted to be more sensitive to cisplatin.

The same research group reported 2 years later [6] another GC classification based on the evaluation of gene expression in 248 tumors. According to this classification, GC can be divided into three subgroups: proliferative, metabolic, and mesenchymal. Proliferative subtypes are characterized by genomic instability, p53 mutations, and DNA hypomethylation; in the metabolic type, there is an increased activity of spasmolytic polypeptide-expressing metaplasia (SPEM metaplasia), while the mesenchymal type shows an epithelial mesenchymal transition (EMT) signature with high level of N-cadherin and low level of E-cadherin that leads to poorly differentiated tumors. Again, some interesting translational implications emerged: metabolic subtype seems more sensitive to 5-fluorouracil than the other two, while the mesenchymal subtype (probably due to "oncogenic addiction" to PI3K-AKT-mTOR pathway) seems to be more sensitive to drugs that block PI3K or mTOR, opening the way for a more precise therapy for GC.

In 2014, the Cancer Genome Atlas (TCGA) investigators published the most important and comprehensive study that we have to date on molecular GC classification. Four subtypes of gastric cancer have been described: Epstein-Barr virus (EBV)-positive, 9% of cases; microsatellite instability (MSI-H), 22% of cases; genomically stable (GS), 20% of cases; and chromosomal instability (CIN), 50% of cases ([7]; Fig. 36.3).

Each subtype shows different features and it is enriched for selected molecular abnormalities. In particular, the EBV-positive type is characterized by the posi-

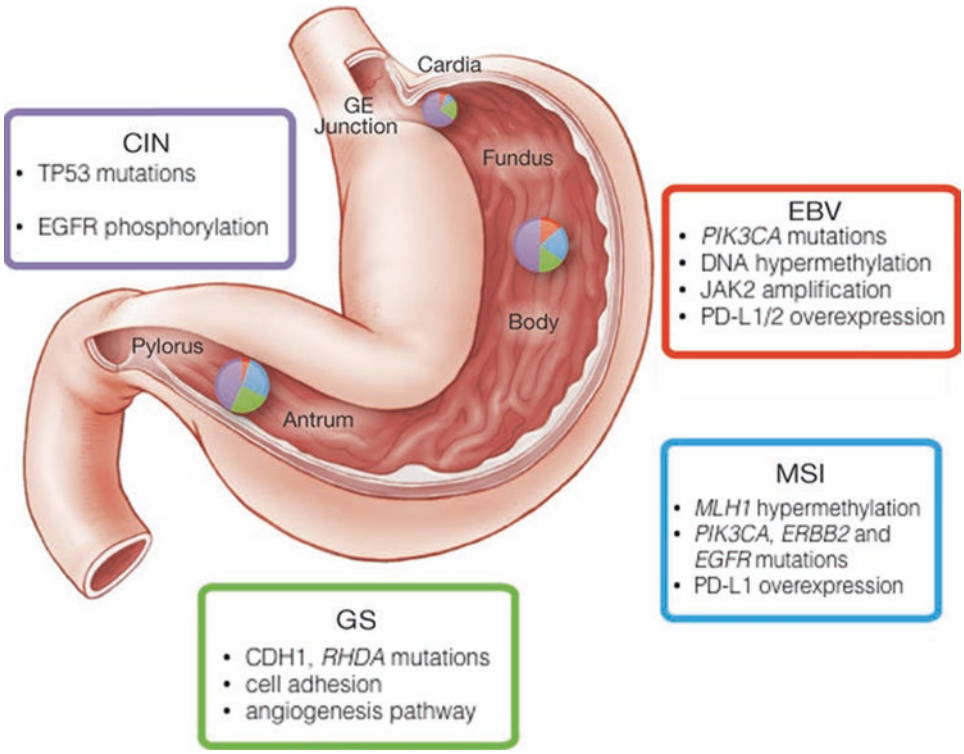


Fig. 36.3 Molecular subtypes of gastric cancer as emerged from TCGA. See the text for more information

tivity for EBV, mutations, or amplifications of PI3K, PD-L1, and JAK2; these cancers can mostly arise in the fundus or gastric body and are more frequent in men.

MSI-H tumors are more frequent in older women and comprise especially intestinal-type cancers. From a molecular point of view, this group is characterized by mutations of p53, EGFR, HER2, HER3, PTEN, or silencing of the promoter of MLH1, a gene involved in the mismatch repair process.

GS gastric cancers are frequently diffuse and arise in younger age: they lack somatic copy number aberrations and are more related to Lauren's diffuse histology than the other ones. A pathway frequently destroyed in this subtype is that related to "cell adhesion," with the most relevant genes mutated CDH1, RHOA, and chromosomal translocation involving CLDN18 and ARHGAP.

Finally, the CIN subtype is enriched for copy number changes in key receptor tyrosine kinase oncogenes such as HER2, EGFR, fibroblast growth factor receptor 2 (FGFR2), and MET. This type is composed mostly of intestinal tumors, and it involves predominantly the gastroesophageal junction. These findings have potentially important therapeutic implications in order to improve the founding of target therapies against the specific key pathways driving the tumor in each individual patient.

Recently, the Asian Cancer Research Group [8] proposed a third molecular classification based on molecular and genetic alterations in gastric cancer. According to this one, it can distinguish four groups of gastric cancer: MSI (23%), microsatellite stable with intact (MSS/TP53-, 36%), microsatellite stable with p53 mutations (MSS/TP53+, 26%), and microsatellite stable with epithelial-mesenchymal transition (MSS/EMT, 15%) [8]. Unlike the TGCA classification, the ACRG reported different outcomes for each gastric cancer's subgroup. In particular, MSI had a better prognosis, whereas MSS/EMT had a worse prognosis with high rate of recurrence and peritoneal involvement. However, further studies are needed to translate these results in clinical practice.

In the next sections, we describe the most relevant therapeutic targets in gastric cancer with notable information about pivotal clinical trials conducted in this area and some resistance mechanisms to targeted agents.

36.5.2 Human Epidermal Growth Factor Receptor 2 (HER2)-Related Pathways: Therapeutic Targeting and Resistance Mechanisms

One of the first molecular pathways studied in gastric cancer was the epidermal growth factor receptor (EGFR) family pathway, which includes EGFR/HER1, HER2/neu, HER3, and HER4 receptors. Each receptor consists of an extracellular ligand-binding domain, an intracellular domain with kinase activity, and a short, lipophilic, transmembrane domain. The binding of ligands to their own receptor leads to homodimerization or heterodimerization with other members of the EGFR family, phosphorylation of intracellular domain, and activation of downstream pathways including the Ras/Raf/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathways. Stimulation of these pathways influences many aspects of tumor cell biology, such as proliferation, differentiation, migration, and apoptosis (Fig. 36.4). Among these receptors, HER2 plays a key role in gastric cancer.

HER2, encoded at chromosome 17q21, acts as proto-oncogene in many human cancers: its main oncogenic mechanism is represented by gene amplification (determining protein overexpression) or, less commonly, by activating mutations.

HER2 lacks of a known exogenous ligand, and it is transactivated by the interaction with other HER family members (EGFR or HER3 overall) or other tyrosine kinase receptors: its activation leads to a complex signaling cascade already described above. In GC, HER2 overexpression is mainly due to gene amplification: it occurs more frequently in proximal tumors (more than 30% of cases), than in distal cancers (less than 20%). Furthermore, Lauren intestinal subtype shows a higher expression of HER2 (up to 34%) than diffuse subtype (6%), while, concerning to TCGA classification, CIN tumors more often express HER2 as consequence of gene amplification. Different strategies to target HER2 were developed over the years: monoclonal antibodies (like trastuzumab) that bind to the extracellular domain of the receptor and TKIs (tyrosine kinase inhibitors). The pivotal phase III ToGA trial [3] showed that in HER2-positive GCs, the addition of trastuzumab to standard platinum-based first-line treatment was effective, with a median overall survival (mOS) of about 13.8 months in the experimental arm versus 11.1 in the standard one (HR: 0.74; $p = 0.0046$). This OS still represents the highest ever reached in a phase III trial recruiting GC patients. The greatest benefit was observed in high HER2-expressing patients (IHC3+ or IHC2+/FISH+), with an mOS of 16 months versus 11.8 in low HER2-expressing patients (IHC0-1+/FISH+). Therefore, this trial led to the approval of trastuzumab in HER2-positive GC, in the first-line setting for patients with IHC3+ or IHC2+/FISH+ (see Fig. 36.2). Next, it has been speculated that in GC, the addition of pertuzumab (another monoclonal antibody targeting a different HER2 domain than trastuzumab) to trastuzumab itself and platinum-based chemotherapy could improve the ToGA survival rates, leading to JACOB trial design. Unfortunately, this study [10] was negative, because mOS was 17.5 months

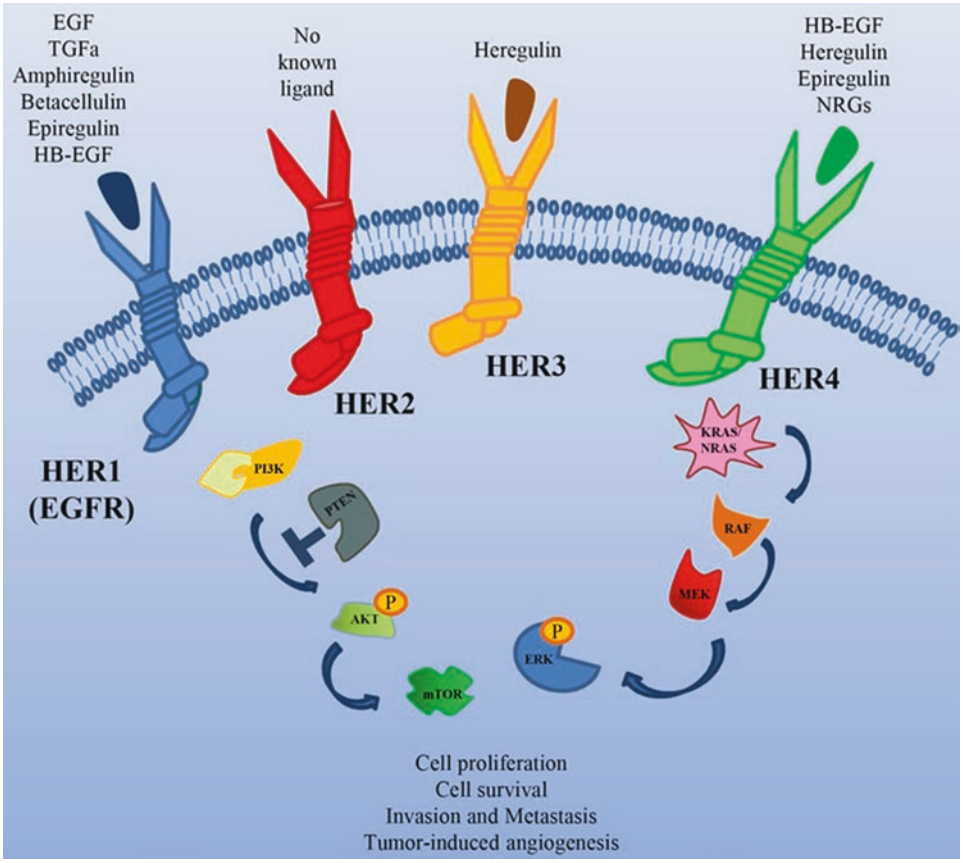


Fig. 36.4 EGFR pathways. (Used with permission from Apicella et al. [9]. See the references for the original source of this material)

in experimental arm versus 14.2 in the standard (HR: 0.84; $p = 0.0565$), a difference that did not find statistical significance. Moreover, trastuzumab emtansine (TDM-1), an antibody-drug conjugate, was studied in second-line therapy of HER2-positive GC (previously treated with trastuzumab) within the GATSBY phase III trial [11]: unfortunately, TDM-1 therapy was not superior to standard taxanes (mOS 7.9 months versus 8.6, respectively, HR: 1.15, $p = 0.86$).

Due to the disappointing results of these trials (JACOB, GATSBY), many researchers began to study mechanisms of targeted therapy resistance in GC, considering that also patients who achieved a significant response to first-line trastuzumab-based treatment can develop resistance within a few months. In fact, one main bias of the second-line trials, especially the GATSBY trial, seems to be the absence of tumor re-biopsy (e.g., at one metastatic site) at screening, taking for granted that the tumor was still HER2-positive on the basis of the "historical" diagnostic biopsy. The study by Pietrantonio et al. [12] clearly showed that a possible acquired resistance mechanism to trastuzumab-based first-line treatment could be the loss of HER2 receptor, especially for patients with dubious immunohistochemistry (IHC2+/FISH+). In that way, the negative results of the GATSBY study could be related to the fact that in a significant proportion of cases, the authors have treated with TDM-1 patients who had become HER2-negative de facto at the beginning of the second line.

More important, even primary resistance to first-line anti-HER2 drugs seems to exist: in fact, objective response rates to trastuzumab plus chemotherapy in ToGA trial was about 50% only, which implies that at least 50% of HER2-positive tumors could have coexisting molecular alterations that confer resistance. In support of this hypothesis, the group lead by Adam Bass [13] clearly showed that almost 50% of HER2-amplified gastroesophageal cancers have preexisting co-amplifications or co-mutations in key oncogenes (others than HER2), for example, cell cycle-related genes (CCNE1, CDK6, and CCND1), RTK-related genes (EGFR, HER3, MET, FGFR2), or PI3K-related genes (PIK3CA, PIK3R1, PTEN). These amplifications/mutations confer resistance to anti-HER2-targeted drugs in cell line experiments. This preliminary report was then confirmed by Pietrantonio et al. [14], who showed that mutations of EGFR, MET, KRAS, PIK3CA, and PTEN or amplifications of EGFR, MET, and KRAS can co-occur in HER2-positive GC and could explain the lack of trastuzumab efficacy and/or the appearance of primary resistance.

Among others, EGFR (or HER-1) is amplified in around 5% of gastric cancers characterized by poor prognosis.

36.5.3 Epidermal Growth Factor Receptor (EGFR)-Related Pathways: Therapeutic Targeting and Resistance Mechanisms

Epidermal growth factor receptor (EGFR) or ERBB1 is a transmembrane tyrosine kinase receptor, expressed approximately in 30% of GC, especially those with chromosomal instability.

Several studies evaluated the safety and efficacy of different anti-EGFR drugs: these therapies include – as we just discussed for HER2 – monoclonal antibodies (like cetuximab or panitumumab) and TKIs (gefitinib, erlotinib). Initial phase II trials combining these agents with cytotoxic chemotherapy in unselected patient population have encouraging results for first-line patients. Unfortunately, all of the phase III published trials investigating the role of anti-EGFR therapy in GC were negative. The EXPAND study [15] randomized first-line GC patients between cetuximab plus capecitabine/cisplatin and chemotherapy alone, showing no advantage for cetuximab arm. However, the patient recruitment was unselected for EGFR positivity, and in a post hoc analysis, the highest survival benefit was observed in a small subset of patients with high EGFR expression. The REAL-III trial [16] demonstrates that adding panitumumab to epirubicin-oxaliplatin-capecitabine was even detrimental, as the mOS for the experimental arm was 8.8 months versus 11.3 months for the standard one (HR: 1.37, $p = 0.013$).

The shocking failure of all anti-EGFR drugs in gastric cancer could be explained with the lack of a proper patient selection. In fact, a recent work by Catenacci et al. [17] showed that EGFR amplified tumors (almost 5% in this study) seem very prone to respond to cetuximab or ABT-806 (an investigational anti-EGFR drug), with an ORR of 58%, a DCR of 100%, and an mPFS of about 10 months. Thanks to the next-generation sequencing (NGS) and circulating tumor DNA (ctDNA) studies, the authors also showed the mechanisms of resistance to anti-EGFR drugs, such as the presence of EGFR-negative tumor clones, KRAS mutation/amplifications, PTEN deletion, and NRAS/HER2/MYC amplifications. This study definitively demonstrates that EGFR amplification is able to predict response to anti-EGFR therapies, despite the negative results in prior unselected phase III trials (EXPAND and REAL-III), but also showed crucial mechanisms of resistance.

36.5.4 MET Pathway: Therapeutic Targeting

MET (mesenchymal-epithelial transition) oncogene, also called hepatocyte growth factor receptor (HGF), is a receptor tyrosine kinase that appears to be deregulated in many human cancers, included in GC. The main known mechanism of MET overexpression in GC is gene amplification, which occurs in about 6% of the TCGA dataset (especially in CIN tumors). However, even tumors without gene amplification can express (or overexpress) MET, although it is not clear whether these tumors really depend on MET for survival and malignant properties. Two monoclonal antibodies, rilotumumab (an anti-HGF antibody) and onartuzumab (an anti-MET antibody), were tested in clinical trials in GC: both phase III clinical trials evaluating onartuzumab and rilotumumab were negative.

The METGastric phase III trial [18] evaluated the addition of onartuzumab to a chemotherapy backbone (mFOLFOX6) and enrolled 562 GC patients with HER2-negative/MET-positive tumors. The enrollment was early stopped due to sponsor decision, for a lack of efficacy. Unluckily, the addition of onartuzumab to mFOLFOX6 did not result in an improvement of OS (11 months in the experimental arm versus 11.3 in standard, HR: 0.82, $p = 0.24$). Negative results were obtained also with rilotumumab within the RILOMET-1 phase III trial [19], which used a different chemotherapy backbone (epirubicin plus cisplatin and capecitabine). As for the previous trial, results were clearly negative with a detrimental effect (mOS was 8.8 in experimental arm versus 10.7 in the placebo group, HR: 1.34, $p = 0.003$), and, again, study treatment was stopped early, because an independent data monitoring found a higher number of deaths in the rilotumumab group. Probably the main limit of RILOMET and METGastric trials is to have included mostly patients in whom MET was not a clear "driver" of the disease, since the highest expressing tumors (MET gene amplification) are underrepresented, which can explain the negative results described.

36.5.5 VEGF Pathway: Therapeutic Targeting

In the TCGA "CIN" subtype, vascular endothelial growth factor (VEGF), a crucial mediator of normal and pathogenic angiogenesis, is frequently amplified (up to 7% of cases). However, initial studies with bevacizumab (a monoclonal antibody targeting VEGF-A) were negative, such as the AVAGAST trial [20] and the Asiatic AVATAR trial [21], in which bevacizumab was combined with platinum-based chemotherapy

in the first-line setting. Subsequently, ramucirumab, a fully human monoclonal antibody directed against VEGFR2 (vascular endothelial growth factor receptor 2), the main receptor of the VEGF system, has been used in the second-line setting alone [22] or in combination with weekly paclitaxel [23]. Both studies were positive, with the REGARD trial showing a significant improvement in OS with ramucirumab alone versus BSC (mOS 5.2 months versus 3.8, respectively, HR: 0.776, $p = 0.047$) and the RAINBOW trial showing a significant superiority of combination arm (ramucirumab plus paclitaxel) versus paclitaxel alone (mOS 9.63 months versus 7.36 months, respectively, HR: 0.807, $p = 0.017$).

On that positive basis, ramucirumab has been tested in first-line setting in combination with cisplatin-based standard chemotherapy within the RAINFALL trial [24]: although the study formally met its primary endpoint, with an improvement in mPFS from 5.4 months (placebo arm) to 5.7 months (ramucirumab arm) (HR: 0.75, $p = 0.011$), there was no survival benefit for patients in the experimental arm, making the results negative de facto and not significant for clinical practice. Therefore, the role of antiangiogenic agents seems to be essential in second-line setting, but in the first line, like the AVAGAST and AVATAR trial, showed for bevacizumab, probably we need to better understand the patients who really benefit from this strategy.

36.5.6 Tumor Microenvironment: The Biological Basis of Immune Checkpoint Usage in Metastatic Gastric Cancer

Immunotherapy deeply changed the therapeutic landscape for several malignancies (advanced melanoma, lung, urothelial, kidney cancer, etc.) determining a completely unexpected improvement of survival by boosting the body's natural defenses to fight cancer.

As already reported, comprehensive molecular characterization performed by the TGCA group showed a relatively high mutational load (up to 10–15 mutations per megabase) in about 34% of gastric adenocarcinomas analyzed and a subset of tumors with microsatellite instability-high (MSI-H, 22%) or with an ideally favorable immune environment (the "EBV-related" subgroup that shows molecular hallmarks of sensitivity to immunotherapy, such as intratumoral or peritumoral immune cell infiltration and PD-L-1/PD-L-2 expression), suggesting that also gastric cancer could be a promising "fertile soil" for immunotherapy, especially based on immune checkpoint inhibitors [25].

36.6 Prognostic Factors

Despite the expanding knowledge about molecular mechanisms that lead to a better comprehension of GC, the prognosis of this tumor is still poor, especially in case of locally advanced or metastatic disease. In this context, the research for prognostic and predictive factors became particularly relevant.

Diffuse histotype, performance status, and number and location of distant metastasis are the principal prognostic factors in the metastatic setting. According to these and other biochemical factors, different prognostic scores have been validated over the past years. The Royal Marsden prognostic score [26, 27] divides GC patients into three risk groups on the bases of four parameters: performance status, liver metastasis, peritoneal metastasis, and serum alkaline phosphatase. Patients with peritoneal metastasis, performance status ≥2, and serum alkaline phosphatase ≥100 U/L had the worse prognosis, with a 1-year survival of 11% compared to 25.7% and 48.5% in the moderate- and low-risk groups, respectively.

In addition to these parameters, many trials showed that tumor prognosis may be influenced not only by tumor features themselves but also by tumor microenvironment. In this context, the neutrophil/lymphocyte ratio (NLR) in venous peripheral blood has been highly investigated in order to find a possible simple and quick prognostic factor. A recent research [28] showed that in a clinical cohort of 151 metastatic gastric cancer patients, NLR obtained before starting first-line chemotherapy is a strong independent predictor of poor survival, suggesting its utility for a quick and cheap patient prognostic stratification.

Regarding prognostic scores for mGC patients receiving a second-line treatment, an Italian model (Gastric life nomogram) showed to predict 12-week life expectancy for these patients [29]. However, all these promising factors need to be further validated in prospective clinical trials.

36.7 Treatment

Chemotherapy represents the standard treatment for unresectable locally advanced and metastatic gastric cancer, showing improvement of survival and quality of life compared with best supportive care [30]. ◘ Figure 36.5 summarizes the current "state of the art" for treatment selection in metastatic GC patients.

Despite of the term "advanced gastric cancer" comprising also patients with inoperable locally advanced tumors, it is important to distinguish this group of patients from the metastatic one, because in this case patients have not distant metastasis and tumor could be

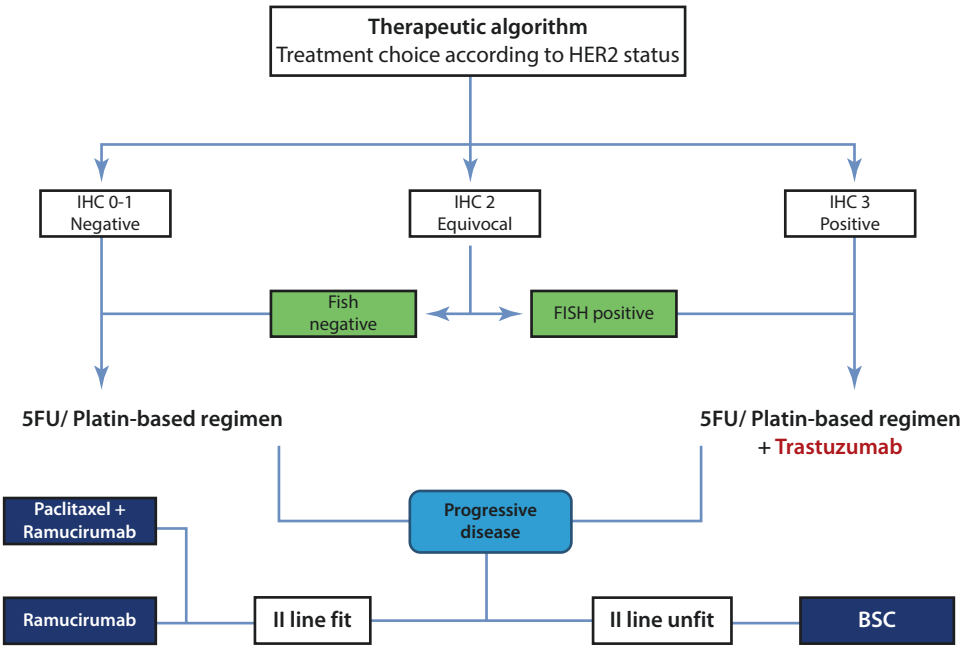


Fig. 36.5 Biomarker-driven therapy for advanced gastric cancer in 2020

converted into an operable disease after a chemotherapy response. Therefore, more aggressive and active chemotherapy schedules are recommended for these patients as a conversion therapy in order to obtain a tumor downsizing and downstaging. On the other hand, it is important to consider that the target of treatment in case of metastatic disease is the palliation, because we still do not have sufficient evidence to support the recommendation of tumor resection in this population, and surgery does not prolong survival and can even produce a detrimental effect (see below for more details). Moreover, the general clinical condition of these patients are frequently poor so a multidisciplinary evaluation of different aspects of disease, comprising a nutritional and toxicity evaluation as well as the palliation of symptoms, is fundamental to improve the efficacy of active treatments.

The nutritional assessment is crucial since the first take charge in order to prevent malnutrition and to avoid the poor compliance and tolerability caused by nutritional condition decline.

Because of tumor locations (cardia or antrum) and possible luminal obstruction, it is necessary sometimes to resort to parenteral nutrition.

Response to systemic treatments should normally be assessed with interval imaging of the chest, abdomen, and pelvis, mostly with computer tomography (CT) scan, although alternative imaging techniques may be used if required to monitor known sites of disease (e.g., magnetic resonance imaging for brain lesions). The evaluation of response is according to standard radiologic criteria for solid tumor, also known as RECIST criteria, except in case of immunotherapy in which the immune-modified RECIST (iRECIST) should be used.

36.7.1 First Line

The determination of HER2 status is essential before starting a first-line therapy in order to distinguish HER2-negative and HER2-positive gastric cancer, selecting patients for appropriate treatment with trastuzumab (an anti-HER2 monoclonal antibody). However, a more complete molecular dissection before starting a first-line chemotherapy is today highly desirable, considering the promising results of the recently presented KEYNOTE-062 trial [31], in which first-line metastatic GC patients with a MSI-H disease or a high expression of PD-L1 received greater benefit from anti-PD-1 pembrolizumab compared to standard chemotherapy arm (HR: 0.29, 95% IC 0.11–0.81). For this reason, MSI testing is absolutely recommended, although immune checkpoint inhibitors are not yet approved for this indication in EU nowadays.

No anti-HER2 agent showed a survival benefit beyond the first-line setting indeed.

36.7.1.1 Chemotherapy

In patients with HER2-negative disease, the only effective therapeutic option we have to date is chemotherapy. However, despite the use of the most modern regimens, the survival of these patients remains overall poor (median OS: 11 months), even if a correct "continuum of care" strategy and molecular selection is starting to lead to less rare longer survivals.

Polichemotherapy is still the standard first-line treatment for patients with a good performance status, while best supportive care alone is recommended in cases with poor clinical conditions considered "unfit" for active treatments.

Doublet combinations of platinum (either cisplatin or oxaliplatin) and fluoropyrimidines (5-fluorouracil or capecitabine) showed greater benefit if compared to mono-chemotherapy and are generally used in fit patients as standard regimens [30].

On the other side, the utility of triplet regimens as first-line therapy is still under debate, and their use should be evaluated, in the context of a multidisciplinary discussion, only in selected cases. For example, triplet regimen utility could be speculated in GC patients with:

1. Locally advanced disease, in which a more active regimen (like a triplet one) could lead to tumor downstaging and to a possible rescue to radical surgery on primary tumor
2. High tumor burden disease with severe symptoms, in which a rapid clinical response (such as that obtainable with triplet regimen) could be required to improve patient general clinical conditions and to achieve a more rapid symptom recovery (i.e., for severe dysphagia)
3. Oligo-metastatic diseases, in which a triplet-based "neoadjuvant" approach (e.g., with a taxane-based regimen such as "FLOT") could be followed by primary plus metastatic lesion(s) surgical resections, according to preliminary results of the phase II AIO FLOT 3 trial [32]

Triplets containing taxanes (DCF, FLOT) showed survival benefits in first-line setting, while schedules containing anthracyclines, although initially associated with better outcomes, today must not be used anymore, as we later explain.

In the phase III randomized trial TAX-325 [33], the addition of docetaxel to 5-FU/cisplatin in a three weekly regimen named DCF was associated with improved overall survival in first-line therapy (OS: 9.2 versus 8.6 months) but at the cost of significantly more toxic effects, including increased rates of febrile neutropenia. For this reason, other studies have examined the efficacy of alternative taxane-based triplets, like FLOT regimen (docetaxel, fluoropyrimidine, and oxaliplatin), with positive results both in terms of efficacy and tolerability [34].

With regard to anthracycline-based triplets, the REAL-II trial [35] demonstrated non-inferiority between ECF, ECX, EOF (epirubicin, oxaliplatin, 5-FU), and EOX (epirubicin, oxaliplatin, and capecitabine), making the substitution of 5-FU with capecitabine and cisplatin with oxaliplatin possible. However, as already anticipated, anthracycline-containing regimens should not be considered anymore for GC patient treatment: in fact, according also to a famous editorial by Jaffer Ajani, only three drugs have demonstrated an OS improvement in first-line setting – forming level I of evidence – and they are docetaxel, cisplatin, and trastuzumab, while epirubicin has never gained this "honor." As a matter of fact, a standard doublet has been demonstrated to be as effective as an anthracycline-base triplet but with significant less toxicity. For this reason and for the increased cardiac risk that is associated with these drugs, we can assert that today no GC patient should continue to receive epirubicin-based triplet.

To reinforce this concept, we refer to a fundamental study lead by Guimbaud R et al.: in this trial, the FOLFIRI regimen (irinotecan plus leucovorin and infusional 5-FU) was compared to the anthracycline-based ECX regimen in first-line setting. The authors showed a non-inferiority of doublet versus triplet regimen combination, supporting once more the necessity to avoid anthracycline from gastric cancer therapy, because it cannot add nothing to survival benefit.

Furthermore, in a different setting (neoadjuvant) the taxane-based triplet FLOT showed its superiority, in terms of responses and survival, over the epirubicin-based triplet [36].

The S1 fluoropyrimidine is an another orally choice to be evaluated in association with cisplatin in first-line setting in Asiatic population, while it is not recommended in the Caucasian due to high rate of toxicity in this population [37].

In conclusion, data are not supporting the use of triplet regimens in all patients with metastatic gastric cancer, but only in selected patients (see above), even if an increase of side effects should be considered.

36.7.1.2 Chemotherapy for HER2-Positive Disease

In the first-line treatment of HER2-positive gastric cancer, the phase III ToGA trial demonstrated clinically and statistically significant improvements in response rate, progression-free survival (PFS), and OS with the addition of trastuzumab to cisplatin/fluoropyrimidine doublet [3], especially in patients with higher expression of the protein (HER2 3+ at IHC or 2+ IHC with FISH amplification).

Based on the ToGA results, trastuzumab was approved in many countries in addition to cisplatin-fluoropyrimidine doublet as first-line standard of care in patients with HER2-positive disease. This drug is currently used at the same dose of HER2-positive breast cancer (8 mg/Kg in the first induction dose and then 6 mg/Kg every 21 days), even if today it is clear that HER2-positive gastric cancer is biologically different from the breast one. However, the addiction of trastuzumab with different schedule to chemotherapy did not show any benefit in patients with HER2-positive metastatic gastric cancer [18, 38]. Moreover, trastuzumab is actually investigated in adjuvant and neoadjuvant setting for HER2-positive gastric cancer.

Unfortunately, trastuzumab remains the only anti HER2 target therapy approved in the first-line setting.

Lapatinib, an oral inhibitor of tyrosine kinase domain of EGFR and HER2, failed to add the same efficacy as trastuzumab in addiction to capecitabine and oxaliplatin.

Similarly, negative results were achieved by Pertuzumab within the Jacob trial [10], as already reported in the previous section. For this reason, pertuzumab is not actually approved in addition to standard first-line treatment.

Anti-HER2 strategy beyond first-line setting is actually not recommended. The TDM-1 (an "antibody-drug conjugate" in which the molecule of trastuzumab is combined with a cytotoxic drug) did not show a survival benefit in the second-line treatment of patients previously treated with trastuzumab [11].

36.7.2 Second Line

Approximatively 40% of patients (and even more in high-volume centers) with metastatic gastric cancer patients receive a second-line treatment after the first-line failure. Second-line treatment is recommended in patients with a progressive disease and with a good performance status. An active treatment is associated with an improvement in OS and quality of life compared with best supportive care.

Among different chemotherapy agents and schedules investigated in this setting, taxanes, irinotecan [39], and ramucirumab (alone or in association with paclitaxel) showed a survival benefit with a good toxicity profile.

In particular, the COUGAR trial showed a benefit in OS for docetaxel if compared to best supportive care (median OS: 5.2 vs 3.6 months) [40], and the randomized phase III trial by Hironaka directly compared weekly paclitaxel with irinotecan and demonstrated similar efficacy and feasibility for both regimens [41].

In 2014, two randomized phase III clinical trials [22, 23] demonstrated the efficacy of ramucirumab (alone or in combination with weekly paclitaxel, respectively) in second-line setting. To note, until this moment, no target agents have shown a benefit in second line in association with chemotherapy with the exception of this drug. Ramucirumab is in fact a fully humanized monoclonal antibody that binds the extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR2). Its mechanism of action prevents the binding with VEGF-A, VEGF-C, and VEGF-D leading to a strong antiangiogenetic property. As a single agent in the REGARD trial [22], ramucirumab was associated with a survival benefit versus best supportive care alone (median OS: 5.2 versus 3.8 months). Moreover, in addition to paclitaxel in RAINBOW trial [23], it was reported a survival benefit compared with paclitaxel alone of 2.2 months (median OS: 9.6 versus 7.4 months), with improvement also in PFS and objective response rate.

In patients with disease progression >6 months following first-line chemotherapy, the evaluation of a rechallenge with the same drug combination used in first line may be also appropriate.

Ramucirumab remains the only biological agent approved in second-line treatment for HER2-positive and HER2-negative gastric cancer today, while specific anti-HER2 drugs, such as lapatinib and TDM-1, did not improve survival in HER2-positive gastric cancer that progressed after a first-line treatment containing trastuzumab. In particular, TDM1, as already mentioned above, was studied in the GATSBY trial [11] and compared to taxanes showing no superiority in patients with previously treated, HER2-positive advanced gastric cancer. Similar results were reported for lapatinib associated with paclitaxel in the TYTAN phase III study [42], without significant difference in OS and PFS compared to paclitaxel alone.

Other targeted therapies investigated in this setting, such as sorafenib and sunitinib, did not show clinical benefit. Due to these reasons, the actual second-line treatment in HER2-positive gastric cancer is not different from HER2-negative one.

36.7.3 Third-Line Therapy and Beyond

Thanks to the novel drugs and the improvement of supportive care (especially nutritional support), a biggest amount of patient (20–25% approximately) is arriving in good clinical condition beyond a second line of treatment.

This is why a correct "continuum of care strategy" should be always supposed and tailored on the single patient features.

Current European guidelines do not recommend any specific treatment for patients with disease refractory to two or more previous regimens.

Despite this assumption, a third-line strategy with active chemotherapy should be taken into account for selected patients, if we consider the positive results of the recently published TAGS trial [43].

This was the first phase III clinical trial to evaluate GC patients who had received at least two previous chemotherapy lines: subjects were randomly assigned to receive oral trifluridine/tipiracil (TAS102) or placebo. The study met its primary endpoint, and in fact, median OS was considerably better in the experimental arm compared to placebo arm (5.7 months versus 3.6 months, HR: 0.69, $p = 0.00029$), and the treatment was well tolerated, with manageable adverse events (the most common in the TAS102 arm were neutropenia and anemia, compared to abdominal pain and deterioration of clinical condition in the placebo arm). So for the first time ever, the TAGS trial paved the way to a real "con-

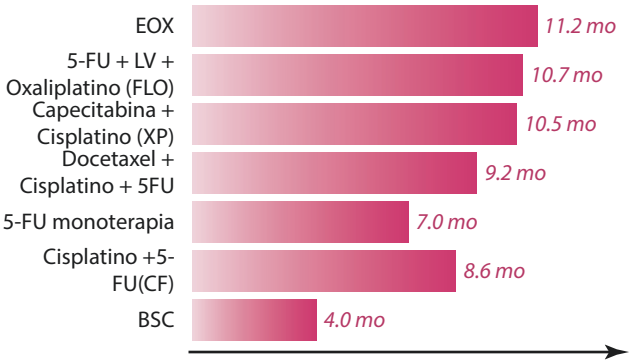


Fig. 36.6 Median OS in patients with advanced/metastatic gastric cancer. The "continuum of care" (see next in the text) has greatly improved quantity and quality of life

tinuum of care" concept even in GC, because we now have effective first-, second-, and third-line therapies, and their sequential usage could greatly expand the survival of GC patients (see Fig. 36.6) as well as their quality of life.

Moreover, a multidisciplinary evaluation is crucial in every step of natural history of gastric cancer due to the particular worsening of clinical condition that this disease produces. For example, as already reported, a nutritional support should be evaluated after all lines of treatment as well as the palliation of dysphagia or pain. After the third line, if the patient is still in good clinical conditions, the choice of new chemotherapy schedule should be done according to previous treatments, patient's preference, performance status, and clinical trials eventually available.

As reported below, in this setting of treatment, there is also a possible place for immunotherapy.

36.7.4 Immunotherapy

Emerging data from early-phase trials have suggested that the use of immunotherapy may improve survival in patients with advanced gastric cancer. In particular, the research focused on immune checkpoint of programmed cell death 1 and its ligands (PD-1/PD-L1). PD-1 is a receptor expressed on the surface of tumor cells, macrophages, activated dendritic cells, and T and B lymphocytes. As mentioned above, this receptor acts as a coinhibitor, leading to suppression of immunological T-lymphocyte-mediated response in tumor microenvironment. The TCGA molecular classification identified elevated PD-L1 expression especially in the EBV subtype.

Cancer cells use these factors and other mechanisms in order to elude the immune system reaction.

Monoclonal antibodies that target either PD-1 or PD-L1, such as pembrolizumab, nivolumab, and avelumab, can block this checkpoint inhibition and stimulate the immune response against tumor.

In a certain way, the immune system is "remodulated" in order to fight the cancer cells itself.

The phase III trial ONO-4538-12 "ATTRACTION-2" represents the current milestone for the development of immunotherapy with nivolumab (anti-PD-1 antibody) in the chemotherapy-refractory molecularly unselected population. In this entirely Asian trial, surprising survival rates of 27.3 and 10.6% at 1 year and 2 years, respectively, have been achieved in the nivolumab arm. Responders to immunotherapy had a 12-month survival rate of 86.7%, suggesting the presence of a subset of patients who greatly benefit from "checkpoint inhibition" strategy.

This trial is the only phase III positive one to date.

Immunotherapy is quickly evolving also for GC, and the correct patient selection is going to be clarified, even if the results of trials available are controversial and often negative across the different settings of treatment.

As a matter of fact, in first- and second-line setting, immunotherapy did not significantly improve survival compared to standard chemotherapy both in Asian and Western patients in two recent phase III randomized trials: KEYNOTE-062 and KEYNOTE-061.

However, although these trials have been formally negative on the whole unselected population, they have been able to recognize a subgroup of patients who benefited most from immunotherapy. Exploratory analyses identified MSI-H status and PD-L1 positivity (with CPS >1% and especially 10%) as strong positive predictor factor for immunotherapy with pembrolizumab, leading to regulatory agency approval in the USA (as previously in some Asian countries according to ATTRACTION-2 trial).

At current time, European guidelines do not recommend immunotherapy in the routine clinical practice, but the future perspectives for these drugs are promising also for GC, thanks to brilliant results in well-selected population.

36.7.5 Particular Conditions

36.7.5.1 Surgery of Primary Tumor and Metastasectomy

Surgery of primary tumor in case of metastatic disease is recommended only in the event of bleeding or luminal obstruction with a palliative intent.

Patients with metastatic cancer in fact do not benefit from addition of gastrectomy to chemotherapy as demonstrated by the randomized phase III REGATTA trial [44]. Furthermore, the surgical approach may determine a detrimental effect delaying the systemic treatment, favoring immunosuppression and aggravating the nutritional status of the patient [45].

Anyway the REGATTA trial had a number of limitations (first of all, it did not provide for the resection of the metastatic lesions, while a good surgery has always to be radical in oncology), and further trials are investigating the possible role of surgery in the "oligometastatic" population, in order to give a survival benefit in selected patients and not only a palliative meaning [46].

The most important one is currently the phase II FLOT-3 trial [32].

This trial demonstrated a possible role of surgery (both primary and metastatic lesions resection) in patients with limited metastatic disease who received neoadjuvant chemotherapy and had a good response. In patients with only retroperitoneal lymph node involvement, liver or lung involvement, and localized peritoneal involvement (all with a significant change of margin-free resection of the primary tumor and at least a macroscopic complete resection of the metastatic lesions at the posttreatment restaging), surgery showed a favorable survival (median overall survival of 31.3 months, while survival in unresected patients was 15.9 months).

This data needs a further validation and a dedicated phase III trial is ongoing at current time [47].

36.7.5.2 Peritoneal Involvement

The role of specific peritoneal treatment using hyperthermic intraperitoneal chemotherapy (HIPEC) is still controversial. Several small randomized trials in Asian patients have demonstrated a significant survival benefit for adjuvant HIPEC after cytoreductive surgery, but actually there are no solid data in non-Asian population [48–50]. For these reasons, the HIPEC is currently considered an experimental approach that should not be used in daily clinical practice, as well as the more modern PIPAC (pressurized intraperitoneal aerosol chemotherapy) [51–53].

Summary of Clinical Recommendations

- *AIOM*
  - Polichemotherapy should be considered in the first-line treatment of fit patients with advanced gastric cancer.
  - Trastuzumab in combination with platinum and fluorouracil should be considered the standard treatment for first-line HER2-positive gastric cancer patients.
  - Anti-EGFR drugs, such as cetuximab and panitumumab, are not recommended in treatment of gastric cancer.
- *ESMO*
  - Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced gastric cancer.
  - Trastuzumab is recommended in conjunction with platinum- and fluoropyrimidine-based chemotherapy for patients with HER2-positive advanced gastric cancer.
  - Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as a single agent or in combination with paclitaxel is recommended for patients who are of PS 0–1.
- *NCCN*
  - Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma.
  - Trastuzumab is not recommended for use with anthracyclines.
  - Two drug cytotoxic regimens are preferred because of lower toxicity, while three-drug regimens should be reserved for medically fit patients.

Case Study: An Unusual Clinical Progression

Man: 54 years old

- *Family history*: Negative for malignancy
- *APR*: Hypertension, psoriasis
- *APP*: For nearly 2 months fatigue and epigastralgia
- *Objective examination*: Negative. Performance status 0 according to ECOG
- *Blood tests*: Hb 7.1 g/dl
- *Esofagogastroduodenoscopy*: Presence of ulcerative area in the antrum of the stomach
- *Pathological report*: Gastric adenocarcinoma (diffuse type according to Lauren's classification)
- *TC chest and abdomen mdc*: Lesion at the antrum of the stomach with multiple perigastric lymphadenopathies. No distant metastasis

⇩

- *Surgery*: Partial gastrectomy with D2 lymphadenectomy
- *Pathological report*: Diffuse gastric adenocarcinoma limited to the mucosa with involvement of 4/20 lymph nodes resected. No margins or perivascular invasion
- *Pathological stage*: pT1N2
- Stage: pT1N2cM0 (stage IIA)

Question

What action should be taken?

(1) Follow-up (2) Adjuvant chemotherapy (3) Adjuvant chemoradiotherapy

Answer

Adjuvant Chemotherapy

Patient received 12 cycles of FOLFOX chemotherapy

⇩

Follow-up according to international guidelines for 5 years

- *After 3 years from the last follow-up visit*: Appearance of the right eyelid swelling with ptosis, cutaneous nodules at the neck and in the frontal region

Question

What action should be taken?

(1) Dermatologic visit (2) Cutaneous biopsy

Answer

Cutaneous biopsy

Tumor cells with an upper gastrointestinal origin. In consideration of the clinical history of patient, this record is in line with a cutaneous progression of disease.

⇩

- *Clinical evaluation*: Presence of nodules with increased consistency, no defined margins. Performance status 0 according to ECOG. No weight loss
- *CT scan*: No distant metastasis
- *Diagnosis*: Progression of disease (cutaneous non-resectable metastasis)

Question

What action should be taken?

(1) First-line chemotherapy upfront (2) Definition of HER2 status

Answer

Definition of HER2 status

HER2 status (IHC): 0

⇩

- *First-line chemotherapy with 12 cycles of Xelox schedule*: Major cutaneous response with reduction of all nodules and reduction of consistence
- *Clinical and instrumental follow-up every 3 months*: Maintenance of response
- *After PFS of 9 months*: Increase of known cutaneous lesions

Question

What action should be taken?

(1) Second-line chemotherapy upfront (2) Re-biopsy with definition of HER2 status

Answer

Re-biopsy with definition of HER2 status

Tumor cells with an upper gastrointestinal origin. HER2 status (IHC): 0

Question

What action should be taken?

(1) Rechallenge of Xelox (2) Taxolo + Ramucirumab (3) Ramucirumab (4) Irinotecan

Answer

Second-line with Taxolo + Ramucirumab. The decision was based on time of oxaliplatin exposure

Good performance status (0 according to ECOG)

Multidisciplinary evaluation

Key Points

- The importance of a correct diagnosis even in case of unusual clinical presentation
- The importance of a correct choose of treatment based on HER2 status of tumor
- Importance of re-biopsy after progression to evaluate changes in tumor characteristic

Case Study: A 32-Year-Old Man with a Metastatic Gastric Cancer

Man: 32 years old

- *Family history*: Negative for malignancy
- *APR*: Negative
- *APP*: Weight loss of 12 Kg in the last 3 months, fatigue
- *Blood tests*: Hb 10.2 g/dl
- *Esofagogastroduodenoscopy*: Presence of ulcerative area in the body of the stomach. Diffuse involvement of all stomach's wall
- *Pathological report*: Gastric adenocarcinoma (diffuse type according to Lauren's classification)
- *TC chest and abdomen mdc*: Diffuse involvement of stomach, perigastric and lombo-aorthic lymph nodes. Presence of multiple liver metastases with a maximum diameter of 12 cm

Question

What action should be taken?

(1) Surgery (2) First-line chemotherapy (3) Multidisciplinary group evaluation

Answer

Multidisciplinary group evaluation

Nutritional assessment

Pain evaluation

Oncological assessment → stage IV, performance status 1 according to ECOG

Question

What action should be taken?

(1) First-line chemotherapy upfront (2) Definition of HER2 status

Answer

Definition of HER2 status. HER2 status (IHC): 0

- *First-line chemotherapy with cisplatin/fluorouracil schedule*, ongoing
- *First instrumental assessment after three cycles*: Stable disease

Key Points

- Surgery is not recommended in case of metastatic disease at the diagnosis even in case of young patient
- Importance of multidisciplinary approach
- Importance of evaluation of performance status and HER2 status before starting treatment

Expert Opinion

Clara Montagut
Medical Oncology Department, Hospital del Mar, Barcelona, Spain.

Key Points

1. The prognosis of this neoplasm is still poor above all in case of locally advanced or metastatic disease. Diffuse histotype, performance status, and number and site of distant metastasis are the principal prognostic factors in the metastatic setting. The Royal Marsden prognostic score individualizes three risk groups of patients on the base of four parameters: performance status, liver metastasis, peritoneal metastasis, and serum alkaline phosphatase.
2. In the metastatic setting, the research of prognostic and predictive factors is more than relevant in order to select patients to treat. Other important aspects are tumor microenvironment, immunological state of the patient, and molecular features of the neoplasm.
3. Polichemotherapy (doublet or triplet platinum/fluoropyrimidine) should be considered in the first-line treatment of fit patients with advanced gastric cancer.
4. Trastuzumab in combination with platinum and fluorouracil should be considered the standard treatment for first-line HER-2-positive gastric cancer patients.
5. Anti-EGFR drugs, such as cetuximab and panitumumab, are not recommended in treatment of gastric cancer.
6. Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as a single agent or in combination with paclitaxel is recommended for patients who are of PS 0–1.
7. Trastuzumab is not recommended for use with anthracyclines.
8. Two-drug cytotoxic regimens are preferred because of lower toxicity, while three-drug regimens should be reserved for medically fit patients.

Recommendations

- *ESMO*
  ► https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Pan-Asian-adapted-ESMO-Clinical-Practice-Guidelines-for-the-management-of-patients-with-metastatic-gastric-cancer
- *ASCO*
  ► https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/gastrointestinal-cancer#/14446

Hints for a Deeper Insight

- Progress in the treatment of advanced gastric cancer: ► https://www.ncbi.nlm.nih.gov/pubmed/28671042
- Expression Profile of Markers for Targeted Therapy in Gastric Cancer Patients: HER-2, Microsatellite Instability and PD-L1: ► https://www.ncbi.nlm.nih.gov/pubmed/31595457
- From Tumor Immunology to Immunotherapy in Gastric and Esophageal Cancer: ► https://www.ncbi.nlm.nih.gov/pubmed/30577521
- Prognostic value and association of Lauren classification with VEGF and VEGFR-2 expression in gastric cancer: ► https://www.ncbi.nlm.nih.gov/pubmed/31611999

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