Monoclonal Antibody-Based First-Line Treatment in Gastric Cancer

Subjects: Oncology

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Gastric cancer is the fifth most common malignancy worldwide and one of the main causes of cancer-related death. While surgical treatment is the only curative option for early disease, many have inoperable or advanced disease at diagnosis. Treatment in this case would be a combination of chemotherapy and immunotherapy. Gastro-esophageal (GEJ) and gastric cancer (GC) genetic profiling with molecular diagnostic techniques has significantly changed the therapeutic landscape in advanced cancers. The identification of key players in GEJ and GC survival and proliferation, such as human epidermal growth factor 2 (HER2), vascular endothelial growth factor (VEGF), and programmed cell death protein 1 (PD-1)/programmed cell death ligand-1 (PD-L1), has allowed for the individualization of advanced cancer treatment and significant improvement in overall survival and progression-free survival of patients.

advanced gastric cancer monoclonal antibodies targeted therapy immune-checkpoint inhibitors

1. Introduction

Gastric cancer, including adenocarcinoma of the stomach and gastro-esophageal junction (GEJ), is one of the most prevalent malignancies [1]. It also represents the third leading cause of cancer-related death worldwide [1][2][3]. Despite recent improvements in treatment options, the outcome of patients with advanced gastric cancer remains poor. Up to a third of those diagnosed with gastric cancer present with an advanced and unresectable disease [2]. With a median survival of 10–12 months, fewer than 5% of patients are still alive five years after their diagnosis [3].

Gastric cancer can be categorized according to the Lauren and WHO classifications, both of which rely solely on histopathologic findings [4]. In 2014, The Cancer Genome Atlas (TCGA) proposed a molecular classification of gastric cancer and distinguished four subtypes of gastric tumors: EBV positive tumors, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability [5]. This classification allowed for a better understanding of the pathogenesis of the different subtypes of gastric cancer and helped uncover potential novel biomarkers. These biomarkers are of the uttermost importance in today's era of precision medicine in oncology, as they provide clues to new targeted therapeutic agents. As an example, a loss of expression of mismatch-repair (MMR) genes results in an accumulation of mutations in microsatellites, which are short repeats of nucleotides distributed throughout the entire genome [6][7]. Tumors in which a loss of expression of two or more MMR genes is identified, either by polymerase chain reaction (PCR) or immunohistochemistry (IHC), are said to

have high microsatellite instability (MSI-high/dMMR) [5][6][7][8]. As will be discussed later, an MSI-high status correlates with response to immunotherapy and confers a better prognosis; as such, it is critical that such testing be carried out thoroughly and accurately [9].

2. Anti-HER2 Receptor

HER2, a member of the human epidermal growth factor receptor family, is an important biomarker involved in the carcinogenesis of many tumors, including gastric cancer [10][11][12]. HER2 receptors are present on the surface of non-cancerous cells and are activated when they bind to another receptor from the HER family via a process known as protein dimerization [13][14]. The dimerization of HER receptors results in the activation of many signaling pathways involved in cell growth and survival. With that in mind, it is easier to understand how HER2 overexpression can promote carcinogenesis: being overexpressed, receptors come together more frequently, dysregulating intracellular signaling cascades and leading to aberrant cellular growth and proliferation [14]. Reported rates of HER2 overexpression in patients with gastric cancer vary from 10 to 30%, with a higher rate of HER2 positivity in GEJ or stomach cardia tumors [10][11][12][15]. HER2 overexpression is also more prevalent in the intestinal type by Lauren's classification and in well- to moderately differentiated gastric cancers. Previous studies showed that HER2 overexpression was an independent prognostic marker, correlating with tumor size, serosal invasion, and lymph-node positive disease as well as a higher risk of recurrence and a reduced overall survival [16][17][18].

HER2 status can be either determined by immunohistochemistry (IHC) to assess protein overexpression, or by fluorescence in situ hybridization (FISH) to test for HER2 gene amplification [10][11][12][19]. Accurately determining the HER2 status of GEJ or GC is crucial as HER2-positive patients can benefit from the addition of the monoclonal antibody trastuzumab to their first-line systemic chemotherapy regimen (**Table 1**). This combination stems from the pivotal ToGA (Trastuzumab for Gastric Cancer) trial and is now considered a standard of care for this population of patients [15]. In the ToGA trial, the addition of trastuzumab to systemic chemotherapy, combining cisplatin and 5-FU, showed a significant improvement in overall survival (OS) from 11.1 to 13.8 months in HER2-positive patients with inoperable or advanced disease. Trastuzumab was subsequently the first molecular targeted agent to be approved in gastric cancer and significantly influenced the field of oncology, paving the way for the development of other targeted therapies for GEJ and GC.

Table 1. Key phase 3 clinical trials for anti-HER2, anti-VEGF, and anti-VEGFR-2 combined with chemotherapy in first-line treatment in advanced GC/GEJ cancers.

Target	Trial	Agent	Experimental Arm	Control Arm	Primary Endpoints	Results (Experimental vs. Control)	Reference in the Text
HER2	ToGA	Trastuzumab	Trastuzumab + chemotherapy (cisplatin + 5-	Cisplatin/5-FU or cisplatin/capecitabine	OS	OS: 13.8 vs. 11.1 months (HR 0.74;	[15]

Target	Trial	Agent	Experimental Arm	Control Arm	Primary Endpoints	Results (Experimental vs. Control)	Reference in the Text
			FU or cisplatin + capecitabine)			95% CI 0.60–0.91)	
	JACOB	Pertuzumab + trastuzumab	Pertuzumab + Trastuzumab + chemotherapy (cisplatin or capecitabine or 5-FU)	Trastuzumab + chemotherapy (cisplatin or capecitabine or 5-FU)	OS	OS: 17.5 vs. 14.2 months (HR 0.84; 95% CI 0.71–1.00)	[20]
	LOGiC	Lapatinib	Lapatinib + chemotherapy (capecitabine + oxaliplatin)	Capecitabine + oxaliplatin	OS	OS: 12.2 vs. 10.5 months (HR 0.91; 95% CI 0.73–1.12)	[21]
VEGF	AVAGAST	Bevacizumab	Bevacizumab + chemotherapy (cisplatin + capecitabine or cisplatin + 5-FU)	Cisplatin + capecitabine or cisplatin + 5-FU	OS	OS: 12.1 vs. 10.1 months (HR 0.87; 95% CI 0.73–1.03)	[22]
VEGFR-2	RAINFALL	Ramucirumab	Ramucirumab + chemotherapy (cisplatin + capecitabine or cisplatin + 5-FU)	Cisplatin + capecitabine or cisplatin + 5-FU	PFS	PFS: 6.7 vs. 5.4 months (HR 0.753; 85% CI 0.607–0.935)	[23]

Another signal protein worthy of mention when examining the use of monoclonal antibodies in gastric cancer is vascular endothelial growth factor (VEGF). VEGF is a protein that cells produce and release in the interstitial fluid surrounding them to induce vessel growth [24]. Tumor cells are no exception to the rule and need nutrients to remain viable. Thus, angiogenesis is critical to carcinogenesis, and tumor cells also secrete VEGF to maintain a blood supply. It is in that context that anti-vascular endothelial growth factor therapies have garnered significant attention in the field of oncology (**Table 1**). Bevacizumab, notably, was the first monoclonal antibody targeting VEGF to make its appearance on the market [25]. More precisely, it is a humanized immunoglobulin G that recognizes and binds VEGF. VEGF being neutralized, it cannot attach to its receptor nor activate the cascade that would ultimately lead to vascular growth and tumor survival. After proving bevacizumab's safety and efficacy in various tumor types, including colorectal cancer, it was studied in gastric cancer. The AVAGAST study, a prospective, randomized, double-blind, placebo-controlled phase 3 trial, was initiated to assess the impact of bevacizumab on treatment-naïve patients with locally advanced unresectable or metastatic gastric cancer [22]. While this study failed to meet its primary endpoint of a 2.8-month improvement in OS, it did demonstrate favorable outcomes in PFS and ORR. Moreover, although effective in first-line treatment of hepatocellular carcinoma, the

combination of anti-VEGF and anti-PD-1/PD-L1 agents (which will be discussed in the next section) has yet to be studied in first-line treatment of advanced GEJ and GC [26].

Table 1 summarizes the key phase 3 clinical trials just discussed regarding anti-HER2, anti-VEGF, and anti-VEGFR2 agents.

4. Anti-PD-1/PD-L1

Programmed death-1 (PD-1) is an inhibitory checkpoint receptor protein mainly expressed on the T cell surface [27]. When bound to programmed death-ligand 1 (PD-L1), it induces the downregulation of immune response, ultimately promoting immune evasion and tumor growth. The introduction of monoclonal antibodies targeting these checkpoint proteins, called immune-checkpoint inhibitors (ICI), has changed the treatment landscape of several cancers [28]. In gastric cancer, the inhibition of the PD-1/PD-L1 pathway with ICI including pembrolizumab and nivolumab has led to durable responses and improved survival in chemo-refractory patients [29].

Before proceeding further, it must be emphasized that biomarkers, such as PD-L1 combined positive score (CPS) and tumor mutational burden (TMB), have been developed to help better predict responses to immunotherapy [30] [31]. First, PD-L1 expression is determined by IHC staining and is reported using a combined positive score (CPS), which is defined as the proportion of all tumor cells that stain for PD-L1 on immunohistochemistry, multiplied by 100 [30]. Tumors are PD-L1-positive if the CPS is ≥1. On the other hand, TMB estimates the number of mutations in a cell's DNA and is assessed on a biopsy specimen using next-generation sequencing [31]. However, authors disagree regarding the cut-off value that should be used to separate "TMB-high" from "TMB-low" tumors, a correlation between TMB-high tumors and responses to immunotherapy in gastric cancer has yet to be made, and the technique is not readily accessible [32]. Nonetheless, PD-L1 CPS remains the most important predictive biomarker of responses to immunotherapy. The estimated prevalence of PD-L1 expression in patients with gastroesophageal adenocarcinomas ranges between 40% and 57%, as reported, respectively, in KEYNOTE-012 and KEYNOTE-059, both early phase trials to evaluate the safety of pembrolizumab in patients with gastric cancer [33][34].

The efficacy of ICI in the first-line setting for patients with advanced GC has been the subject of several trials (**Table 2**). The discussion presented in the following paragraphs will summarize trials and clinical data supporting the use of immunotherapy in HER2-negative advanced gastric cancer.

The following table summarizes the key phase 3 clinical trials just discussed regarding anti-PD-1/PD-L1 agents.

Table 2. Key phase 3 clinical trials for anti-PD-1/PD-L1 and summary of their results for first-line immunotherapy in advanced GC/GEJ cancers.

Trial	Agent	Experimental Arm	Control Arm	Primary Endpoints	Results (Experimental vs. Control)	Reference in the Text
CheckMate-649	Nivolumab	Nivolumab + chemotherapy (XELOX or FOLFOX)	XELOX or FOLFOX	OS and PFS in patients with CPS ≥ 5	OS: 14.4 vs. 11.1 months (HR 0.71; 98.4% CI 0.59–0.86) PFS: 7.7 vs. 6.05 months (HR 0.68; 98% CI 0.56–0.81)	[35]
ORIENT-16	Sintilimab	Sintilimab + chemotherapy (CAPOX)	CAPOX	OS in patients with CPS ≥ 5 and OS in all patients	OS in patients with CPS ≥ 5: 18.4 vs. 12.9 months (HR 0.660; 95% CI 0.505–0.864) OS in all patients: 15.2 vs. 12.3 months (HR 0.766; 95% CI 0.626–0.936)	[36]
RATIONALE 305	Tislelizumab	Tislelizumab + chemotherapy (CAPOX or cisplatin + 5-FU)	CAPOX or cisplatin + 5-FU	OS	OS: 17.2 vs. 12.6 months (HR 0.74; 95% CI 0.59–0.94)	[37]
ATTRACTION-4	Nivolumab	Nivolumab + chemotherapy (SOX or CAPOX)	SOX or CAPOX	PFS and OS	PFS: 10.45 vs. 8.34 months (HR 0.68; 98.51% CI 0.51–0.90) OS: 17.45 vs. 17.15 months (HR 0.90; 95% CI 15.67–20.83)	[38]
KEYNOTE-859	Pembrolizumab	Pembrolizumab + chemotherapy (cisplatin + 5-FU or CAPOX)	Cisplatin + 5-FU or CAPOX	OS	OS: 12.9 vs. 11.5 months (HR 0.78; 95% CI 0.70–0.87)	[39]
KEYNOTE-062	Pembrolizumab	Pembrolizumab or pembrolizumab	Cisplatin + 5-FU or	OS and PFS in patients	Pembrolizumab vs. chemotherapy	[40]

Trial	Agent	Experimental Arm	Control Arm	Primary Endpoints	Results (Experimental vs. Control)	Reference in the Text
		+ chemotherapy (cisplatin + 5-FU or cisplatin + capecitabine)	cisplatin + capecitabine	with CPS ≥ 1	OS: 10.6 vs. 11.1 months (HR 0.91; 99.2% CI 0.69–1.18) PFS: 2.0 vs. 6.4 months (HR 1.66; 95% CI 1.37–2.01) Pembrolizumab + chemotherapy vs. chemotherapy: OS: 12.5 vs. 11.1 months (HR 0.85; 95% CI 0.70–1.03) PFS: 6.9 vs. 6.4 months (HR 0.84; 95% CI 0.70–1.02)	
KEYNOTE-811	Trastuzumab + pembrolizumab	Trastuzumab + pembrolizumab + chemotherapy (cisplatin + 5-FU or CAPOX)	Cisplatin + 5-FU or CAPOX	OS and PFS	Interim results ORR: 74.4% vs. 51.9%	[41]

unctions [42][43][44]. The overexpression of CLDNs has been reported to increase aberrant localization and function in various cancer types, promoting metastasis and progression [45][46]. CLDN18.2 is a tight junction protein that is normally exclusively expressed in gastric mucosa cells [47]. In gastric and GEJ adenocarcinomas, CLDN18.2 expression is commonly retained. A loss of cell polarity during malignant transformation may expose CLDN18.2 on the cell surface, rendering it more accessible to antibodies, and has thus recently become a promising emerging therapeutic target [48][49][50]. The CLDN18.2 status and degree of expression can be determined by IHC. Reported rates of moderate to strong CLDN18.2 overexpression in gastric and GEJ cancers vary between 30 and 52% [51][52].

Zolbetuximab is a first-in-class immunoglobulin monoclonal antibody that targets CLDN18.2 and mediates immune lysis via complement-dependent toxicity and antibody-dependent cellular toxicity [49][53][54]. The recent phase 3 trial SPOTLIGHT investigated the role of first-line zolbetuximab combined with cytotoxic chemotherapy in advanced gastric or GEJ cancers [55]. All 565 patients with a CLDN18.2-positive (≥75% of tumor cells with moderate-to-strong CLDN18.2 expression), HER2-negative, previously untreated locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma were randomly assigned to mFOLFOX6 combined with zolbetuximab or placebo. The combination of zolbetuximab and mFOLFOX6 resulted in a clinically significant improvement in median PFS of 10.61 vs. 8.67 months (HR 0.751; 95% CI 0.589–0.941; p = 0.0066) in the placebo group. The median OS in the

Zolbetuximab arm was 18.23 months compared to 15.54 months in the placebo group (HR 0.750; 95% CI 0.601–0.936; $p = 0.0053$). Both the objective response rate (60.7 vs. 62.1%) and the duration of response (8.51 vs. 8.11 months) were similar in both groups. Grade 3 or worse adverse events led to the discontinuation of the treatment in 14% of patients in the zolbetuximab group and in 6% of patients in the placebo group.

Table 3 below summarizes the phase 3 trials just discussed regarding anti-CLDN18.2.

Table 3. Key phase 3 clinical trials for anti-CLDN18.2 combined to chemotherapy in first-line treatment in advanced GC/GEJ cancers.

Trial	Agent	Experimental Arm	Control Arm	Primary Endpoint	Results (Experimental vs. Control)	Reference in the Text
SPOTLIGHT	Zolbetuximab	Zolbetuximab + chemotherapy (mFOLFOX6)	mFOLFOX6	PFS	PFS: 10.61 vs. 8.67 months (HR 0.751; 95% CI 0.589–0.941)	[55]
GLOW	Zolbetuximab	Zolbetuximab + chemotherapy (CAPOX)	CAPOX	PFS	PFS: 8.21 vs. 6.80 months (HR 0.687; 95% CI 0.544–0.866)	[56]

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