International Journal of Clinical Oncology (2019) 24:779–788
https://doi.org/10.1007/s10147-019-01441-x

INVITED REVIEW ARTICLE

Dawn of precision medicine on gastric cancer

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Received: 25 February 2019 / Accepted: 2 April 2019 / Published online: 11 April 2019

Abstract

Background In recent years, a better understanding of tumor biology and molecular features of gastric cancer has been reached. It may serve as a roadmap for patient stratification and trials of targeted therapies. The apparent efficacy of PD-1 blockade might be limited to a relatively small subset of advanced gastric cancer patients.

Materials and methods In this study, preclinical and clinical studies, which investigated molecular features, promising treatment targets, and immune checkpoint inhibitor in gastric cancer, were reviewed via PubMed and the congress webpages of the American Society of Clinical Oncology and European Society of Medical Oncology.

Results Next-generation sequencing technologies have defined the genomic landscape of gastric cancer. Indeed, several molecular classifications have been proposed, and distinct molecular subtypes have been identified. Based on these molecular profiles, clinical trials of new agents such as receptor tyrosine kinases inhibitors, antibody–drug conjugates, and IMAB362 (anti–Claudin 18.2) are ongoing. In addition, biomarkers to predict response during immune checkpoint inhibitors and combination therapy have been enthusiastically investigated.

Conclusion Remarkable advances in an understanding of molecular profiles of gastric cancer enable the development of novel agents. The better treatment selection of immune checkpoint inhibitors or combination therapy should be established. These developments could facilitate precision medicine on gastric cancer in the near future.

Keywords Gastric cancer · Molecular profiles · Receptor tyrosine kinases · Claudin 18.2 · Immune checkpoint inhibitors

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer mortality worldwide [1]. Although some chemotherapy (CTx) regimens, including a platinum and fluoropyrimidine combination, trastuzumab (for HER2-positive cases), taxanes, irinotecan, and ramucirumab have been shown to improve the survival outcomes of patients (pts) with advanced GC (AGC) [2–6], the prognosis remains poor, with the median survival being approximately 1 year. Although a phase III ATTRACTION-2 trial of anti-PD-1 antibody, nivolumab, demonstrated a survival benefit in AGC [7], the overall response rate (ORR) was around 10% and half of pts exhibited early disease progression. Therefore, the establishment of the better selection of pts who may derive greater benefit from PD-1 blockade is needed. Trifluridine/tipiracil (TAS-102) also showed a survival benefit compared with placebo in heavily pretreated AGC pts [8]. However, until recently, many phase III trials of targeting agents for AGC failed to show a survival benefit (Table 1). Importantly, single-agents activity for AGC is very limited and a few trials try to identify possible biomarkers before phase III trials, thus better patients' stratification based on molecular profiles must be important.

Here, we reviewed molecular features, promising treatment targets and biomarkers of immune check point inhibitors which could facilitate precision medicine on GC in the near future.

Molecular profiles in GC

Recently, the molecular characterization of GC is rapidly evolving. Several molecular classifications have been proposed, and distinct molecular subtypes have been identified [9–14]. Several receptor tyrosine kinases (RTKs), such

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Table 1 Recent phase 3 of new agents for GC

Target	Trial/author	Line	Screening	Agent	Control	Endpoint	Result	Difference mOS (m) (HR)
HER2	ToGA	1st	HER2	Trastuzumab	(+chemo)	OS	Positive	+2.7 (HR 0.74)
HER2	Logic	1st	HER2 (FISH)	Lapatinib	PBO (+chemo)	OS	Negative	+1.7 (HR 0.91)
HER2	JACOB	1st	HER2	Pertuzumab	PBO (+chemo+Tmab)	OS	Negative	+3.3 (HR 0.84)
HER2	TyTAN	2nd	HER2 (FISH)	Lapatinib	(+chemo)	OS	Negative	+3 (HR 0.84)
HER2	GATSBY	2nd	HER2	T-DM1	Taxanes	OS	Negative	−0.7 (HR 1.15)
EGFR	REAL-3	1st	–	Panitumumab	(+chemo)	OS	Negative	−2.5 (HR 1.37)
EGFR	EXPAND	1st	–	Cetuximab	PBO (+chemo)	PFS	Negative	−1.3 (HR 1.0)
EGFR	ENRICH	2nd	EGFR (IHC)	Nimotuzumab	(+chemo)	OS	Negative	
mTOR	GRANITE-1	2nd/3rd	–	Everolimus	PBO	OS	Negative	+1.05 (HR 0.9)
mTOR	GRANITE-2	2nd	–	Everolimus	PBO (+chemo)	OS	Negative	+1.0 (HR 0.92)
HGF	RILOMET1	1st	MET (IHC)	Rilotumumab	PBO (+chemo)	OS	Negative	−2.9 (HR 1.36)
MET	METgastric	1st	MET (IHC)	Onartuzumab	PBO (+chemo)	OS	Negative	−0.3 (HR 0.82)
VEGF-A	AVAGAST	1st	–	Bevacizumab	PBO (+chemo)	OS	Negative	+2 (HR 0.87)
VEGFR2	RAINFALL	1st	–	Ramucirumab	PBO (+chemo)	OS	Negative	+0.4 (HR 0.96)
VEGFR2	REGARD	2nd	–	Ramucirumab	PBO	OS	Positive	+1.4 (HR 0.776)
VEGFR2	RAINBOW	2nd	–	Ramucirumab	PBO (+chemo)	OS	Positive	+2.2 (HR 0.807)
VEGFR2	Li. et al.	3rd	–	Apatinib	PBO	OS	Positive	+1.8 (HR 0.71)
PARP	GOLD	2nd	ATM (IHC)	Olaparib	PBO (+chemo)	OS	Negative	+1.9 (HR 0.79)
STAT3	BRIGHTER	2nd	–	Napabucasin	PBO (+chemo)	OS	Negative	−0.4 (HR 1.01)
PD1	Keynote061	2nd	PD-L1 (IHC)	Pembrolizumab	Paclitaxel	OS	Negative	+0.8 (HR 0.82)
PD1	JAVELIN300	3rd	–	Avelumab	Irinotecan/taxanes/BSC	OS	Negative	−0.4 (HR 1.1)
PD1	ATTRACTION-2	3rd	–	Nivolumab	PBO	OS	Positive	+1.2 (HR 0.63)

PBO placebo

as the human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor 1 (EGFR), mesenchymal-epithelial transition factor (MET) and fibroblast growth factor receptor 2 (FGFR2), have been reported to be amplified in GC, and targeted therapies involving these molecules have been developed [15–18]. Importantly, these amplifications are frequently but not universally mutually exclusive [15–18]. In 2014, The Cancer Genome Atlas (TCGA) network characterized 295 gastric adenocarcinoma based on 6 molecular platform [9]: somatic copy number analysis, whole-exome sequencing, DNA methylation profiling, messenger RNA sequencing, microRNA sequencing and reverse-phase protein array. Microsatellite instability (MSI) testing and whole-genome sequencing were also performed. Then, 4 subtypes of GC have been described: (1) tumors positive for Epstein–Barr-Virus (EBV), (2) MSI-high

Table 2 The new molecularly based classification of GC according to The Cancer Genome Atlas (TCGA) 2014

Subtype	Epstein–Barr-virus-infected (EBV)	Microsatellite instability (MSI)	Genomically stable (GS)	Chromosomal instability (CIN)
Typical molecular features	EBV-positive Profound hyper methylation CDKN2A silencing 80% PIK3CA mutation PD-L1/2 overexpression	DNA hyper-methylation Silencing of MLH1 Elevated somatic mutations (PIK3CA 42%, and ERBB3 26%)	Tumors lacking aneuploidy and elevated rates of mutation or hyper-methylation Somatic RHOA and CDH1 mutations CLDN18-ARHGAP6 or ARHGAP26 fusions	Marked aneuploidy TP53 mutations Recurrent amplifications of receptor tyrosine kinases (HER2 24%)
Association with anatomy or traditional subtypes	Fundus and body	Fundus, body, and antrum	Mostly diffuse subtype	Majority of tumors at the esophago–gastric junction

(MSI-H) tumors, (3) genomically stable (GS) tumors, and (4) tumors with chromosomal instability (CIN) (Table 2). EBV+ tumors display recurrent PIK3CA and ARIDIA mutations, extreme DNA hypermethylation, and high amplification of JAK2, PD-L1 and PD-L2. MSI-H tumors show elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins. GS tumors are enriched for the diffuse histological variant and mutations of CDH1 and RHOA or CLDN18–ARHGAP fusion. CIN tumors are frequently observed at the gastroesophageal junction/cardia with recurrent TP53 mutation and relatively numerous amplifications of RTKs genes. In 2015, The Asian Cancer Research Group (ACRG) proposed 4 molecular subtypes, composed of (1) MSI-H, (2) microsatellite stable with epithelial-to-mesenchymal transition features (MSS/EMT), (3) MSS/TP53 mutant (MSS/TP53), and (4) MSS/TP53 wild-type (MSS/TP53–) [10]. In the MSS/EMT subtype, approximately 70% of recurrences were at peritoneum, with a significantly poorer prognosis compared with other subtypes, which highlights the need for therapy development for peritoneal dissemination [10]. The future clinical trials of targeted and immune therapy in AGC should be deigned based on differences of genomic or immunological features, as they may impact treatment response and clinical outcomes. Importantly, these molecular profiles have been investigated in Japanese AGC. According to GI-screen as the Nationwide Cancer Genome Screening Project, the frequently detected mutations were TP53 (47.8%), PIK3CA (9.2%), KRAS (6.0%), SMAD4 (5.1%), APC (4.1%), TET2 (3.9%), ERBB2 (3.3%) and copy number variant were ERBB2 (11.3%), CCNE1 (11.1%), KRAS (3.7%), FGFR2 (3.3%), ZNF217 (3.3%), MYC (2.7%), CCND1 (2.3%) and CDK6 (2.1%) [19]. In stage IV AGC, MMR-deficient (D-MMR), and EBV tumors are identified in 6.2, and 6.2% cases, respectively [20]. These profiles are not largely different from previously mentioned reports mainly conducted outside Japan, which support global development of new agents for AGC. Recently, multiplex gene panels such as NCC Oncopanel and FoundationOne CDx to advancing personalized medicine were approved in Japan, leading to the further genomic profiling in a large cohort of Japanese AGC pts.

Meanwhile, heterogeneity of genomic alterations is one of the problems in gastric cancer [21, 22]. Discordance of dominant oncogenic alterations between primary and metastatic tumor is reported in 32% of AGC tumor samples; in contrast, 87.5% concordance for targetable alterations in metastatic tissue and circulating tumor DNA (ctDNA). Also, other studies suggest the dynamic landscape of ctDNA profile before and after molecular targeting agents [23, 24]. These analyses should be also incorporated in clinical trials of new agents for AGC to clarify better treatment biomarkers.

Promising treatment targets

Targeting HER2

Approximately 60% of pts with GC belong to the CIN subtype and may depend on RTKs signaling for growth and development [9, 10, 25, 26]. HER2 is a therapeutically relevant RTK in 10–20% of the overall GC population and upto 30% of gastroesophageal junction adenocarcinomas harboring HER2 gene amplification or protein overexpression. In the Trastuzumab for GC (ToGA) trial pts treated with trastuzumab (a HER2-directed monoclonal antibody) and CTx had a significant improvement in OS (13.8 versus 11.1 months, HR 0.74, $P = 0.0046$) [27]. The OS benefit was the highest in the subset of tumors defined as HER2 immunohistochemistry (IHC) 3+ or IHC2+/fluorescence in situ hybridization (FISH) with unprecedented OS of 16 in the trastuzumab group versus 11.8 months with CTx alone (HR 0.68, 95% CI 0.5–0.83) [27], thus became a standard of care for this patient population.

Several recent reports demonstrated potential utility of tissue-based next-generation sequencing (NGS) and ctDNA NGS for biomarkers of HER2-tageted therapy [28–30]. Kim et al. showed that CCNE1 amplification and low-level HER2 amplification detected by NGS were associated with lack of response [28]. Analysis of cfDNA showed that detectable ERBB2 copy number amplification in plasma was predictive to the response and changes in plasma-detected genomic alterations were associated with sensitivity and/or resistance of HER2-tageted therapy [28]. Moreover, serial ctDNA sequencing demonstrated that there were emergences of other genomic aberrations such as MYC, EGFR, FGFR2, and MET amplifications at disease progression [28]. ctDNA NGS may overcome tissue biopsy errors related to intratumor heterogeneity, particularly at progression after treatment.

Recently, antibody–drug conjugates have emerged as a promising strategy in cancer therapy and combine the ability of monoclonal antibodies to specifically target tumor cells with the highly potent killing activity of drugs with payloads too toxic for systemic administration. However, trastuzumab-emtansine (T-DM1, an antibody–drug conjugate consisting of trastuzumab linked to the cytotoxic agent DM1), which demonstrates remarkable effectiveness in breast cancer, did not prolong OS in HER2-positive AGC [31]. This may be in part due to intratumoural heterogeneity in HER2 expression and amplification as compared with breast cancer [21, 32]. Available evidence suggests that most of HER2-positive gastric cancers are heterogeneous with downregulation in HER2 status post-progression on trastuzumab, as well as diverse intratumoral molecular features [29, 33, 34]. Therefore, assessment of the HER-2 status just before molecular-targeted therapy might be important for achieving therapeutic success. Trastuzumab deruxtecan (DS-8201a) is an antibody–drug conjugate comprised of a humanised antibody against HER2, a novel enzyme-cleavable linker, and a topoisomerase I inhibitor payload. Preclinical study showed that DS-8201a had a potent bystander effect due to a highly membrane-permeable payload and was beneficial in treating tumors with HER2 heterogeneity that are unresponsive to T-DM1 [35]. Indeed, a phase I study of DS-8201a showed anti-tumor activity in pts with breast cancer and AGC previously treated with T-DM1 or trastuzumab, and in pts with HER2-low tumors [36]. In 44 pts with AGC, the ORR and the disease control rate (DCR), and the median PFS were 43.2%, 79.5%, and 5.6 months, respectively [37]. A phase II study (DESTINY-Gastric01) in Japan and South Korea evaluating the safety and efficacy of DS-8201a in pts with HER2-positive AGC resistant or refractory to trastuzumab is ongoing (NCT03329690).

Other receptor tyrosine kinases

A variety of molecular targeting drugs for HER2, EGFR, HGF, MET, and mTOR has been examined. However, most did not demonstrate significant benefit in phase III trials partly due to inappropriate patient selection and molecular stratification (Table 1). Although EGFR, MET or FGFR inhibitors have shown anti-tumor activity for pts with homogenous amplification of these RTKs genes, these cases are rare [38–40].

Pearson et al. demonstrated that AGC pts with high-level clonal FGFR2 amplification have a high response rate to FGFR-1, 2, 3 tyrosine kinase inhibitor AZD4547, whereas those with subclonal or low-level amplification did not respond [41]. A randomized phase II trial (SHINE study) of AZD4547 monotherapy versus paclitaxel for the treatment of AGC pts with FGFR2 polysomy or gene amplification showed that AZD4547 did not significantly improve median PFS compared to paclitaxel [42]. Exploratory biomarker analyses of SHINE study revealed marked intratumor heterogeneity of FGFR2 amplification and poor concordance between amplification/polysomy and FGFR2 mRNA expression, suggesting that the failure to adequately enrich a clonally amplified population might contribute to the failure of this study [42]. Also, AGC pts with high-level FGFR2 amplification achieved an objective response for TAS-120, a highly selective covalent FGFR inhibitor [43]. FPA144, an antibody-dependent cell-mediated cytotoxicity (ADCC)-enhanced, FGFR2b Isoform-specific Monoclonal Antibody, showed anti-tumor activity in pts with FGFR2b+ high (IHC 3+ $\geq$ 10% tumor membrane staining) AGC with the ORR of 19% and the DCR of 57%, respectively. A phase III trial evaluating FPA144 and mFOLFOX6 in pts with previously untreated AGC is ongoing. Recently, FGFR2–ACSL5 fusion was identified in an AGC patient with acquired resistance to FGFR inhibition in FGFR2-amplified AGC. Also, JHDM1D-BRAF fusion results in resistance for FGFR inhibitor-resistant cell line, which warrant further investigations [44, 45].

Subgroup analysis of the EXPAND study, in which adding cetuximab to first-line capecitabine and cisplatin chemotherapy failed to improve clinical outcome in pts with AGC, showed that there was a tendency for improved OS, PFS, and the ORR in a small population of pts with high tumor EGFR IHC scores [46]. Moreover, Maron et al. showed that anti-EGFR treatment achieved an objective response in a small population of pts with high-level EGFR amplification detected by both tissue-based NGC and ctDNA NGS [47].

Olaparib is an oral poly (ADP-ribose) polymerase (PARP) inhibitor that blocks DNA base-excision repair and causes synthetic lethality in tumors with homologous recombination repair deficiencies. Ataxia telangiectasia mutated (ATM) is a gene essential to the cellular double strand DNA breaks response necessary to maintain genome stability levels. In a phase II trial of olaparib combined with paclitaxel versus placebo combined with paclitaxel as second-line therapy, a greater OS benefit was noted in AGC pts with ATM-negative tumors (HR 0.35, $p = 0.002$) [48]. Unfortunately, a phase III GOLD trial did not show the improvement of OS with olaparib in pts with ATM-negative tumors (HR 0.73, $p = 0.25$) as well as overall population (HR 0.79, $p = 0.026$) [49], suggesting that patient selection by ATM status was not sufficient. Biomarker analysis of GOLD study showed that none of other genetic markers of DNA damage repair, which have proven predictive in other tumor types for full-dose olaparib monotherapy, were associated with sensitivity to low-dose olaparib combination with paclitaxel in pts with AGC [50].

Targeting therapy for Stemness-related pathway or cancer stroma

Cancer stemness

Cancer stem cells (CSCs) have self-renewal capability and may contribute to malignant tumor growth, disease relapse, and metastasis. BBI608 (Napabucasin) is an orally administered investigational small molecule thought to affect multiple oncogenic cellular pathways implicated in providing CSCs with stemness characteristics [51]. Encouraging anti-tumor activity of BBI608 and paclitaxel in refractory AGC was observed in a phase-1b and subsequent phase-2 study with an ORR of 31% and disease control rate of 75% [52]. However, a phase III trial (BRIGHTER) of BBI608 plus

Weekly Paclitaxel vs. Placebo plus Weekly Paclitaxel in pts with AGC failed to improve OS [53].

MMP-9

Matrix metalloproteinases-9 (MMP-9) is an extracellular enzyme involved in matrix remodeling, angiogenesis, tumor growth, and metastasis [54]. Preclinical studies demonstrate that MMP-9 inhibition alters the tumor microenvironment, which is associated with greater chemotherapy penetration and improved anti-tumor immunity. Andecaliximab is a monoclonal antibody that inhibits MMP-9 and has been combined with various chemotherapy regimens. A phase I/Ib trial of mFOLFOX6+ Andecaliximab revealed encouraging anti-tumor activity in AGC pts with median PFS of 9.9 months in first-line setting and the ORR of 50% [55]. However, a subsequent phase III study of Andecaliximab combined with mFOLFOX6 in first-line setting for pts with AGC did not significantly improve OS [56].

Wnt

Dickkopf-1 (DKK1) is a modulator of the Wnt and PI3 K/AKT signaling pathways and contributes to an immunosuppressive tumor microenvironment by activating MDSCs and Tregs. DKN-01, a monoclonal antibody against DKK1, acts on innate immune cells, and a preclinical study demonstrated upregulation of both PD-L1 and IFNγ-related chemokines, suggesting a rational for immune checkpoint combination. Phase Ib trial of DKN-01 in combination with pembrolizumab demonstrates encouraging anti-tumor activity in AGC with the ORR of 23.5% and the DCR of 58.8%, which warrants further evaluations [57].

Claudin 18.2

Claudin18.2 (CLDN18.2) is a member of the claudin family of more than 20 structurally related proteins which form the important components of the tight cell junctions in epithelia and endothelia [58]. It is not expressed in any healthy tissues except stomach mucosa but broadly expressed in various cancer types including AGC especially in diffuse-type GCs [59]. Also, CLDN18-ARHGAP26/6 fusions have been identified in GCs, with a predominance in GS type tumors based on the TCGA classification [9]. It has been reported that almost all CLDN18-ARHGAP26/6 fusion-positive GCs expressed CLDN18.2 protein with a higher prevalence of lymphatic and distant organ metastases especially in the younger age pts [60]. The TCGA data also showed that the CLDN18-ARHGAP26/6 fusion was mutually exclusive with driver genes such as RHOA and CDH1 mutations which were frequently observed in GS type tumors [9].

IMAB362 (claudiximab) is a novel chimeric IgG1 antibody highly specific for CLDN18.2. It binds to CLDN18.2 on the tumor cell surface to stimulate cellular and soluble immune effectors that activate antibody-dependent cytotoxicity and complement-dependent cytotoxicity [61]. A phase II study (MONO) showed the efficacy and safety of IMAB362 as monotherapy in pts with metastatic, refractory, or recurrent GC [62]. Among 40 pts who received IMAB362 600 mg/m^2, the ORR was 10%, and the disease control rate was 30%. A randomised phase II study (FAST) showed that IMAB362 in combination with first-line chemotherapy provided clinically relevant benefit in PFS and OS in pts with CLDN18.2-positive AGC [63]: IMAB362 plus EOX significantly improved PFS (median 7.9 vs 4.8 months; HR 0.47; $p = 0.0001$) and OS (median 13.3 vs 8.4 months; HR 0.51, $p < 0.001$) compared to EOX alone. Subgroup analysis showed that CLDN18.2 expression in ≥ 70% of tumor cells was associated with better OS (HR 0.44), leading to further patient enrichment (≥ 75% of tumor cells) in an ongoing phase III study (Spotlight) which evaluates the efficacy of IMAB362 plus mFOLFOX6 compared with placebo plus mFOLFOX6 as first-line chemotherapy. It has been reported that claudin18.2 high expression (≥ 75% of tumor cells) was detected in 36% of pts with AGC [63].

Immune check point inhibitors

Recently, blockade of immune checkpoint molecules with monoclonal antibodies has emerged as a promising strategy in several malignancies [64–69]. Programmed death 1 (PD-1), which belongs to the CD28 family of proteins, is a negative costimulatory receptor expressed on the surfaced of activated T cells [70]. The binding of PD-1 and its ligands, PD-L1 and PD-L2 in tumor or immune cells, can inhibit a cytotoxic T cell response, which leads tumor cells to escape from immune surveillance [70]. Accordingly, blockade of this interaction restores the anti-tumor activity of T cells [70]. Clinical trials of anti-PD-1/PD-L1 monoclonal antibodies have shown durable anti-tumor response and improved overall survival in several malignancies [64–69].

A phase III ATTRACTION-2 trial of nivolumab, a fully human IgG4 monoclonal antibody against PD-1, for pts with AGC after two or more previous line chemotherapies showed a survival benefit, leading to the approval of nivolumab for AGC in Japan as 3rd-line or later-line treatment [7]. However, subsequent randomised trial of anti-PD1/PD-L1 in earlier trials failed to show survival benefit compared with standard chemotherapy, thus better treatment selection must be important to use anti- PD1/PD1 in earlier treatment lines.

Biomarkers of immune check point inhibitors

PD-L1 expression

Exploratory analysis of ATTRACTION-2 suggested no predictive value of PD-L1 expression on tumor cells [7]. Also, in JAVELIN 300, which recently failed to demonstrate a survival benefit for avelumab compared with investigator choice of chemotherapy with paclitaxel or irinotecan for pts with AGC, no difference in OS was observed according to PD-L1 expression, which was defined as PD-L1 staining on 1% of tumor cells [71]. Results were the same when PD-L1 was also assessed on immune cells, although the methodology for this assessment is not described. However, a relationship between greater PD-L1 expression [using the combined positive score (CPS), which is a proportional assessment of PD-L1 staining on both tumor and immune cells] and a greater treatment effect was suggested in phase II (KEYNOTE-059) and III trials (KEYNOTE-061) of pembrolizumab [68, 72]. In KEYNOTE-059, the ORR in the third-line setting was 22.7% for pts with PD-L1 expression (CPS ≥ 1) as determined by 22C3 IHC assay, while the ORR was 8.6% for those with PD-L1-negative tumors, leading to the US Food and Drug Administration (FDA) approval of pembrolizumab for PD-L1-positive AGC and PD-L1 22C3 IHC as a companion diagnostic assay [68]. Although KEYNOTE-061 failed to show improvement in OS with pembrolizumab in CPS ≥ 1 population, pts who expressed high levels of PD-L1 (CPS ≥ 10) had a pronounced benefit from treatment with pembrolizumab (HR 0.64, 95% CI 0.41–1.02) [72]. The ORR of pembrolizumab in pts with CPS ≥ 10, CPS ≥ 1, and CPS < 1 (PD-L1-) was 25, 16, and 2%, respectively [29]. Impact of CPS on the efficacy of PD-1 blockade will also be evaluated in the ongoing phase III trial (KEYNOTE-062), which compared the efficacy of cytotoxic agents combined to pembrolizumab with that of cytotoxic agents and that of pembrolizumab monotherapy in pts with untreated AGC (NCT02494583).

MSI-H/MMR-D

FDA approved pembrolizumab for pts with microsatellite instability-high (MSI-H) or mismatch repair-deficient (MMR-D) solid tumors including AGC based on the durable response in several trials [73–75]. It has been well known that MSI-H/MMR-D colorectal cancers had higher mutation loads compared with microsatellite stable (MSS)/MMR proficient (MMR-P), leading to high infiltration of CD8+ T cells presumably due to recognition of a high number of tumor neoantigens and its corresponding expression of immune checkpoints in the tumor microenvironment [76].

Most recently, pembrolizumab for pts with MSI-H/MMR-D solid tumors was approved also in Japan. In a phase II KEYNOTE-158 trial of pembrolizumab showing that the ORR was 37.2% for 94 pts with MSI-H/MMR-D non-colorectal solid tumors including pts in Japan, 6 of 13 pts with AGC achieved an objective response (ORR 46.2%). Also, subgroup analysis of KEYNOTE-059 and KEYNOTE-061 showed that the ORR was 57.1% and 46.7% for pts with MSI-H/MMR-D AGC, respectively [68, 72, 77]. Based on these evidences, Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer recommended that pembrolizumab or nivolumab could be a treatment option for pts with MSI-H/MMR-D AGC in 2nd-line settings [78].

TMB, EBV, and other factors to predict response

However, pts with MSI-H/MMR-D form a small minority of AGC pts, and therefore novel biomarkers to predict response to immunotherapy among MSS/MMR-P are also essential. Recently, Kim et al. reported that high tumor mutation burden (TMB) was a potential biomarker of pembrolizumab for AGC [79]. However, most pts with high TMB had MSI-H/MMR-D status, and not all pts with high TMB achieved an objective response [79].Thus, precise mechanism regarding the influence of TMB to the efficacy of PD-1/PD-L1 blockade should be investigated in the near future. The TCGA reported that amplification of the CD274 gene (which encodes PD-L1) and the PDCD1LG2 gene (which encodes PD-L2) was frequently observed in EBV-positive GC [9]. Indeed, AGC pts with EBV-positive status have been reported to derive greater benefit from pembrolizumab [79]. Importantly, Panda et al. reported that a patient with EBV+ AGC showed durable response from treatment with the anti-PD-L1 antibody avelumab, although this tumor had low mutation burden [80]. Most recently, it has been reported that the ORR of nivolumab for AGC after two or more chemotherapy regimens was significantly higher in pts with MMR-D than in those with MMR-P (75% vs. 13%), PD-L1+ in tumor cells than in those with PD-L1- in tumor cells (57% vs. 13%), and PIK3CA mutation in those with PIK3CA wild-type (44% vs. 14%) [81]. Interestingly, the ORR was 31% in pts with at least one of the following factors; MMR-D, high TMB, EBV+, and PD-L1+ in tumor cells vs. 0% in those without these factors, suggesting that pre-screening of these biomarkers might be useful to predict clinical benefit of anti-PD-1/PD-L1 blockade in AGC. Moreover, the diversity and composition of gut microbiome have been reported to predict the effect of PD-1 blockade for pts with AGC [82]. Most recently, subgroup analysis of ATTRACTION-2 suggested that pts with hyponatremia along with high neutrophil-to-lymphocyte ratio might show low benefit with nivolumab in terms of early progression and death [83].

Hyperprogressive disease and combination therapy

Recently, anti-PD-1/PD-L1 antibodies have anecdotally been reported to cause rapid progression of some types of cancers, which is called hyperprogressive disease (HPD) [84–87], although exact incidence in gastric cancer remains unclear. Since HPD has been suggested to be associated with poor prognoses, it is necessary to identify predictive factors of HPD. Kato et al. identified EGFR mutations and MDM2 amplification as possible molecular predictors of HPD in pts with several solid tumors [86]. It has been reported that FBXW7 mutation or KRAS amplification might be associated with HPD in pts with AGC who received nivolumab [88]. Recently, Togashi et al. reported an increase in regulatory T (Treg) cells with proliferative capacity among tumor-infiltrating lymphocytes in AGC pts who showed HPD after treatment with an anti-PD-1 antibody [89]. Moreover, an in vitro study showed that PD-1 blockade activated not only effector T cells but also Treg cells, which promoted tumor progression in a fraction of patients [89]. Further investigations in larger cohorts are needed to confirm HPD-associated biomarkers. Most recently, Lo Russo et al. demonstrated the role of innate immunity in mediating hyperprogression via Fc/FcR triggering on macrophages by anti-PD-1 antibody [90]. Previous in vivo study showed that selective inhibition of VEGF pathway with anti-VEGF antibody or anti-VEGF tyrosine kinase inhibitors (TKIs) were effective at controlling tumor growth and inhibiting the infiltration of suppressive immune cells such as Treg and tumor-associated macrophages, myeloid-derived suppressor cells, while increasing the mature dendritic cell fraction [91]. Currently, clinical trials of anti-PD-1 antibodies in combination with VEGF TKIs are investigated, which might not only enhance antitumor activity but also reduce HPD.

Acknowledgements No specific funding, financial disclosures or assistance declared.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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