REVIEW ARTICLE

The beginning of the era of precision medicine for gastric cancer with fibroblast growth factor receptor 2 aberration

Akira Ooki[1] · Kensei Yamaguchi[1]

Abstract
Despite recent advances in the systemic treatment of metastatic gastric cancer (GC), prognostic outcomes remain poor. Considerable research effort has been invested in characterizing the genomic landscape of GC and identifying potential therapeutic targets. FGFR2 is one of the most attractive targets because aberrations in this gene are frequently associated with GC, particularly the diffuse type in Lauren's classification, which confers an unfavorable prognosis. Based on the preclinical data, the FGFR2 signaling pathway plays a key role in the development and progression of GC, and several FGFR inhibitors have been clinically assessed. However, the lack of robust treatment efficacy has hampered precision medicine for patients with FGFR2-aberrant GC. Recently, the clinical benefits of the FGFR2-IIIb-selective monoclonal antibody bemarituzumab for FGFR2b-positive GC patients were shown in a randomized phase II FIGHT trial of bemarituzumab combined with the first-line chemotherapy. This trial demonstrates proof of concept, suggesting that FGFR2 is a relevant therapeutic target for patients with FGFR2b-positive GC and that bemarituzumab brings new hope for diffuse-type GC patients. In this review, we summarize the oncogenic roles of FGFR2 signaling and highlight the most recent advances in FGFR inhibitors based on the findings of pivotal clinical trials for patients with FGFR2-aberrant GC. Thus, the era of precision medicine for patients with FGFR2-aberrant GC will be opened.

Keywords FGFR · Chemotherapy · Gastric cancer · Diffuse type · Molecular target agent

Introduction

Gastric cancer (GC) remains a major clinical challenge, as it is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1]. GC is still frequently diagnosed in the later stages [2]. Systemic chemotherapy is the main therapeutic option for patients with metastatic GC [3, 4] and includes three types of treatment: (1) cytotoxic agents, including fluoropyrimidines, platinum compounds, taxanes, trifluridine/tipiracil, and irinotecan; (2) immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1); and (3) molecular targeted agents for human epidermal growth factor receptor 2 (HER2; trastuzumab and trastuzumab deruxtecan) [5, 6] or vascular endothelial growth factor receptor 2 (VEGFR2; ramucirumab) [7,

8]. Despite advances in treatment, the clinical benefits are limited because metastatic GC is essentially impossible to cure, and the prognosis of GC patients is unfavorable, with a 5-year overall survival (OS) rate of 5–20% [9]. Therefore, further development of novel agents is required to improve prognostic outcomes as an unmet medical need.

Many of the identified molecular target agents have failed to demonstrate significantly improved OS in clinical trials, partially due to a lack of selective biomarkers or intratumor heterogeneity, and HER2-targeted agents (trastuzumab and trastuzumab deruxtecan) are the only personalized molecular-targeted medicine approved for HER2-positive GC patients by the United States (US) Food and Drug Administration (FDA). GC can be classified into four molecular subtypes based on the results of comprehensive molecular analyses, according to The Cancer Genome Atlas (TCGA) project: (1) microsatellite instability (MSI) tumors that have been enriched for a higher tumor mutation burden, (2) Epstein–Barr virus (EBV)-positive tumors that have been enriched for programmed death-ligand 1 and 2 (PD-L1/2) amplification, (3) chromosomal instability (CIN) tumors that

✉ Akira Ooki
  sp9y9tq@piano.ocn.ne.jp

1 Department of Gastroenterological Chemotherapy, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan

have been enriched for aneuploidy and focal amplification of receptor tyrosine kinases (RTKs), and (iv) genomically stable (GS) tumors that have been enriched for the diffuse-type histology or are fusions of claudin-18 (CLDN18) [10]. These subtypes have the potential for specific treatments, such as ICIs for MSI and EBV subtypes, agents targeting RTKs for the CIN subtype, and agents targeting CLDN18 for GS subtypes. Thus, an in-depth understanding of the complexity and diversity of molecular characterization will pave the way for the development of optimal therapeutic strategies based on the molecular profiles of individual patients.

The mammalian fibroblast growth factor receptor (FGFR) family includes four highly conserved receptors (FGFR1, FGFR2, FGFR3, and FGFR4). A growing body of evidence demonstrates that the ligand fibroblast growth factors (FGFs)–FGFR pathway plays a crucial role in the development and progression of cancer [11]. FGFs–FGFR signaling pathways are frequently dysregulated by their overexpression and genetic alterations [12]. Notably, several clinical trials have demonstrated the therapeutic efficacy of FGFR-selective tyrosine kinase inhibitors (TKIs) for urothelial carcinoma with FGFR2/3 fusions or FGFR3 mutations [13] and cholangiocarcinoma with FGFR2 fusions or rearrangements [14]. In GC, FGFR2 amplification and overexpression are observed, which confers poor prognosis [15–21]. FGFR2 amplification is predominantly enriched in the GS subtype in molecular classification or the diffuse type in Lauren's classification [10, 17, 22]. Furthermore, FGFR2 amplifications are mutually exclusive with genetic alterations of other RTKs/RAS, such as HER2, EGFR, KRAS, and MET [15, 18], indicating a distinct molecular phenotype exists in GC. Since dysregulated FGFR2 signaling is critical in diffuse-type GC patients with unfavorable survival outcomes, precision medicine approaches targeting FGFR2 are arguably needed. Recently, an anti-FGFR2-IIIb antibody was shown to have promising results in patients with FGFR2-IIIb isoform-overexpression or FGFR2 gene amplification GC in a phase II FIGHT trial [23], which supports a strong rationale for anti-FGFR inhibitors. Thus, the FGFR signaling pathway has attracted considerable attention as a targetable molecule in GC. In this review, we focus on the relevance of FGFR2 signaling in GC from both basic and preclinical viewpoints and highlight FGFR2 as a potential therapeutic target based on the findings of pivotal clinical trials in patients with FGFR2-aberrant GC.

FGFR2 in gastric cancer

Gene amplification and overexpression of FGFR2 in gastric cancer

Dysregulated activation of FGFR signaling is driven mainly by genomic alterations in FGFRs, including their gene amplifications, active mutations, and chromosomal translocations/fusions. Of the 4,853 solid tumors tested using next-generation sequencing (NGS), FGFR genomic alterations were detected in 7% [12]. Gene amplifications were the most common alteration, with 66% of the cases having FGFR aberrations, while translocations/fusions were rare (8%).

In GC, FGFR2 has the most frequent genetic alteration among the FGFR family members [12]. In a hybrid capture-based genomic profiling study, FGFR2 alterations were found in 269 (4.0%) of 6,667 tissue samples from advanced GC patients, and the frequencies of amplifications, mutations, translocations/fusions, and multiple alterations were 72%, 13%, 8.6%, and 6.3% of a total case with FGFR2 alterations, respectively [24]. Based on the definition of amplification as a FGFR2/centromere of chromosome 10 ratio ≥ 2 [25], FGFR2 amplifications were found in 59 (10%) of 578 GC patients using in situ techniques [26]. The incidence of FGFR2 amplification is similar in East Asian and Western regions [15]. Thus, FGFR2 amplification is the most frequent alteration, ranging from 3 to 15% of GCs [10, 15, 17, 18, 21, 27, 28]. However, FGFR2 amplification is unlikely to be homogeneous in each cancer cell within a tumor [15, 28], and intratumoral heterogeneity has been observed in 24% of FGFR2-amplified GC [15].

Gene amplification is a common mechanism of the transcriptional overexpression of FGFR2. In fact, FGFR2 mRNA expression levels were associated with gene amplification, and FGFR2 mRNA overexpression was detected in 29 (4%) of 718 GC patients by in situ hybridization technique using RNAscope® [26]. At the protein level, FGFR2 is predominantly localized in the cell cytoplasm and membrane in both the intestinal and diffuse types in Lauren's histological classification [27]. Of the two major FGFR2 isoforms (FGFR2-IIIb and IIIc), which are determined by alternative splicing of a ternary extracellular immunoglobulin (Ig) domain III (Fig. 1A), the FGFR2-IIIb protein is predominantly overexpressed in GC [29, 30]. Overexpression of the FGFR2-IIIb protein was detected in 73 (4%) of 1,974 GC patients using immunohistochemistry (IHC), and all tumors with FGFR2-IIIb overexpression had FGFR2 amplification by fluorescence in situ hybridization [20]. The incidence of FGFR2 overexpression is dependent on the methodology and cohort, ranging from 4 to 60%
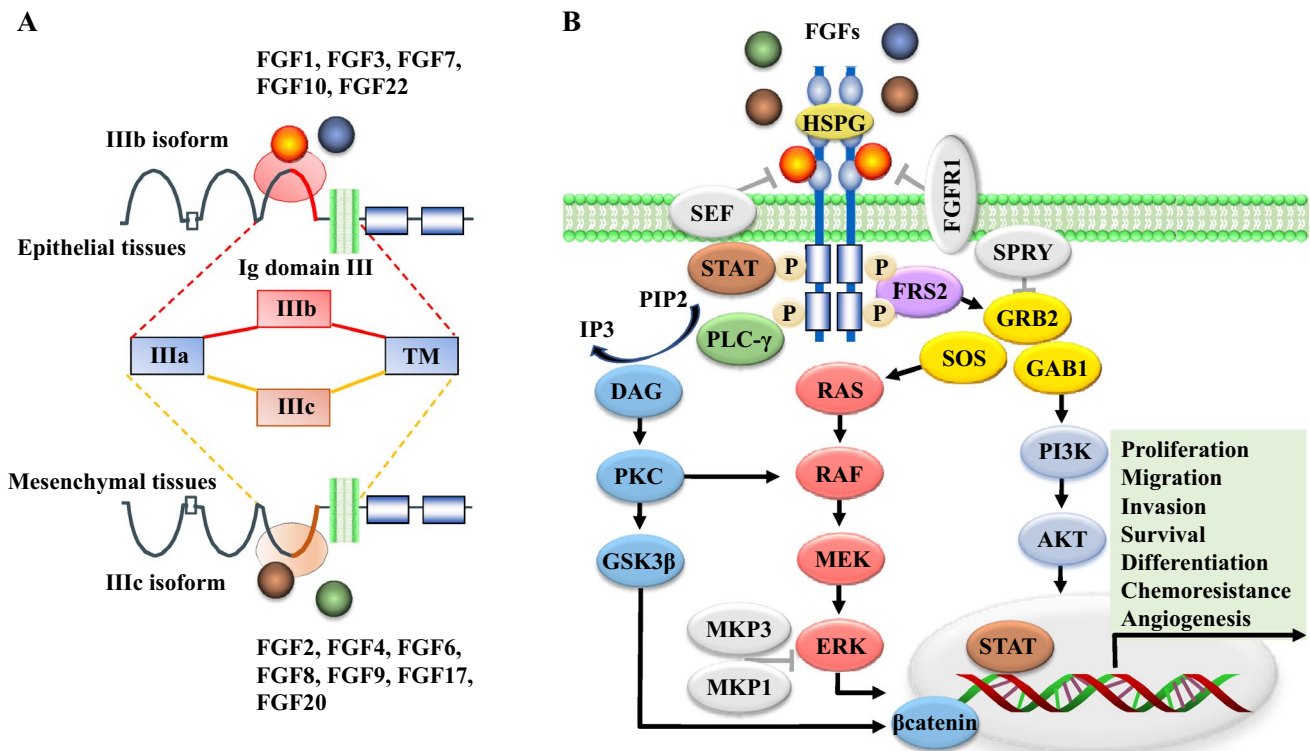
Fig. 1 FGFR signaling pathway. **A** Basic structures of FGFR. The mammalian FGFR family has a ternary extracellular Ig domain (domain I, II, III), a single transmembrane helix domain, and an intracellular tyrosine kinase domain as the RTK superfamily. As basic structures of the extracellular domains, there is an acidic box region between Ig domains I and II to interact with certain molecules other than FGFs, and domains II and III have heparin and FGF binding sites. The ligand specificity and affinity of FGFR1/2/3 are determined by alternative splicing of Ig domain III. The first half of Ig domain III is encoded by an invariant exon IIIa, while the remaining half is spliced to either encoded exon IIIb or IIIc in tissue-dependent manner. The FGFR-IIIb isoform is predominantly expressed in epithelial cells, and the FGFR-IIIc isoform is expressed in mesenchymal cells. The FGFR2-IIIb isoform specifically binds to FGF1, FGF3, FGF7, FGF10, and FGF22, while the FGFR2-IIIc isoform has a high binding affinity for FGF2, FGF4, FGF6, FGF8, FGF9, FGF17, and FGF20. However, FGFR4 has a single paralogous isoform for FGFR-IIIc. **B** The FGFR signaling pathway. Most FGFs function in a classic autocrine or paracrine fashion. In humans, 22 members of the FGF family have been identified, but four FGFs (FGF11, FGF12, FGF13, and FGF14) do not function as FGFR ligands. Canonically, FGFRs are monomers in their inactivated state. In the activation process of the FGFs–FGFR signaling pathway, the first step is binding the FGF ligand to FGFR and subsequent receptor dimerization. A stable FGFs–FGFR complex is formed by heparin sulfate-binding motifs on both the FGF ligands and FGFRs via heparan sulfate proteoglycan (HSPG). Ligand-dependent dimerization leads to kinase activation and the cross-phosphorylation of tyrosine residues in the intracellular domain, leading to the docking of adaptor proteins and the activation of key downstream cascades. FGFR substrate 2 (FRS2) binds to the juxtamembrane region in the intracellular part of activated FGFRs as an adaptor protein, leading to the recruitment of son of sevenless (SOS) and growth factor receptor-bound 2 (GRB2) to activate the RAS-dependent MAPK pathway. The PI3K-AKT pathway is activated by the recruitment of GRB2-associated binding protein 1 (GAB1). As an FRS2-independent substrate of FGFR, PLC-γ binds to a phosphor-tyrosine residue in the carboxyl terminal tail of FGFR, resulting in activation of the MAPK pathway via PKC. In addition, Janus kinase-signal transducers and activators of transcription (JAK–STAT), and Jun N-terminal kinase (JNK) pathways are activated by FGFR signaling in a context-dependent manner. FGFs–FGFR signaling cascades also crosstalk with Hedgehog, Notch, and Wnt/beta-catenin pathways. However, several inhibitory factors attenuate the FGFR pathway due to the modulation of ligand binding by interleukin-17 receptor D (IL17RD, also known as SEF) and FGFR-like 1 (FGFRL1) and due to interference with intracellular signaling by sprouty (SPRY) and MAPK phosphatase 1 and 3 (MKP1 and MKP3). FGFR signaling is cancer-specifically dysregulated by ligand-dependent and ligand-independent mechanisms. Mechanistically, ligand-dependent activation includes the overproduction of FGF ligands secreted by fibroblasts and cancer cells and increased ligand specificity and affinity of FGFRs due to their splicing and overexpression, resulting in a paracrine and autocrine loop. Ligand-independent activation is established by genomic alterations of FGFR, such as gene amplifications, active mutations, and chromosomal translocations/fusions. Silencing of inhibitory factors, such as SEF, also promotes FGFR signaling

[19, 20, 26, 31]. Although 56% of tumors with FGFR2-IIIb protein overexpression exhibited a heterogeneous expression pattern [21], tumors with a higher expression of FGFR2 exhibit more homogeneous expression compared to those with a lower expression [26]. Furthermore, robust concordance between FGFR2 expression and gene

amplification has been observed in the area with or without FGFR2 protein overexpression within the tumor [32]. Thus, FGFR2 gene amplification plays a pivotal role in its overexpression, regardless of the intratumor heterogeneity of the genetic and expression status in GC.

Intratumoral heterogeneity may have a clinical impact, as relevant to trastuzumab efficacy in patients with HER2-positive GC [33]. Only a small subset of GC cases with FGFR2 gene amplification have a co-occurring gene amplification of RTK/RAS molecules, including HER2 (4%), EGFR (4%), KRAS (2%), and MET (1%) [15, 24, 28, 34, 35]. Even though the tumor showed co-amplifications, gene amplifications were observed in distinct areas of the tumor [15], indicating the presence of an independent alteration in each cancer cell. Similarly, most tumors with FGFR2 overexpression have no concurrent overexpression of HER2, EGFR, and MET in expression profiles using a large cohort of 950 GC patients [31]. Thus, FGFR2 is mutually exclusive among RTK/RAS aberrations in GC.

Molecular and clinicopathological features of FGFR2 aberrations in gastric cancer

Lauren's classification system divides GC into intestinal, diffuse, and mixed types based on cell histochemistry and morphology [36]. Histologically, diffuse-type GC cells mainly consist of poorly differentiated adenocarcinoma, signet ring cell carcinoma, and undifferentiated adenocarcinoma based on World Health Organization (WHO) classification [37, 38]. Pathologically, these cells trend to scatter due to a lack of cell–cell adhesion and are easily disseminated in the abdominal cavity [36]. Furthermore, these cells have more enhanced invasive abilities in the muscularis propria and the lymphatic vessel compared to intestinal type GC cells [38]. Consequently, an aggressive phenotype of diffuse-type GC results in poor survival outcomes via peritoneal dissemination or lymph node metastasis [38].

Based on TCGA molecular classification, GC can be categorized into four subtypes (EBV-positive, MSI, CIN, and GS tumors), and there are no differences in the distribution of molecular subtypes between East Asian and Western regions [10]. Importantly, GS tumors have frequent fusions with CLDN18 or mutations of cadherin 1 (CDH1) or ras homolog family member A (RHOA), which mediates epithelial disintegration and the diffuse-type phenotype [10, 39–41]. In a TCGA cohort, FGFR2 alterations were detected in 8% with the CIN subtype and 9% with the GS subtype, while it was 2% for MSI and 0% for EBV [10]. Notably, FGFR2 amplification was more frequent in the GS molecular subtype and diffuse-type histology [10, 17, 22]. In a pooled analysis, including 2,377 GC patients from eight studies employing odds ratios (ORs) with a 95% confidence interval (CI) for clinicopathologic factors, FGFR2

amplification was significantly associated with poorly differentiated WHO histology [42] (OR = 2.36, 95% CI 1.03–5.39, $p = 0.04$) and lymph node metastasis (OR = 3.93, 95% CI 2.22–6.96, $p < 0.001$) [17]. Overexpression of FGFR2-IIIb isoform protein is also associated with poorly differentiated WHO histology, diffuse-type histology, and lymph node metastasis [20]. Furthermore, FGFR2-IIIb overexpression was more frequently observed in metastatic lymph nodes than in matched primary tumors [20]. These findings manifest that FGFR2 aberrations are enriched in the GS subtype with a molecular classification, the poorly differentiated type in WHO classification, the diffuse type in Lauren's classification, and lymph node metastasis in clinicopathological classification, which are similar populations but do not completely overlap.

FGFR2 amplification confers poor prognostic outcomes, regardless of the ethnic or regional cohort [15, 16]. In the pooled analysis of hazard ratios (HRs) with 95% CIs for OS using the electronic databases of the FGFR2 amplification status in GC, patients with FGFR2 amplification showed significantly worse survival rates than those without FGFR2 amplification (HR = 2.09, 95% CI 1.68–2.59, $p < 0.001$) [17]. A large cohort study found that a high expression level of FGFR2 mRNA was also associated with a low survival rate among GC patients [26] and was an independent adverse prognostic factor for OS [21]. In a pooled analysis, including 4,294 GC patients from ten studies, for OS according to the FGFR2 protein expression status, patients with FGFR2 overexpression showed significantly worse survival than those without FGFR2 overexpression (HR = 1.40, 95% CI 1.25–1.58, $p < 0.001$) [19]. Several studies assessed the association between the expression status of FGFR2-IIIb isoform protein and prognostic outcomes and demonstrated that a high level of FGFR2-IIIb expression correlates with a poor prognosis [20, 21]. In analyses based on Lauren's histological classification [36], FGFR2 overexpression was of prognostic relevance in diffuse-type GC but not in intestinal-type GC [43]. Thus, FGFR2 aberrations are a significant unmet medical need because of an established prognostic factor, especially for patients with diffuse-type GC.

Aberrant FGFR2 signaling pathways in gastric cancer

The canonical FGFs–FGFR signaling cascade is shown in Fig. 1B. FGFs–FGFR signaling pathways are robustly and precisely regulated by the context-dependent expression of FGF ligands, FGFR splicing variants, adaptor proteins, signal transduction enhancers, transcription factors, and co-activators. However, FGFR signaling is cancer-specifically dysregulated by ligand-dependent and ligand-independent mechanisms, inducing oncogenic signaling activation [35, 44].

In normal gastric tissue, the FGFR2-IIIb isoform plays an important role in early stomach epithelial development. FGF10-FGFR2-IIIb signaling regulates stomach progenitor cell maintenance, morphogenesis, and cellular differentiation in terms of the formation of terminal differentiation from a pre-patterned stomach progenitor epithelium [45]. The FGFR2 signaling pathway not only plays a physiological role in normal gastric tissue but also contributes to the development and progression of GC. Knockdown of FGFR2 not only attenuates invasive and proliferative abilities but also triggers apoptosis and chemosensitivity in GC cells [27]. FGFR2 amplification drives an oncogenic function via mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)-AKT signaling as the canonical downstream pathways of FGFR [46, 47]. Furthermore, FGFR-activated phospholipase C-γ (PLC-γ) hydrolyzes phosphatidylinositol-4,5-biphosphate (PIP2) to generate inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) as second messengers, which phosphorylates glycogen synthase kinase 3β (GSK3β) and subsequently localizes β-catenin to the nuclei, depending on the activation of protein kinase C (PKC) [48]. Nuclear β-catenin is complexed with transcription factor T-cell factor/lymphoid enhancer factor (TCF/LEF) to initiate the expression of MYC, FGF18, and FGF20 genes for cell-fate determination [49]. Thus, the FGFR2-PKC-GSK3β-β-catenin axis may promote tumor progression in GC. In diffuse-type GC cells, FGFR2 mRNA levels were significantly correlated with Twist-related protein 1 (Twist1), which is one of the important transcription factors in potentiating epithelial-mesenchymal transition (EMT) [50]. FGFR signaling is also required for JAK–STAT3 activation and thus contributes to the transcriptional regulation of tumor progression [51].

Yes-associated protein1 (YAP1), a downstream transcription coactivator of the Hippo signaling pathway, has been identified as a prominent downstream molecule of FGFR2 signaling, especially in diffuse-type GC [27]. YAP1 acts not only as an oncogenic initiator but also as a driver of GC via the activation of MYC [52–54]. There is substantial evidence implicating YAP1 in the expansion of cancer stem cell (CSC)-like populations and properties in various tumor types [55–57]. In GC, YAP1 is overexpressed in peritoneal metastatic cells, conferring CSC-like traits [58], and FGFR2 maintains stemness by activating MYC transcription [59], indicating that FGFR2 plays a crucial role in the CSC-like phenotype in GC.

As a ligand-dependent activation of the FGFR2 signaling pathway, FGF7 is overproduced by cancer-associated fibroblasts, which promotes tumor growth in diffuse-type GC but not intestinal-type GC [60, 61]. FGF10 contributes to the tumor's invasive ability, and its amplification has been reported in 3% of GC [51]. Given the high frequency of FGFR2-IIIb overexpression in diffuse-type histology [20]

and the specific binding of FGFR2-IIIb with FGF7 and FGF10 [62], the FGF7/10-FGFR2-IIIb axis may be constantly activated in a paracrine manner and, in turn, stimulate the invasion and migration abilities of diffuse-type GC cells. Furthermore, FGF18 is overexpressed in GS and in CIN subtypes of GC, and FGF18-FGFR2 signaling promotes tumor growth via MAPK, TGF-β–SMAD2/3 pathways in GC [63]. Several inhibitory effectors, including interleukin-17 receptor D (IL17RD, also known as SEF), sprouty (SPRY), and MAPK phosphatase 3 (MKP3), are also attenuated in GC [51]. Collectively, these preclinical findings provide a rationale for targeting FGFR2 as a potential treatment strategy for GC patients with FGFR2 aberrations.

FGFR inhibitors

Based on the genetic and biological background of GC, targeting FGFs–FGFR signaling is a major area of drug development (Fig. 2). FGFR inhibitors can be categorized into four classes according to the mechanism of action: (1) small molecule TKIs, including non-selective and selective FGFR inhibitors; (2) antagonistic monoclonal antibodies, which competitively bind to the FGFR extracellular domain and block activation of FGFs–FGFR signaling; (3) FGF ligand traps, which block the activity of multiple FGF ligands and ligand-receptor interaction; and (4) antibody–drug conjugates (ADCs), which comprise a cytotoxic payload conjugated by linkage to an FGFR antibody.

Non-selective FGFR-TKIs

Phylogenetically, FGFRs are closely related to VEGFRs and platelet-derived growth factor receptors (PDGFRs). First-generation FGFR-TKIs, therefore, non-specifically target a broad range of additional RTKs.

Since FGFR and VEGFR independently and synergistically promote tumor vascularization and mutually compensate for angiogenetic signaling when either pathway is blocked [64], a broad range of targets is expected not only for blocking FGFR signaling but also for the anti-antiangiogenic effects of FGFR-driven cancers. Nintedanib is a triple angiokinase inhibitor that blocks FGFR1/2/3, VEGFR1/2/3, and PDGFRα/β [65]. A single-arm phase II trial of nintedanib was conducted in patients with genetically characterized esophagogastric adenocarcinoma, including 15 GC patients [66]. Because the anti-tumor activity of nintedanib was similar to the efficacy reported for the VEGFR2 inhibitor alone, the development of nintedanib in treating esophagogastric cancer was discontinued. Regorafenib is a novel oral multi-kinase inhibitor of angiogenic (VEGFR1/2/3, TIE2), stromal (PDGFR-β, FGFR2), and oncogenic kinases (KIT, RET, and RAF) [67]. In a randomized phase II
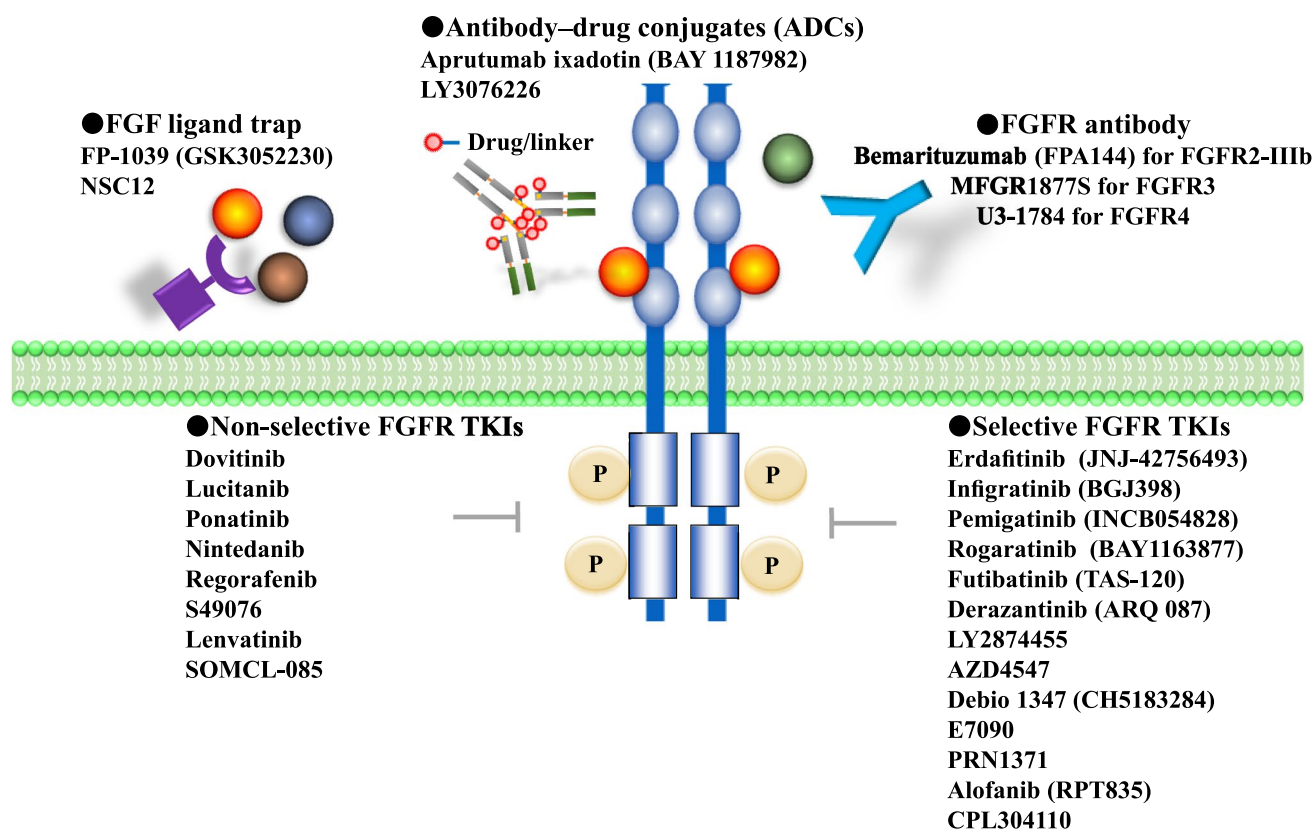
●**FGF ligand trap**
FP-1039 (GSK3052230)
NSC12

●**Antibody–drug conjugates (ADCs)**
Aprutumab ixadotin (BAY 1187982)
LY3076226

○— **Drug/linker**

●**FGFR antibody**
Bemarituzumab (FPA144) for FGFR2-IIIb
MFGR1877S for FGFR3
U3-1784 for FGFR4

●**Non-selective FGFR TKIs**
Dovitinib
Lucitanib
Ponatinib
Nintedanib
Regorafenib
S49076
Lenvatinib
SOMCL-085

●**Selective FGFR TKIs**
Erdafitinib (JNJ-42756493)
Infigratinib (BGJ398)
Pemigatinib (INCB054828)
Rogaratinib (BAY1163877)
Futibatinib (TAS-120)
Derazantinib (ARQ 087)
LY2874455
AZD4547
Debio 1347 (CH5183284)
E7090
PRN1371
Alofanib (RPT835)
CPL304110

Fig. 2 FGFR inhibitors. FGFR inhibitors can be categorized into four classes according to the mechanism of action: (i) small molecule TKIs, including non-selective and selective FGFR inhibitors; (ii) antagonistic monoclonal antibodies; (iii) FGF ligand traps; and (iv) antibody–drug conjugates (ADCs)

INTEGRATE trial of regorafenib in GC patients, regorafenib significantly prolonged progression-free survival (PFS) compared to placebo [68]. A phase IIII INTEGRATE II trial (NCT02773524) of regorafenib versus placebo is ongoing in GC.

Lucitanib is a potent oral inhibitor of FGFR1/2, VEGFR1/2/3, and PDGFRα/β [69]. In a phase I/IIa trial of lucitanib in advanced solid tumors, FGF-aberrant (FGFR1 or FGF3/4/19 amplifications) tumors showed clinical benefit with an overall response rate (ORR) of 30% and a disease control rate (DCC) of 78% [70]. Although GC patients were not included in this trial, it might be sensitive to dovitinib in GC patients with FGFs–FGFR aberrations. Dovitinib is a potent multi-kinase inhibitor that targets VEGFR1/2/3, FGFR1/2/3, PDGFRβ, KIT, RET, tropomyosin receptor kinase A (TrkA), colony-stimulating factor-1 receptor (CSF-1R), and fetal liver tyrosine kinase receptor 3 (FLT-3) [71]. In a phase I study of 35 advanced solid tumors, including two GCs, it was unsatisfactory that neither GC patient had a partial response [72]. However, the potent growth inhibitory activity of dovitinib was demonstrated specifically in FGFR2-amplified GC cell lines [18], and a phase II GASDOVI-1 trial of dovitinib is ongoing in GC harboring FGFR2 amplification (NCT01719549). Moreover, promising preclinical data have been reported for several other non-selective inhibitors, including S49076 [73], ponatinib [74], and SOMCL-085 [75].

Importantly, it remains unclear whether these non-selective FGFR inhibitors preferentially have treatment efficacy for patients with FGFR-driven GC. FGFR2-amplified GC was sensitive to regorafenib in cell line and xenograft models [76, 77], but FGFR aberrations were not associated with improved PFS and objective response in the phase II INTEGRATE trial cohort [77]. Similarly, FGFR2 amplifications were not predictive of clinical benefit in a phase II trial of nintedanib [66], regardless of the anti-proliferative effects in GC cell line models with FGFR2 amplification [65]. This discrepancy between preclinical and clinical results may be partially explained by intratumoral heterogeneity in GC. Additionally, these non-selective inhibitors cause frequent and severe dose-limiting toxicities (DLTs) due to the targeting of multi-RTKs and off-target effects [67, 70, 72], resulting in a less potent blockade of FGFR signaling [44].

Selective FGFR-TKIs

Pharmaceutical development has led to highly selective and bioactive FGFR-TKIs as the next generation of cancer treatment. However, the amount of data available regarding the use of these inhibitors in GC is limited. Almost all of the compounds are characterized by reversible, ATP-competitive binding to the FGFR kinase domain. Recently, the development of selective kinase inhibitors has focused on (1) targeting unique allosteric sites that have the potential to alter enzymatic activity by disrupting access to upstream activators or preventing the phosphorylation of select downstream substrates, such as alofanib [78]; (2) targeting both the ATP-binding site and a unique structural feature on a specific protein kinase, such as E7090 [79]; and (3) irreversible compounds that form selective covalent interactions with protein kinase to provide sustainable inhibitory effects, such as futibatinib [80].

Pemigatinib (INCB054828) is a highly selective oral inhibitor of FGFR1/2/3, and a phase I/II FIGHT-101 trial of pemigatinib was conducted in patients with advanced solid tumors [81]. In the part 2 cohort, three patients with partial response (PR) had cholangiocarcinoma. In a single-arm phase II FIGHT-202 trial in patients with cholangiocarcinoma with and without FGF/FGFR alterations, patients with FGFR2 fusion or rearrangement had PR of 35%, but there was no objective response in patients with other FGF/FGFR alterations or without any alterations [14]. The FDA granted accelerated approval of pemigatinib for patients with FGFR2 fusion or rearrangement in cholangiocarcinoma. In GC xenograft models with FGFR2 amplification, pemigatinib suppressed tumor growth [82]. Based on preclinical findings that the FGFR3/AKT axis was an escape pathway responsible for trastuzumab resistance in HER2-positive GC [83], a phase II FiGhTeR trial of pemigatinib in GC patients with trastuzumab resistance is ongoing [84].

Erdafitinib (JNJ-42756493) is a selective TKI for FGFR1/2/3/4. In a multicenter phase I study of erdafitinib in 187 patients with advanced solid tumors, all patients with urothelial carcinoma and cholangiocarcinoma who responded to erdafitinib had FGFR mutations or fusions [85]. Subsequently, a phase II BLC2001 trial of erdafitinib, including 99 patients with urothelial carcinoma harboring FGFR3 mutations or fusion genes involving FGFR2 or FGFR3, the ORR of 40% was observed [13], and the FDA granted accelerated approval to erdafitinib for urothelial carcinomas harboring FGFR2–3 alterations. A preclinical study showed that erdafitinib was sensitive to GC cell lines harboring amplification of FGFRs [77].

Infigratinib (BGJ398) is an ATP-competitive FGFR1/2/3 selective TKI. In a phase II study of infigratinib in patients with previously treated advanced cholangiocarcinoma harboring FGFR2 gene fusion or translocation, infigratinib was associated with promising anti-tumor activity and a manageable adverse event (AE) profile [86]. Infigratinib has been granted fast-track designation by the FDA for the first-line treatment of cholangiocarcinoma through the phase III PROOF trial (NCT03773302). In an OCUM-14 GC cell line model established from the malignant ascites of a patient with diffuse-type GC with FGFR2 amplification, infigratinib significantly decreased cell proliferation [87].

Rogaratinib (BAY1163877), a selective FGFR1/2/3/4 TKI, has shown promising efficacy in patients with advanced solid tumors with high FGFR1/2/3 mRNA overexpression in a phase I trial (NCT01976741), in which an objective response was observed in ten (67%) of the 15 patients with FGFR1/2/3 mRNA overexpressing tumors without apparent FGFR genetic aberration [88]. However, the ORR was only 5% in a phase I trial (NCT03762122) for patients with non-small cell lung cancer (NSCLC) histology with high FGFR1/2/3 mRNA levels [89], and further studies are required to confirm the validity of patient selection based on FGFR mRNA levels. Notably, in the phase I trial (NCT0197641), long-lasting tumor shrinkage was observed in patients with FGFR3 mRNA-positive GC [90]. A phase II parallel assignment trial (NCT04077255) of either an anti-EGFR antibody or rogaratinib in combination with weekly paclitaxel as a second-line therapy in GC, based on targeted NGS, is ongoing.

Despite the striking initial clinical activity of FGFR inhibitors, the emergence of acquired resistance limits the long-term benefits [91]. One of the resistance mechanisms is gatekeeper mutations of FGFR [92], and futibatinib (TAS-120) is attracting attention as having the potential to overcome the gatekeeper mutations responsible for resistance to reversible ATP-competitive FGFR-TKIs, such as infigratinib [93]. Promising clinical benefits were also reported in cohorts with cholangiocarcinoma harboring FGFR2 gene fusions and other rearrangements in a phase 2 FOENIX-CCA2 trial of futibatinib [94]. Based on the results of the FOENIX-CCA2 trial, the FDA granted breakthrough therapy designation for futibatinib in patients with cholangiocarcinoma. A phase II trial (NCT02052778) of futibatinib that involves GC cohort harboring FGFR2 amplifications is ongoing [95].

As expected, almost no responders were observed among patients without FGFR aberrations in early trials of selective FGFR inhibitors [81, 85, 88, 96–98]. Notably, FGFR amplifications also have very limited clinical activity in selective FGFR-TKIs [85, 97, 99]. Thus, early-phase trials highlight that biomarker selection for the specific molecular alteration is mandatory to enrich the efficacy of FGFR inhibitors, revealing FGFR mutations and fusions as strong predictors of benefitting from FGFR-TKIs, in contrast to FGFR amplification.

FGFR monoclonal antibody

Anti-FGFR2 monoclonal antibodies have preclinical anti-tumor effects and less toxicity [51, 100]. Bemarituzumab (FPA144) is a first-in-class humanized immunoglobulin G1 (IgG1) monoclonal FGFR2-IIIb isoform-selective antibody, afucosylated using a glycoengineering approach for enhanced antibody-dependent cell cytotoxicity (ADCC) [101]. In preclinical GC models, bemarituzumab remarkably attenuated tumor growth, along with decreased levels of both phosphorylation of FGFR2-IIIb and the downstream effector FGFR substrate 2 (FRS2) [29]. Further details regarding the clinical data associated with bemarituzumab are described in a later section.

FGF ligand trap and antibody–drug conjugates (ADCs)

FP-1039 (GSK3052230) is a soluble fusion protein consisting of extracellular FGFR1 fused to the Fc domain of IgG1, and it neutralizes multiple FGFs that normally bind to FGFR1 [102]. A first-in-human phase I trial of FP-1039 was conducted in an unselected population of patients with advanced solid tumors [103]. Although there was no objective response, decreased free plasma FGF2 levels following FP-1039 treatment and the absence of FGFR-TKI-associated toxicities were observed. Since the soluble pattern recognition receptor long-pentraxin 3 (PTX3) is a natural multi-FGF antagonist, pharmacophore modeling identified NSC12, a PTX3-derived small molecule, as an extracellular FGF trap with preclinical anti-tumor activity [104]. Although there are no clinical data for GC patients, the FGF ligand trap is a novel approach due to the comprehensive targeting of FGFs–FGFR signaling within the tumor-microenvironment.

ADCs comprise a cytotoxic payload conjugated by a linker to a monoclonal antibody against tumor-specific surface molecules, resulting in efficient drug delivery to tumor cells with minimum systemic exposure and off-target toxicity [105]. Aprutumab ixadotin (BAY 1,187,982) is a novel ADC comprising a fully human anti-FGFR2 monoclonal antibody (BAY 1,179,470) tethered to a cytotoxic drug, auristatin [106]. In a first-in-human phase I study of aprutumab ixadotin in patients with advanced solid tumors, including two GC patients, no objective response was observed, and it had an intolerable toxic profile and narrow therapeutic threshold, resulting in early termination of the study [107].

Clinical trials for FGFR inhibitors in gastric cancer

As described in the previous section, FGFR2 amplification is most common in diffuse-type GC with poor prognosis, and preclinical studies have demonstrated the robust anti-tumor efficacies of FGFR inhibitors in FGFR2-amplified GC models. Consequently, several trials of FGFR inhibitors were conducted to evaluate their safety and early efficacy in a subset of GC patients with FGFR aberrations.

Clinical trials for FGFR-TKIs in gastric cancer

LY2874455 is a reversible FGFR1/2/3/4 TKI that competes for the ATP-binding pocket in the kinase domain, and it has slow absorption and linear pharmacokinetics [108]. In FGFR2-amplified GC xenograft models, LY2874455 has shown anti-tumor activity. Clinically, a GC cohort was included for dose-expansion in a phase I study of LY2874455 in advanced solid tumors, and only one patient had an objective response among the 15 evaluable patients [98].

E7090 has a basic structure that lacks dimethoxyphenyl moiety and inhibits kinase activity with a binding mode that exhibits rapid and potent binding of FGFR1/2/3, and its kinetics are similar to type V inhibitors [79]. E7090 preclinically suppressed the phosphorylation of FGFR2 in FGFR2-amplified GC cell line models and showed anti-tumor activity in the GC xenograft model [79]. In a first-in-human phase I study of E7090 in patients with advanced solid tumors, one patient with FGFR2-amplified GC achieved an objective response among a total of 24 patients [109]. Although a dose escalation study was conducted in two cohorts with cholangiocarcinoma harboring FGFR2 fusion and GC harboring FGFR2 amplification or protein overexpression (GC cohort), treatment efficacy of the GC cohort was limited, with an ORR of 10% (1 in 10 GC patients) and median progression-free survival (mPFS) of 2.8 months [110].

AZD4547 is a selective FGFR1/2/3 TKI with potent preclinical activity in FGFR2-amplified GC patient-derived xenograft models established from malignant ascites [111]. In a randomized phase II SHINE trial, which evaluated the treatment efficacy of AZD4547 versus paclitaxel as a second-line treatment for 71 patients with GC harboring FGFR2 gene amplification or polysomy, the primary endpoint, mPFS, was not met (1.8 vs. 3.5 months, HR = 1.57, $p = 0.958$) (Table 1) [25]. The ORR was 2.6% for AZD4547 and 23.3% for paclitaxel, and the median OS was 5.5 and 6.6 months (HR = 1.31, $p = 0.815$), respectively. The limited treatment efficacy was observed even

Table 1 Results of phase II SHINE and FIGHT trials

Trial	SHINE [25]		FIGHT [23]	
Phase	II		II	
Line	2nd-line		1st-line	
Inclusion	FGFR2 amplification or polysomy		FGFR2b positive	
Treatment	Paclitaxel	AZD4547	mFOLFOX6 + placebo	mFOL-FOX6 + Bema
Number of patients	30	41	78	77
ORR (%)	23.3	2.6	33.0	44.0
DCR (%)	56.7	21.1	96.6	96.2
PFS				
Median (months)	3.5	1.8	7.4	9.5
HR (95% CI)	1.57 (1.12–2.21)		0.68 (0.44–1.04)	
OS				
Median (months)	6.6	5.5	13.5	19.2
HR (95% CI)	1.31 (0.89–1.95)		0.60 (0.38–0.94)	

Bema bemarituzumab, *ORR* overall response rate, *DCR* disease control rate, *PFS* progression-free survival, *OS* overall survival

when analyzed in patients with FGFR2 amplification; the ORR was 0% for AZD4547 and 20.0% for paclitaxel, and the median OS was 4.9 months for AZD4547 and 4.6 months for paclitaxel (HR = 1.26, 80% CI 0.72–2.25). An exploratory biomarker analysis showed marked intra-tumor heterogeneity for FGFR2 amplification and poor concordance between FGFR2 amplification/polysomy and FGFR2 expression [25]. Interestingly, patients with GC harboring high-level clonal FGFR2 amplification, but not subclonal or low-level amplification, had a high objective response rate to AZD4547, although the frequency is relatively rare, approximately 5% in GC [112]. Thus, clonality assessment may be important in predicting a patient's response to FGFR inhibitors.

Clinical trial of an FGFR antibody in gastric cancer

Recently, the FGFR2-IIIb isoform-selective antibody bemarituzumab (FPA144) demonstrated promising clinical efficacy in GC patients with FGFR2 amplification or FGFR2-IIIb overexpression. A first-in-human phase I FPA144-001 trial of bemarituzumab monotherapy was designed in two parts, in which part 1 involved dose escalation in patients with advanced solid tumors (part 1A) and GC (part 1B), and part 2 divided GC patients into four cohorts stratified according to their expression levels of FGFR2-IIIb (high, medium, low, and no expression) [113]. No DLTs were observed during dose escalation in part 1, and no maximum-tolerated dose was determined. High FGFR2-IIIb expression levels were observed in 28 of the 52 evaluable GC patients enrolled across the trial, and all of their tumors exhibited FGFR2 amplification, consistent with its expression status. In 28 patients with high FGFR2-IIIb expression, the ORR and disease control rate (DCR) were 17.9% and 64.3%, respectively.

In contrast, there was only one responder among the 26 patients without high FGFR2-IIIb expression (moderate, low, and non), and none of the tumors without high FGFR2-IIIb expression had FGFR2 amplification [113].

In addition to the safety, tolerability, and clinical activity of bemarituzumab monotherapy in the FPA144-001 trial [113], the preclinical data demonstrated the additive anti-tumor effects of bemarituzumab with chemotherapy, which included 5-fluoruracil plus platinum [29], indicating the rationale for a combinational strategy of bemarituzumab plus chemotherapy. The clinical benefits of adding bemarituzumab to first-line mFOLFOX treatment in patients with FGFR2b-positive GC, defined as FGFR2-IIIb overexpression using IHC or FGFR2 gene amplification determined by ctDNA, were demonstrated in the international, randomized, double-blind, placebo-controlled phase II FIGHT trial, with PFS as the primary endpoint and OS, ORR, and safety as secondary endpoints (Table 1) [23]. FIGHT trial was initially intended to be a registrational phase III trial [114], but the design was changed to a phase II proof-of-concept trial after 155 individuals signed on. Patients with HER2-poisitive GC were excluded. Pre-screening was performed in 910 GC patients, 275 (30.2%) of which were FGFR2b positive. Finally, 155 patients, including 149 with FGFR2-IIIb overexpression and 26 who were ctDNA positive, were treated with bemarituzumab (n = 77) or placebo (n = 78) in combination with mFOLFOX. After a median follow-up period of 10.9 months at the data cutoff date (September 23, 2020), the mPFS were 9.5 months for bemarituzumab and 7.4 months for placebo, respectively (HR = 0.68, 95% CI 0.44–1.04, p = 0.0727). Since the statistical design was set as an HR ≤ 0.76 at a 2-sided alpha of 0.2 for the PFS benefit from bemarituzumab, the primary endpoint was met. The ORR was higher with bemarituzumab than with placebo

(53% vs. 40% among patients with measurable disease). After a median follow-up period of 12.5 months, the median OS was 19.2 months for bemarituzumab and 13.5 months for placebo (HR = 0.60, 95% CI 0.38–0.94) [115]. The rates of grade ≥ 3 AEs were 83% for bemarituzumab and 74% for placebo, and AE-induced discontinuation was more frequent with bemarituzumab compared to placebo (34.2% vs. 5.2%). Although hyperphosphatemia is the most common toxicity due to FGFR-TKIs [13, 14, 86, 94], there were no hyperphosphatemia AEs with bemarituzumab. However, bemarituzumab caused a higher incidence of stomatitis (31.6% vs. 13.0%) and corneal AEs (67.1% vs. 10.4%) compared to placebo. FGFR-TKIs and FGFR2-IIIb-specific antibodies probably have different toxicity profiles, indicating that special attention should be paid to bemarituzumab-related AEs.

Discussion

From the treatment resistant, immunogenic, and patient-selective viewpoints, we discuss the possible reasons why the FGFR2-IIIb monoclonal antibody bemarituzumab has shown a clinical benefit for GC patients in contrast to FGFR-TKIs, which have demonstrated anti-tumor activity in patients with cholangiocarcinoma and urothelial carcinoma.

Considering the low ORR of FGFR-TKIs for GC patients in clinical trials, primary resistance is a major concern in treatment with FGFR-TKIs. As described in the previous section, most patients benefitting from FGFR have FGFR mutations or fusions (but not gene amplification) in cholangiocarcinoma and urothelial carcinoma. Furthermore, in early trials of advanced solid tumors, treatment with FGFR-TKIs resulted in almost no response, not only in patients without FGFR aberrations but also in patients with FGFR amplification [81, 85, 88, 96–99]. As FGFR mutations and fusions activate the signaling pathway via phosphorylation of tyrosine residues in the intracellular domain of FGFR, FGFR-TKIs may confer robust anti-tumor activity in tumors harboring FGFR mutations and fusions, which are most likely to be responsible for oncogene addiction to FGFR. Therefore, the rarity of FGFR mutations and fusions represents a substantial concern for primary resistance to FGFR-TKIs in GC [12]. In terms of FGFR2 amplification, high-level clonal amplification (but not subclonal or low-level amplification) may be required for response to FGFR-TKIs because of the oncogene-addicted phenotype initiated by high-level amplification [112]. Although the assessment of ctDNA indicates the contributions of FGFR-TKIs to treatment response by identifying high-level and clonal amplified tumors among GCs with intratumoral heterogeneity, the very low prevalence of high-level clonal amplification also represents a barrier to FGFR-TKIs in GC patients [112].

On the other hand, it is likely that the clinical efficacy of the FGFR2-IIIb monoclonal antibody bemarituzumab does not necessarily require FGFR2 amplification. In fact, the clinical benefits of bemarituzumab have been observed in patients with FGFR2-IIIb overexpression even without ctDNA amplification, with HRs of 0.63 for PFS (95% CI 0.40–0.99) and 0.66 for OS (95% CI 0.39–1.12) in the phase II FIGHT trial [115]. Thus, bemarituzumab has mechanisms of action in addition to blockading the FGFR2 signaling. ADCC is an adaptive immune response mediated mainly by natural killer (NK) cells through binding of the FcγR IIIa receptor with the Fc portion of the antibodies linked to the target tumor cells, which induces tumor cell cytotoxicity via secretion of cytotoxic granules containing perforin and granzyme [116]. Bemarituzumab is glycoengineered for enhanced ADCC activity, and it effectively mediates ADCC against cells with FGFR2-IIIb expression but not cells with other FGFR isoforms [101]. In an immune-competent mouse model with FGFR2-IIIb expression but not FGFR2 amplification, treatment with bemarituzumab resulted in a regressed tumor burden and concomitant recruitment of NK cells within the tumor microenvironment [117]. Thus, bemarituzumab-induced ADCC may be critical for anti-tumor efficacy in tumors with expression of FGFR2-IIIb, regardless of genetic status [101]. Importantly, the clinical benefits increased with more homogenous FGFR2-IIIb overexpression, with HRs of 0.44 for PFS (95% CI 0.25–0.77) and 0.41 for OS (95% CI 0.22–0.79) in GC patients with ≥ 10% FGFR2-IIIb overexpression, highlighting the need to identify the optimal cutoff value of FGFR2-IIIb positivity to more precisely select bemarituzumab-sensitive patients [23]. Collectively, FGFR2-IIIb monoclonal antibodies will be a main therapeutic pillar for patients with more homogenously FGFR2-IIIb overexpressing GC. Although the mechanisms of acquired resistance to the FGFR2 antibody are not yet understood, they potentially include loss of FGFR2-IIIb expression, epithelial-mesenchymal transition, upstream response, and activation of downstream pathways via bypass signaling or genomic aberrations, which are reported as exhibiting resistance to trastuzumab [118].

Two anti-PD-1 antibodies, pembrolizumab and nivolumab, have dramatically changed therapeutic paradigms in previously treated GC patients, as a durable clinical response is achieved by disrupting immune tolerance and activating cytotoxic T cells [119–122]. Recently, the clinical benefits of nivolumab in combination with first-line chemotherapy for patients with HER2-negative GC were demonstrated in a phase III CheckMate 649 trial [123, 124] and in a phase III ATTRACTION-4 trial [125]. Thus, the combination of nivolumab and chemotherapy represents a new standard first-line treatment for patients with HER2-negative GC. From the anti-tumor immunogenic perspective according to the GS molecular subtypes [10], FGFR2b-positive

tumors may be immune "cold" type with low infiltrating lymphocytes (TILs), low immunogenicity, and low PD-L1 expression, and the immunologically ignorant phenotype may have a poor response to ICIs [126]. This situation is similar to that of HER2-positive tumors, in which HER2 signaling acts as the inhibitory anti-tumor immune response through downregulation of both major histocompatibility complex (MHC) molecules and PD-L1 in tumor cells [127]. Importantly, trastuzumab-induced ADCC and the blockade of HER2 signaling promote the increased TILs with PD-1 expression, high neoantigens on the MHC, and upregulation of PD-L1 expression by tumor cells, indicating synergistic effects between trastuzumab and anti-PD-1 antibody [127]. This therapeutic strategy for HER2-positive GC showed promising efficacy and manageable safety in a phase II trial [128], and the FDA granted accelerated approval to pembrolizumab in combination with trastuzumab plus chemotherapy for first-line treatment based on findings with significantly increased ORR in the prespecified interim analysis of a phase III KEYNOTE-811 trial [129]. Similarly, preclinical treatment with bemarituzumab converted immune "cold" tumors into "hot" tumors through a reprogrammed tumor-microenvironment by enhancing TILs, recruiting NK cells to the tumor, and upregulating PD-L1 expression [117]. Furthermore, the addition of bemarituzumab with anti-PD-1 antibody resulted in significant tumor shrinkage, but anti-PD-1 antibody monotherapy did not. These preclinical findings provide a rationale for combination treatment with bemarituzumab plus anti-PD-1 antibody. A randomized phase III trial is planned to evaluate the treatment efficacy of adding bemarituzumab to nivolumab plus chemotherapy as a new standard first-line treatment in patients with FGFR2b-positive GC.

Conclusion

There is still scarce evidence of the clinical benefits of FGFR-TKIs in GC patients, regardless of the relevance of FGFR2 signaling. The main issues are the FGFR2 blockade approach and intratumoral heterogeneity, which have hampered the development of precision medicine for patients with FGFR2-aberrant GC. The impressive results of the FIGHT trial demonstrate proof of concept, suggesting that the FGFR2-IIIb-selective monoclonal antibody bemarituzumab is a promising approach for patients with more homogenous FGFR2b-positive GC, defined using IHC or ctDNA. Thus, the era of precision medicine for patients with FGFR2-aberrant GC will be opened in the near future.

Declarations

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