

Targeting FGFR2 Positive Gastroesophageal Cancer: Current and Clinical Developments

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Abstract: Despite recent advances in the systemic treatment of gastroesophageal cancers, prognosis remains poor. Comprehensive molecular analyses have characterized the genomic landscape of gastroesophageal cancer that has established therapeutic targets such as human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor receptor (VEGFR) and programmed death ligand 1 (PD-L1). The aberrant fibroblast growth factor receptor 2 (FGFR2) pathway is attractive for targetable therapy with FGFR inhibition based on preclinical data showing a pivotal role in the progression of gastric cancer (GC). *FGFR2* amplification is the most common *FGFR2* gene aberration in gastroesophageal cancer, and most associated with diffuse GC, which is often linked to poorer prognostic outcomes. There has been considerable progress with drug development focused on FGFR inhibition. At present, there is no approved FGFR inhibitor for FGFR2 positive gastroesophageal cancer. A selective FGFR2b monoclonal antibody bemarituzumab is currently being investigated in the first phase III randomized trial for patients with first line advanced GC, which may change the treatment paradigm for FGFR2b positive GC. The role of FGFR signalling, specifically *FGFR2*, is less established in oesophageal squamous cell cancer (ESCC) with a paucity of evidence for clinical benefit in these patients. Precision medicine is part of the wider approach in gastrointestinal cancers; however, it can be challenging due to heterogeneity and here circulating tumour DNA (ctDNA) for patient selection may have future clinical utility. In our review, we outline the FGFR pathway and focus on the developments and challenges of targeting FGFR2 driven gastroesophageal cancers.

Keywords: gastric cancer, gastroesophageal cancer, FGFR2, molecular targets, novel therapies

Introduction

Gastroesophageal cancer encompasses three major subdivisions which are histologically, epidemiologically, and pathologically different: gastric adenocarcinoma, gastroesophageal junctional (GEJ) adenocarcinoma and oesophageal cancer, which is further classified into squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Gastric and oesophageal cancers are the fifth and seventh most common cancers globally, however fourth and sixth leading cause for cancer mortality.¹

Gastroesophageal cancer is aggressive and challenging to treat due to molecular heterogeneity, limited selective biomarkers and approved targeted therapies. Fluoropyrimidine and platinum-based chemotherapy remains at the forefront of systemic treatment in gastroesophageal cancer, with taxanes, irinotecan, trifluridine/tipiracil² used in subsequent lines. There are limited targeted therapies available but targeted monoclonal antibodies including trastuzumab and trastuzumab deruxtecan for HER2³ and ramucirumab for VEGFR2⁴ have been approved for GC. Recently, immune checkpoint inhibitors (ICIs) including nivolumab and pembrolizumab have been approved for select patients with advanced gastroesophageal cancer due to positive results from pivotal phase III trials.^{5–11} Despite these advances prognosis remains poor and there may be further opportunities through understanding the molecular biology for development of novel drug targets.

The Cancer Genome Atlas (TCGA) network provided a comprehensive molecular analysis and helped identify the genomic landscape of each major subtype. Gastric adenocarcinoma was classified into four subtypes: microsatellite instability (MSI), Epstein-Barr virus (EBV)-positive, chromosomal instability (CIN) and genomically stable (GS) tumours.¹⁵ Oesophageal adenocarcinoma is strongly characterized by CIN, noting some oesophageal adenocarcinomas were more

enriched with DNA hypermethylation, and ESCC were divided into three molecular subclasses: ESC1, ESC2 and ESC3.¹¹ Whilst these comprehensive analyses are useful for providing a molecular roadmap, there is yet to be therapeutic exploitation based on these broader groups, hitherto drug development is still focused on individual molecular targets.

The FGFR pathway has emerged as an attractive target for novel therapies in several cancers. It is known to mediate multiple processes including cell proliferation, survival, and differentiation through activation of the downstream signalling RAS, RAF and MAPK pathways.¹² Dysregulation of FGFR signalling can culminate in tumorigenesis and cancer progression. *FGFR2* amplification is the most common *FGFR2* gene aberration and is associated with GC, specifically the diffuse subtype and accounts for 2% to 9% of GC.^{13–17} *FGFR2* overexpression varies from 31 to 61% and correlates with aggressive features including higher grade T stage, more frequent lymph node dissemination and inferior overall survival.^{18–20} In ESCC, a distinct role for FGFRs remains to be elucidated.

This review article focuses on the relevance of *FGFR2* signalling in GC and highlights the potential for *FGFR2* as a target. We outline the evolution of FGFR drug development from a tumour-agnostic and GC viewpoint based on the current clinical evidence and discuss future developments as well as challenges pertaining to FGFR positive gastro-esophageal cancer.

The FGFR Signalling Pathway

The FGFR family is comprised of four transmembrane receptor tyrosine kinase (RTKs); FGFR1, FGFR2, FGFR3 and FGFR4. A fifth related receptor (FGFRL1) exists however lacks a tyrosine kinase domain which may negatively regulate signalling.¹² FGFR1–4 share a similar configuration, being composed of three major elements including a large extra-cellular ligand binding domain, a single transmembrane helix, and an intra-cellular tyrosine kinase domain. The extra-cellular domain includes three immunoglobulin-like sub-units (D1, D2 and D3).²¹ FGFRs are expressed on the cell membrane, where they are activated by their native ligand FGFs.²² Upon binding with the ligand FGF, FGFRs dimerise causing conformational shifts in structure, which activate the intracellular kinase domain, resulting in phosphorylation of the intracellular domain. Through the recruitment of FRS2, SOS and GRB2 signalling molecules, there is downstream activation of the RAS and the MAPK pathways. The PI3K-mTOR-AKT and STAT3 signalling pathways are also activated by FGFR (Figure 1).¹² FGFRs play a key role in the development and physiology of multiple organ systems and drive key signalling pathways which are responsible for cell proliferation, survival, migration as well as wound healing and angiogenesis.^{12,23}

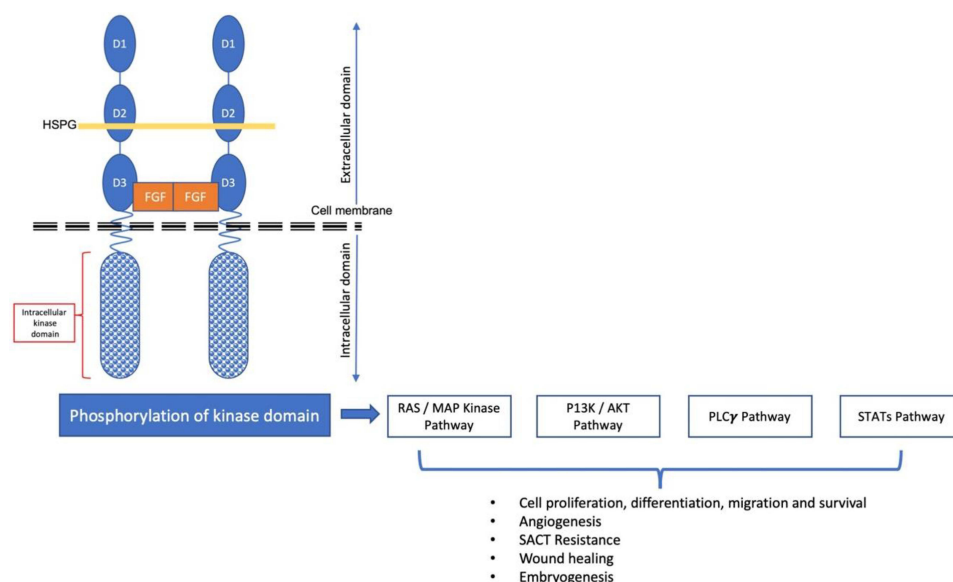


Figure 1 The FGF – FGFR complex and downstream signalling pathways. Two FGFs, two FGFRs and a heparin sulphate proteoglycan (HSPG) form the FGF-FGFR complex. The phosphorylation of the intra-cellular kinase domain results from FGF binding and FGFR dimerization. Consequent activation of multiple downstream pathways, including the RAS-RAF-MAP kinase pathway, PI3K-AKT pathway, PLC γ pathway and STAT pathway results. Triggering these signaling pathways cumulates in the FGFRs role in cell proliferation, differentiation, migration and survival. Additionally, FGFR signaling is pivotal in angiogenesis, wound healing and embryogenesis.

FGFR2 in Gastric Cancer

Gene abnormalities in *FGFR2* can lead to activation of *FGFR2* signalling. In a hybrid capture-based genomic profiling study using 6667 tissue specimens from advanced GC patients, *FGFR2* gene aberrations were found in 269 (4%) with the most frequent alteration being amplification (72%) followed by mutations (13%), translocations (8.6%) and co-occurring alterations (6.3%).²⁴ Rare (<1%) fusions (*FGFR2-TACC2*), and single point mutations (N549K) have been discovered however their clinicopathological characteristics and targeting potential remain unclear.²⁴

Amongst GC, gene amplification is the most common aberration of the *FGFR2* gene which leads to FGFR2 protein overexpression and constitutive signalling of the FGFR pathway. The prevalence of *FGFR2* gene amplification ranges from 2% to 9%^{13–17} depending on the clinical characteristics of the cohort, and the method used to detect amplification. Detection of *FGFR2* amplifications to date have been based upon tissue-based methods. In the largest case-series (n=961) of resected GC, *FGFR2* gene amplification by fluorescent in situ hybridisation (FISH) was observed in 5.6% of cases, with minor differences in the prevalence noted according to geographical location (China 4.6%, Korea 4.2%, and UK 7.4%).²⁵ Amongst early-stage GC, *FGFR2* amplifications are associated with higher grade T stage, more frequent lymph node dissemination and inferior overall survival.^{14,15,25,26} There does not appear to be any association with age, gender, histological subtype, or anatomical location.²⁵ The association with Lauren histological subtype is controversial with some case series suggesting enrichment amongst diffuse type compared to intestinal type.^{15,25,26} In the metastatic setting, *FGFR2* amplifications are also associated with inferior progression free survival (PFS) and overall survival (OS) in patients receiving platinum and fluoropyrimidine chemotherapy.^{18,27,28} *FGFR2* and *HER2* amplifications are mutually exclusive,^{25,28} however rare cases have been reported.²⁴ Nevertheless, approximately 40% of *FGFR2* altered gastroesophageal cancers harbour other mutations (*KRAS*, *MYC*) which may render it resistant to FGFR pathway targeted therapy.²⁵ *FGFR2* amplification occurs in microsatellite stable (MSS) tumours and does not enrich for PD-L1 expression.²⁵

FGFR2 overexpression by immunohistochemistry (IHC) has been reported in a large proportion of GC (31–61%).^{18–20} Overexpression of the FGFR2 receptor promotes aberrant signalling through downstream pathways ultimately leading to tumour cell proliferation. In GC, FGFR2 overexpression correlates with more aggressive clinical features such as higher-grade T stage, lymph node and distant metastases which can lead to poorer patient outcomes.¹⁸ Similar to *FGFR2* amplified cases, FGFR2 overexpression has been associated with worse survival in junctional¹⁸ and gastric tumours.^{29–31} IHC is a relatively inexpensive test and is available in most laboratories, offering a more cost-effective approach than FISH analysis.

FGFR2 has two isoforms (IIIb and IIIc) which are based upon alternate splicing of exon 8 and 9, respectively leading to differing binding affinities of FGFs.¹² *FGFR2b* is the IIIb splice isoform of *FGFR2*. It is expressed in epithelial cells and is the more prevalent in *FGFR2* amplified GC.³² While *FGFR2* amplified tumours exhibit evidence of ligand-independent signalling, the natural ligand for *FGFR2b*, FGF7, plays a role in GC progression where FGFR2 expression is elevated.³³ Paracrine secretion of FGF7 by fibroblasts contribute to proliferation,³⁴ migration and invasion in *FGFR2* expressing cells.³⁵ Small cohorts have suggested *FGFR2b* expression is associated with worse survival³⁶ and therapeutic targeting of *FGFR2b* is currently under active clinical investigation as discussed later in the review.

As a result of its association with aggressive clinical features potentially leading to poorer patient outcomes, therapeutic targeting of *FGFR2* in GC is of interest in those harbouring *FGFR2* amplifications or FGFR2b overexpression. We highlight the relevance of these potential targets later in this review with parallel evaluation from supporting clinical studies.

Drug Development in FGFR Driven Cancer

Oncogenic signalling via the FGFR pathway has emerged as a targetable site in multiple cancers, including GC. FGFR inhibition is established in urothelial carcinomas and cholangiocarcinoma, with FGFR inhibitors only approved for clinical practice in these tumour types. (Table 1) Extensive assessment of the structure of FGFRs and development of FGFR inhibitors is ongoing. This section provides an overview of FGFR drug development from a tumour agnostic viewpoint before focusing on the specific developments within FGFR2 gastroesophageal cancer. FGFR inhibitors can be sub-divided into small-molecule oral tyrosine kinase inhibitors (TKIs), monoclonal antibodies and ligand traps.³⁷

Table I Approved FGFR Inhibitors to Date

Drug	Cancer Type; Indication	Gene Target	Trial Results	Approval
Infigratinib	Advanced CCA; \geq 2nd line	<i>FGFR2</i> rearrangement or fusion	n=108; ORR 14.8% (95% CI, 7.0 to 26.2), mDOR 7.5 months (95% CI, 5.6 to 7.6) ⁴³	FDA May 2021
Futibatinib	Advanced CCA; \geq 2nd line	<i>FGFR2</i> rearrangement or fusion	n=67, ORR 34%, mDOR 6.2mo ⁴⁷	FDA breakthrough therapy designation April 2021
Pemigatinib	Advanced CCA; \geq 2nd line	<i>FGFR2</i> rearrangement or fusion	n=107, ORR 36% (95% CI 26–45.4), mDOR 7.5mo (95% CI 5.7–14.5) ⁴²	FDA April 2020 EMA March 2021
Erdafitinib	Metastatic urothelial carcinoma; \geq 2nd line	<i>FGFR3</i> mutations or <i>FGFR2</i> fusions	n=87, ORR 40% (95% CI 31–50%), mDOR 5.6mo (95% CI 4.2–7.2) ⁴¹	FDA April 2019

Abbreviations: CCA, cholangiocarcinoma; CI, confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; mDOR, median duration of response; ORR, objective response rate.

Oral TKIs

Oral TKIs were part of the first approach for targeting FGFR. TKIs have a similar structure to adenosine triphosphate (ATP) and compete for the ATP binding cleft of the kinase domain on the FGFR receptor. Competitive, reversible inhibition reduces tyrosine kinase phosphorylation, causing blockade of multiple downstream pathways thereby inhibiting cancer cell proliferation.³⁸ First generation FGFR TKIs were non-selective (eg dovitinib, lenvatinib, anlotinib, pontinib) and inhibited multiple other kinase pathways including VEGFR, KIT and RET.³⁹ These TKIs lacked kinase selectivity and were less potent against the FGFR pathway resulting in significant toxicities during initial trials, ultimately limiting their application in clinical practice.⁴⁰

Refining FGFR TKIs to specifically and selectively act on the tyrosine kinase domain led to the development of selective TKIs. Selective TKIs achieve clinical benefit whilst minimising the significant toxicities associated with non-selective TKIs. The benefit of targeting FGFR has been demonstrated in urothelial cancers and cholangiocarcinoma. Erdafitinib, an oral reversible inhibitor of FGFR1 to FGFR4, has been FDA approved for use in second line advanced or metastatic urothelial carcinoma with *FGFR2* or *FGFR3* alterations.⁴¹ Pemigatinib, a potent FGFR1-4 inhibitor, was granted FDA and EMA approval in second line treatment for patients with advanced cholangiocarcinoma harbouring *FGFR2* mutations.⁴² Infigratinib (BGJ398), a FGFR1-3 inhibitor was FDA approved in May 2021 for second line treatment in advanced cholangiocarcinoma with *FGFR2* fusions,⁴³ and is being compared to chemotherapy in the randomised phase III PROOF trial (NCT03773302). Derazantinib (ARQ087), a competitive pan FGFR inhibitor, predominantly targeting FGFR1-3 but also colony stimulating factor-1-receptor (CSF1R) and VEGFR2 has been granted orphan drug designation by FDA and EMA in second line patients with intrahepatic cholangiocarcinoma harbouring FGFR2 abnormalities.⁴⁴ It is currently under investigation in the FIDES-02 trial (NCT03230318) for advanced urothelial cancers and FIDES-03 for advanced GC (NCT04604132).

Further refinement includes the development of irreversible FGFR inhibitors. These inhibitors form a covalent bond and cannot be readily displaced by ATP which aims to provide longer duration of activity.⁴⁵ Futibatinib (TAS-120) is an example of this, binding covalently to ATP resulting in irreversible inhibition of FGFR1 to FGFR4.⁴⁶ Following the Phase II FOENIX-CCA2 trial, futibatinib was granted break through designation by the FDA for use in previously treated locally advanced or metastatic cholangiocarcinoma with FGFR fusion or rearrangement.⁴⁷

The frequently reported toxicities associated with TKIs comprise hyperphosphataemia, stomatitis, palmar-plantar syndrome, nail toxicity, ocular toxicities including retinal detachment, alopecia, fatigue, and gastro-intestinal toxicity including nausea, abdominal pain or altered bowel habit.³⁹ In general, these are manageable with phosphate binders and supportive interventions.⁴⁶

Monoclonal Antibodies

Another strategy for inhibiting the FGFR pathway is targeting the extra-cellular domain using monoclonal antibodies or antibody drug conjugates (ADC). Monoclonal antibodies target a certain FGFR and interferes with ligand binding and receptor dimerization. Bemarituzumab (FPA144), is a humanised monoclonal antibody (IgG1 isotype) which targets the FGFR2b receptor, specifically targeting the third immunoglobulin region of the FGFR2b receptor isoform, which is responsible for ligand specificity.⁴⁸ Bemarituzumab blocks FGF ligands from binding to the receptor, inhibiting downstream pro-tumour signalling by preventing receptor dimerization, decreasing FGFR2b phosphorylation and subsequent phosphorylation of the downstream effector, FRS2.⁴⁹ Unlike small molecule FGFR TKIs, blocking signalling via this route may improve the side effect profile for bemarituzumab as monotherapy or in combination with chemotherapy. Additionally, bemarituzumab promotes antibody-dependent cell (ADCC) mediated toxicity which is another mechanism of action that small molecule FGFR TKIs do not have.⁵⁰

Ligand Traps

The last approach to FGFR inhibition is to prevent FGF ligand binding to the receptor by developing ligand traps. The production of decoy receptors that expresses the extracellular kinase domain only, facilitates binding and trapping of FGF ligands, therefore suppressing FGF pathway activation and signalling.⁵¹ For example, FP-1039 is a ligand trap composed of a fusion between the FGFR1 extra-cellular domain and the human IgG1 Fc fragment, which in pre-clinical studies showed in vivo action against *FGFR2* mutated endometrial cells and lung cancer cells exhibiting *FGFR1* amplification.⁵²

In summary, the landscape of FGFR inhibitors has considerably evolved with an immensity of ongoing clinical development. FGFR inhibition continues to move toward increasing TKI kinase selectivity, creating stronger binding kinetics and interrupting FGF ligand binding and/or receptor dimerization. The sites of action on the FGF-FGFR pathway are outlined in Figure 2.

Targeting FGFR2 in Gastroesophageal Cancer: Clinical Evidence

In gastroesophageal cancer, *FGFR2* has emerged as a therapeutic target with numerous preclinical studies suggesting anti-tumour efficacy of FGFR inhibitors in *FGFR2* amplified GC models. There have been several phase II clinical trials, with some showing promising results and the first phase III trial is currently active. Despite these developments, no FGFR targeted treatment has been approved for *FGFR2* amplified gastroesophageal cancer to date. In this section we review past, current and potential future developments of *FGFR2* as a therapeutic target in gastroesophageal cancer.

Non-Selective TKIs

Dovitinib, an anti-angiogenic agent that inhibits multiple RTKs including FGFRs, PDGFRs and VEGFRs, has shown antitumour potential in preclinical models for various solid tumours.^{53,54} In a preclinical GC cell model study, dovitinib in combination with nab-paclitaxel exhibited an additive effect on tumour growth inhibition, resulting in tumour regression and improved survival in vivo models. In contrast, dovitinib monotherapy did not prolong survival. The synergistic effect of dovitinib in combination with cytotoxic chemotherapy may support a potential future treatment strategy.⁵⁵ The phase II trial, GASDOVI-1 trial (NCT01719549) evaluated the safety and efficacy of dovitinib in patients with chemorefractory metastatic gastric cancer whose tumours had *FGFR2* amplification. At present, there is no preliminary data despite closing several years ago.

Selective TKIs

AZD4547 is a pan FGFR-1,2,3 TKI that exhibited potent antitumour activity in *FGFR2* amplified GC in preclinical studies. AZD4547 inhibited phosphorylation of FGFR2 and its downstream signalling molecules, inducing apoptosis in gastric cell lines, resulting in tumour regression in vivo models.⁵⁶ The SHINE study, a small phase II randomized trial (n=71) evaluated the efficacy of AZD4547 versus paclitaxel in second-line treatment of gastroesophageal adenocarcinoma harbouring *FGFR2*-gene amplifications or *FGFR* polysomy detected by FISH. The trial did not meet the primary endpoint as it failed to demonstrate a PFS benefit in patients randomized to AZD4547 compared to paclitaxel (1.8 vs 3.5 months, HR 1.57, $p=0.95$).⁵⁷ An exploratory analysis revealed marked subclonal heterogeneity of the tumour sections

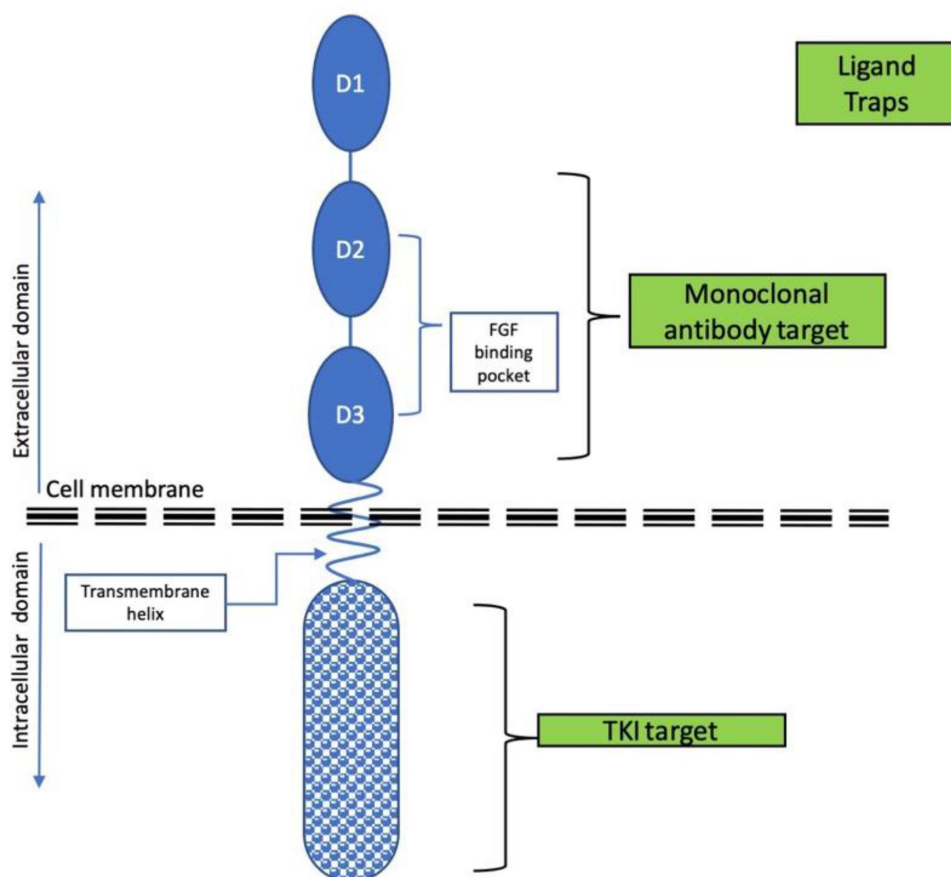


Figure 2 The FGFR structure and targets for FGFR inhibition. FGFRs are composed of a large extra-cellular ligand binding domain, a single transmembrane helix and an intracellular kinase domain. The extracellular domain consists of three immunoglobulin like sub-units (D1-D3), with D2 and D3 forming the FGF binding pocket. TKIs act via competitive ATP inhibition at the ATP binding site on the intracellular kinase domain. Monoclonal antibodies target the extra-cellular domain, competitively inhibiting FGFs and preventing ligand binding. In addition, monoclonal antibodies promote antibody dependent cell mediated toxicity. Ligand traps present decoy receptors which trap FGF ligands and prevent formation of the FGF-FGFR complex.

that displayed *FGFR2* amplification with poor concordance between amplification/polysomy and *FGFR2* mRNA expression using FISH testing, representing the need for an alternative biomarker test.⁵⁷

A multi-cohort, phase II trial investigated AZD4547 monotherapy in FGFR dysregulated tumours. *FGFR1/2* amplification was assessed using FISH and of the 288 patients screened, 12/138 (9%) gastroesophageal cancer patients had an *FGFR2* amplification, with 7/138 (5%) having high-amplification, defined as a ratio of *FGFR2* gene to chromosome-10 centromere signals > 5. The objective response rate (ORR) was 33% (3/9) in *FGFR2* amplified GC and the mean duration of response was 5.7 months in the responders.⁵⁸ All three responding patients had high-level *FGFR2* amplification as detected by digital droplet PCR (ddPCR) assessment of ctDNA, suggesting a potential role for liquid biopsy as a patient selection tool.⁵⁹ High-level *FGFR2* amplification was also associated with sensitivity to FGFR inhibition; the responders exhibited tumours with clonal homogeneously amplified tumours (>99% of tumour cells *FGFR2* amplified) while those who did not respond exhibited subclonal heterogeneity or low-level amplification. In the same study using cell lines and patient derived xenograft models, high-level *FGFR2* amplification initiated a distinct oncogene addiction phenotype, characterized by FGFR2-mediated transactivation of alternative receptor kinases, bringing PI3K/mTOR signalling under FGFR control.⁵⁹ Screening for high-level *FGFR2* amplifications in ctDNA is an area of development and it may identify potential responders. Whilst for an individual patient the relative incidence of these molecular aberrations is low, on a global scale for a global population, this represents a meaningful benefit.

Recently results were presented from a small phase Ib study (n=21) using a compound alofanib (RPT835), a small molecule allosteric inhibitor of FGFR2-IIIC and IIIB isoforms with IC₅₀ < 10 nM in patients with metastatic gastric adenocarcinoma who had progressed on one or more line of systemic therapy. Noting they did not assess for FGFR

mutations or amplifications, preliminary signs of clinical activity was observed with an ORR of 9.5% (2/21) and disease control rate of 71%. No dose limiting toxicities were reported and the recommended phase II dose was established.⁶⁰

Derazantinib has shown anti-tumour activity in GC murine models⁶¹ and has been shown to inhibit CSF1R and downregulate immunosuppressive macrophage activity which may improve susceptibility to therapeutic immune check-point blockade with PD-L1 antibodies.^{62,63} Derazantinib is currently being investigated in a phase Ib/II trial. It consists of three sub-studies which will evaluate derazantinib as monotherapy and in combination with paclitaxel and ramucirumab and/or atezolizumab in previously treated patients with advanced GC or GEJ adenocarcinoma harbouring *FGFR2* gene aberrations confirmed using next-generation sequencing (NGS) of ctDNA. (NCT04604132, FIDES-03).

Futibatinib (TAS-120) is an irreversible selective FGFR inhibitor that demonstrated potent anti-tumour activity in vitro and in vivo models. In the first in human study which analysed 36 patients with FGFR gene abnormalities, six patients were gastroesophageal (gastric; n=3, oesophageal; n=3). A clinical response was shown in one of each tumour type with both harbouring *FGFR2* amplification. In a larger Phase I study consisting of 170 patients treated with futibatinib, nine patients (5%) had GC and two had partial responses with an ORR of 22%.⁶⁴ Futibatinib is being investigated in advanced GC and GEJ cancers with *FGFR2* gene amplifications (target n=35) in a Phase II, multi-cohort clinical trial where the primary endpoint is ORR (NCT04189445).

Infigratinib (BGJ398) is another TKI being investigated in a phase II, single-arm basket trial in patients with locally advanced or metastatic GC or GEJ cancer with *FGFR2* amplification detected by FISH, or other advanced solid tumours with other FGFR alterations who have failed second line treatments (NCT05019794).

Monoclonal Antibodies

Aprutumab ixadotin (BAY 1187982) was the first ADC to target FGFR2 comprising a fully human anti-FGFR1 monoclonal antibody (BAY 1179470) linked to an auristatin-like cytotoxic payload. Preclinical data demonstrated tumour growth inhibition or regression of cell lines in gastric and breast cancer, leading to the first-in-human phase I trial.⁶⁵ Of the twenty patients enrolled, two were GC patients and no responses were reported. The safety profile differed to the preclinical study, and consequently the trial terminated early due to dose-limiting toxicities such as proteinuria, nephropathy, thrombocytopenia and corneal epithelial microcysts.⁶⁶

The FGFR2b selective antibody bemarituzumab (FPA144) has demonstrated promising clinical efficacy in GC patients harbouring *FGFR2* amplification or FGFR2b overexpression. Bemarituzumab monotherapy initially showed tolerability and efficacy in patients with late-line advanced gastroesophageal adenocarcinoma (GEA) who had FGFR2b overexpression in a phase I escalation and expansion study (n=79). Patients were stratified into four cohorts (n=28) based on the level of expression using IHC. Anti-tumour activity was observed in high FGFR2b overexpressing GEA, defined as $\geq 10\%$ of tumour cells with 3+ membranous staining, (n=5) with an ORR of 17.9% and a DCR of 64.3%.⁶⁷ The ORR compares favourably to immunotherapy (11–15%).^{9,68}

This provided the rationale for a combination strategy of bemarituzumab with chemotherapy.^{69,70} The phase II FIGHT trial, a global, randomised, double-blinded, placebo-controlled trial evaluated mFOLFOX6 with or without bemarituzumab in patients with untreated, *HER2* negative, advanced FGFR2b positive gastric or GEJ cancer. Eligible patients had tumours with FGFR2b overexpression detected using IHC (2+/3+) or *FGFR2* gene amplification by ctDNA.⁷¹ It was initially set out to be a registrational phase III trial enrolling 550 patients, however it was changed to a phase II proof-of-concept study after 155 patients were randomized. Patients with GC (n=910) were pre-screened and 275 (30.2%) were FGFR2b positive. Of the 155 randomized, 149 (96%) were FGFR2b positive by IHC, 26 (17%) were *FGFR2* gene amplified by ctDNA and 20 (13%) by both methods. The primary endpoint was met demonstrating a PFS benefit of 2.1 months (9.5 months in the bemarituzumab arm versus 7.4 months in the control arm, HR 0.68, $p=0.07$). With a median follow up of 12.5 months, the bemarituzumab arm had a median overall survival (mOS) of 19.2 months versus 13.5 months in the placebo arm (HR 0.6, 95% CI: 0.38, 0.94).⁷² Among those with measurable disease, the ORR was higher in the bemarituzumab arm, showing an improvement from 40% to 53%.⁷¹ The rate of grade ≥ 3 adverse events (AEs) were 83% versus 74% in the bemarituzumab and placebo arms with serious AEs in 32% and 36% respectively. Stomatitis and corneal AEs were the most common AEs for bemarituzumab. In contrast to FGFR-TKIs, there were no reported AEs of retinal detachment or hyperphosphatemia.⁷¹ An exploratory analysis showed in a subset of patients (n=96) with IHC 2+/3+ staining in $\geq 10\%$ tumour cells, a profound improvement in mOS was observed

(25.4 months in bemarituzumab arm versus 11.1 months for placebo, HR 0.41). Although a more meaningful benefit was observed in those with FGFR2b overexpression and ctDNA gene amplification (IHC+/ctDNA+; PFS HR 0.15 and OS HR 0.10), patients benefited from bemarituzumab irrespective of ctDNA gene amplification (IHC+/ctDNA-; PFS HR 0.63 and OS HR 0.66), supporting further evaluation of bemarituzumab without the gene amplification requirement.⁷²

The FIGHT study has identified a new biomarker for gastroesophageal cancer for molecular targeted therapy. The positive phase II results support the larger, ongoing randomized phase III trial where the target recruitment is 516 and the primary endpoint is OS (FORTITUDE-101, NCT05052801).^{48,71,72} As already highlighted, FGFR2b positive GC is associated with worse survival³⁶ and the combination strategy of bemarituzumab with cytotoxic chemotherapy may improve outcomes in this important subgroup.

Future Developments

From an immunogenic perspective, the role of immunotherapy in FGFR2 gastroesophageal cancer is an area of interest. The GS genomic subtype shares similarities with diffuse-type GC.⁷³ Bemarituzumab is glycoengineered for enhanced ADCC which in vivo models resulted in tumour burden reduction, recruitment of natural killer (NK) cells to the tumour and an influx of PD-L1 expressing cells within the tumour microenvironment. For FGFR2b positive GC, the enhanced ADCC activity from bemarituzumab may reprogram the tumour microenvironment, making these tumours immune “hot” subsequently leading to enhanced anti-tumour activity when combined with PD-1 blockade.⁷⁴ This preclinical data supports the rationale of FORTITUDE-102, a phase Ib/III trial in set up which will compare bemarituzumab plus chemotherapy and nivolumab versus chemotherapy and nivolumab for FGFR2b overexpressed untreated advanced gastric and GEJ cancer (NCT05111626).

The distinct role of FGFR2 in ESCC is still under early investigation. Various preclinical studies have identified potential targetable pathways, however more robust developments are required to understand its clinical significance. A Japanese study demonstrated that FGFR2-AKT signalling was a driver of keratinocyte differentiation suggesting that activation of FGFR2-AKT signalling could be a future therapeutic option for targeting cancer-like stem cells in ESCC.^{75,76} FGFR2 and its upstream regulator miR-671-5p was explored in human ESCC tissue and their matched normal oesophageal tissue (n=35), and an association was observed between higher levels of FGFR2 and lower levels of miR-671-5p. High levels of FGFR2 led to ESCC progression due to activation of the ERK and AKT pathway, while high levels of miR-671-5p specifically reduced the expression of FGFR2. In turn, this led to suppressed progression in vitro and in vivo models, suggesting another prospective treatment approach.⁷⁷

Commensurate with the growth of novel FGFR drugs, directed therapy against FGFR2 in GC has emerged with several small-molecule TKIs and monoclonal antibodies under clinical investigation for treatment of advanced or unresectable GC harbouring *FGFR2* amplification or FGFR2b overexpression (Table 2). FGFR2b overexpression has surfaced as a potential biomarker for molecular targeted therapy in GC but more robust data is needed to constitute its prognostic value, thus results from the first phase III are eagerly awaited.

Challenges in FGFR Positive Gastroesophageal Cancer

Akin to *HER2* amplification or overexpression in gastroesophageal cancer,⁷⁸ tumour heterogeneity is a challenge and has potential to affect the accuracy of *FGFR2* amplification or FGFR2 overexpression detection in tumour tissue and have implications for therapeutic targeting.⁷⁹ This was highlighted in a study of 188 resected GC patients employing FISH, *FGFR2* mRNA ISH and FGFR2-IIIb splice variant IHC staining. Heterogeneity of FGFR2b protein and FGFR2 mRNA overexpression was observed in 55.5% and 85.7% cases, respectively.³⁶ *FGFR2* amplification and expression by IHC can be discordant in ~25% of primary and metastatic lesions.^{13,36} As tissue heterogeneity poses challenges for molecular diagnostic testing, ctDNA is under investigation as a convenient modality with detection rates comparable or higher than tissue-based methods. In the GOZILA study which enrolled 365 patients with advanced GC, *FGFR2* amplification was more frequently detected by Guardant360 ctDNA sequencing (28, 7.7%) compared to tissue-based methods alone (2.6–4.4%). Furthermore, in a paired tissue and plasma cohort (n=44), six additional cases of *FGFR2* amplification were detected by ctDNA which were not detectable by tissue biopsy.⁸⁰ This provides a rationale for potentially selecting patients by either tissue or blood, or both. Assessing amplification clonality in plasma ctDNA is also important as it may predict durable treatment responses to FGFR inhibition. In addition, use of automated in situ heterogeneity mapping by FISH has a potential application in screening patients for rare amplifications.^{58,59}

Table 2 Selected Drugs Targeting FGFR2 Currently Under Investigation in Clinical Trials

Drug	Cancer Type	Phase	Population; Gene Target	Treatment Arms	Primary Outcome	Trial ID
Tyrosine kinase inhibitors						
AZD4547	Urothelial carcinoma	I	≥2nd line, advanced; <i>FGFR2/3</i> gene alterations	AZD4547 monotherapy	DLT	NCT05086666
Infgratinib	CCA	III	1st line, advanced; <i>FGFR2</i> fusion or rearrangement	Infgratinib vs chemotherapy	OS	NCT03773302 (PROOF)
	Gastric or GEJ cancer, solid tumours	II	≥3rd line, advanced; <i>FGFR2</i> amplification or <i>FGFR1-3</i> fusions/rearrangements/mutation	Infgratinib monotherapy	ORR	NCT05019794
Pemigatinib	CCA	III	1st line, advanced; <i>FGFR2</i> rearrangement	Pemigatinib vs chemotherapy	PFS	NCT03656536 (FIGHT-302)
	Colorectal cancer	II	Chemorefractory, advanced; <i>FGFR</i> alterations	Pemigatinib monotherapy	ORR	NCT04096417
Derazantinib	Intrahepatic CCA	II	2nd line, advanced; <i>FGFR2</i> mutation or amplifications	DZB monotherapy	ORR	NCT03230318 (FIDES-01)
	Gastric or GEJ cancer	II	2nd line, advanced <i>HER2</i> - negative; <i>FGFR2</i> translocation or amplifications	DZB monotherapy and in combination with ramucirumab + paclitaxel + atezolizumab	ORR	NCT04604132 (FIDES-03)
	Urothelial carcinoma	II	1st and 2nd line, advanced; <i>FGFR</i> aberrations	DZB monotherapy, DZB ± atezolizumab	ORR	NCT04045613 (FIDES-02)
Futibatinib	Intrahepatic CCA	III	1st line, advanced; <i>FGFR2</i> rearrangements	Futibatinib vs chemotherapy	PFS	NCT04093362 (FOENIX-CCA3)
	Gastric or GEJ cancer, solid tumours, MLN	II	2nd line, advanced; <i>FGFR2</i> amplification, <i>FGFR</i> rearrangements, <i>FGFR1</i> rearrangements	Futibatinib monotherapy	ORR	NCT04189445
	Breast cancer	II	Chemorefractory, advanced; <i>FGFR1</i> high-amplification or <i>FGFR2</i> amplification	Futibatinib monotherapy and in combination with fulvestrant	ORR	NCT04024436 (FOENIX-MBC2)
Erdafitinib	Gastric, oesophageal, NSCLC, urothelial, CCA	II	Chemorefractory, advanced; <i>FGFR</i> alterations	Erdafitinib monotherapy	ORR	NCT02699606
	Urothelial carcinoma	II	2nd line, advanced; <i>FGFR</i> alterations	Erdafitinib monotherapy	ORR	NCT04083976
Monoclonal antibodies						
Bemarituzumab	Gastric or GEJ cancer	III	1st line, advanced; <i>FGFR2</i> amplification by ctDNA or <i>FGFR2b</i> overexpression by IHC	Bemarituzumab plus chemotherapy vs chemotherapy	OS	NCT05052801

Overcoming acquired resistance is a known challenge with most targeted treatments. FGFR kinase mutations are the most common mechanisms of FGFR-TKI acquired resistance which is illustrated mainly in *FGFR2* altered cholangiocarcinoma studies.⁸¹ In vitro studies have identified gatekeeper mutations which induce resistance to FGFR inhibition,⁸² by interfering with TKI access to the hydrophobic ATP binding site.⁸³ Considering the emergence of gatekeeper mutations in FGFRs, focus should continue the development of irreversible covalent FGFR inhibitors, such as futibatinib, to overcome such resistance.⁸⁴ Epithelial-mesenchymal transition (EMT), a complex molecular phenomenon associated with metastasis, poor prognosis, and drug resistance to conventional and targeted therapies, emerged as a potential mechanism of acquired resistance in a study using *FGFR2* amplified resistant GC cell lines. Activation of EMT was associated with loss of *FGFR2* expression and reduced expression/activation of transmembrane receptors such as MET, HER2, HER3 and EGFR.^{85,86} This potential clinically significant finding warrants further evaluation and there may be opportunity for this through exploratory analyses of the active clinical trials. For *FGFR2* GC, the main challenge is inherent resistance. In advanced GC, preclinical studies identified novel fusions such as JHDM1D-BRAF and *FGFR2*-ACSL5 which confer resistance in gastric cell lines.^{87,88} Other mutations have the potential to induce resistance through upregulation of signalling pathways that bypass FGFR inhibition. For example, in a preclinical study using gastric cell models of diffuse-type GC, primary drug resistance to AZD4547 was observed through switching to a protein kinase C (PKC)-mediated inhibition of GSK3 β to gain a survival advantage.⁸⁹ Increased activation of the MAPK-ERK pathway has also shown a role in FGFR resistance.^{31,90–92} It has been suggested that a combinational approach with dual FGFR and MEK inhibition may be a therapeutic strategy to overcome resistance.³¹

Conclusion

The aberrant FGFR pathway has led to an abundance of novel targets, with drug development evolving to refine multi-target kinase inhibitors to more selective TKIs and monoclonal antibodies, to minimise toxicity profiles. In *FGFR2b* gastroesophageal cancer, the phase III FORTITUDE-101 (previously FIGHT) trial has potential to result in the approval of bemarituzumab in combination with chemotherapy for *FGFR2b* positive GC. Bemarituzumab also brings hope for the under investigated diffuse-type GC where it may modify the immune tumour microenvironment and in future provide a strategy for a combinational approach with immunotherapy. Whilst gastroesophageal cancer is a heterogenous disease, further research, and validation of ctDNA methods is needed to establish a standardized patient selection tool. Although there are currently no *FGFR2* approved therapies available in gastroesophageal cancer, there are multiple active trials which if positive, have the potential to change the treatment paradigm for an important subgroup of patients.

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