FGFR Pathway Inhibition in Gastric Cancer

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Gastric cancer (GC) is the third leading cause of cancer-associated death worldwide. The majority of patients are diagnosed at an advanced/metastatic stage of disease due to a lack of specific symptoms and lack of screening programs, especially in Western countries. Thus, despite the improvement in GC therapeutic opportunities, the survival is disappointing, and the definition of the optimal treatment is still an unmet need. Novel diagnostic techniques were developed in clinical trials in order to characterize the genetic profile of GCs and new potential molecular pathways, such as the Fibroblast Growth Factor Receptor (FGFR) pathway, were identified in order to improve patient's survival by using target therapies. The aim of this review is to summarize the role and the impact of FGFR signaling in GC and to provide an overview regarding the potential effectiveness of anti-FGFR agents in GC treatment in the context of precision medicine.

gastric cancer FGFR fusions

1. Introduction

Gastric cancer (GC) is the third leading cause of cancer-associated death worldwide following lung and colorectal cancer [1]. Interestingly, its incidence varies geographically across the globe. While in Western countries, the incidence of GC decreased over the past decades, the numbers of newly diagnosed GC cases increased, especially in Asia and Africa [2][3][4]. Next to *Helicobacter Pylori* infection, lifestyle factors, such as alcohol intake and smoking, as well as genetic risk factors have been associated with GC development [5][6][7][8].

Unfortunately, the majority of patients are diagnosed within an advanced stage of disease [9]. In metastatic GC (mGC), systemic chemotherapy remains the standard of care [10], with median overall survival (OS) around 12 months when treated with combinational cytotoxic agents [10]. Thus, to improve patients' survival, understanding the molecular mechanisms leading to GC development is of great importance.

Histopathological and molecular intra- and intertumoral heterogeneity are major hallmarks of GC and histological classifications, such as Laurén, are not sufficient to stratify patients towards a personalized treatment management [11]. Using novel diagnostic techniques, such as next generation sequencing, the characterization of genetic profile of GCs yielded potential novel therapeutic targets [12][13][14].

One of the first targeted treatments approved in GC was the monoclonal antibody trastuzumab that targets the Human Epidermal Receptor 2 (HER2). HER2 is overexpressed or amplified in 12–20% of all GC cases [15]. Trastuzumab in combination with chemotherapy showed an improved OS and progression-free survival (PFS) in

patients harboring a HER2-positive mGC within the phase III ToGA trial [16]. Furthermore, GCs showing a microsatellite instable-high (MSI-H) or a damaged mismatch repair genes (dMMR) status are sensitive to immune checkpoint inhibitor treatment [17]. The anti-Programmed Cell Death 1 (PD-1) antibody pembrolizumab yielded an impressive response and extension of survival in MSI-H/dMMR mGC patients [18].

In this perspective of precision oncology, various new potential molecular pathways could represent novel targets for drug development in GC, such as the Fibroblast Growth Factor Receptor (FGFR) one [19]. Therefore, this review aims to summarize the role and impact of FGFR signaling and to highlight the effectiveness of anti-FGFR therapeutics in GC.

2. The FGFR Signaling Pathway and Its Alterations in Gastric Cancer

The FGFR has four notable family members, namely FGFR-1, FGFR-2, FGFR-3 and FGFR-4 [20]. The substrate-binding selectivity and tissue distribution of these receptors are different for each receptor [21]. Another source of heterogeneity and ligand-specificity originates from alternative splicing; the four FGFR genes may splice into 48 distinct isoforms [22]. The receptor has three main components: the three extracellular Ig-like domains, a transmembrane helix, and an intracellular tyrosine kinase domain. Alternative splicing of the IgIII loop regulates the FGFR's ligand specificity, resulting in b- and c-variants of the receptors with different biological effects. These splice variants' tissue-specific expression controls interactions in embryonic development, tissue maintenance and repair, and cancer. The IIIb variant is principally expressed by epithelial cells, while IIIc is expressed by mesenchymal cells. The formation of the IIIb and IIIc splice variants are mutually exclusive (**Figure 1**a) [23].

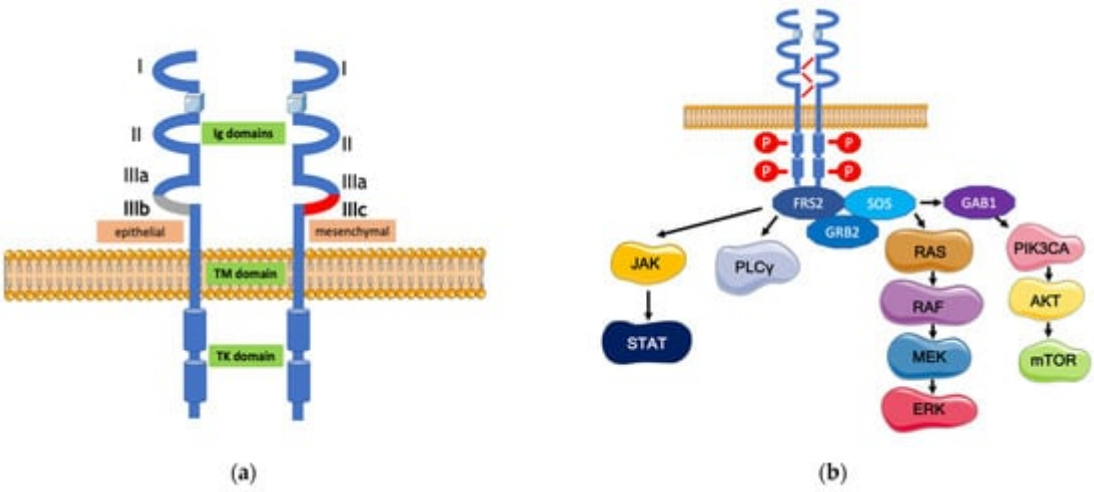

Figure 1. FGFR structure and pathway. (**a**) FGFR structure: FGFR contains three extracellular Ig domains (domains I, II, and III), a single transmembrane helix domain and an intracellular tyrosine kinase domain. The acidic box region between Ig I and II domains can interact with substances other than FGFs. The FGF binding sites are located in domains II and III. For FGFR1-3, the alternative splicing of the second half of the Ig III domain is tissue-dependent. In the case of FGFR4, FGFR contains a single homologous FGFR-IIIc isoform. (**b**) FGFR

pathway: Activation of the FGFR tyrosine kinase domain may activate several cellular pathways, including the RAS-RAF-MEK-ERK, the PIK3CA-AKT-mTOR, and the JAK pathways through the FGFR-associated cytosolic docking protein FRS2.

Beyond the heterogeneity of the receptors, several fibroblast growth factors (FGFs) as ligands may activate each receptor, and some FGFs can also activate several other receptors. In particular, FGFs are the most extensive family of growth factor ligands. The structurally related FGF ligands are further subdivided according to their sequence homology [21][24]: FGFs 1–10 and 16–23 are ligands for the FGFR, whereas FGFs 11–14 are cytosolic FGF molecules that operate independently of the receptor [25].

FGFRs may form both homodimers and heterodimers that are stabilized by a heparin sulfate proteoglycan (HSPG) during activation [26]. When FGFRs are activated, their phosphorylated intracellular tyrosine kinase domain may activate several cellular pathways, including the RAS-RAF-MEK-ERK, the PIK3CA-AKT-mTOR and the JAK pathways. The activation of these downstream pathways requires using the FGFR-associated cytosolic docking protein FRS2 and its interaction with other proteins (GRB2, SOS, GAB1, and phospholipase C gamma) [27][28][29][30][31]. Activating these entire signaling pathways may influence angiogenesis, mitogenesis, differentiation, proliferation, changes in tissue homeostasis, and invasion processes (**Figure 1**b).

Gene fusions, translocations, mutations and amplifications of the FGFR gene have all been reported in cancer. Notably, amplification of the FGF genes was also reported. According to the comprehensive review by Helsten et al., FGFR1 mutations, FGFR2 amplifications and FGFR3 rearrangements are the most common FGFR alterations in GC. These alterations may sometimes be discovered as co-occurring concurrently [32].

A recent article from China summarized the alterations of the FGFR1-4 genes in 5557 solid tumors, including 254 cases of GC. In this analysis, FGFR1-4 aberrations occurred in 12.2% of the GC samples. Amplifications were most prevalent, followed by rearrangements and mutations. Most frequent alterations were detected in the FGFR2 gene, followed by the FGFR1, and to a lesser extent in FGFR3 and FGFR4 genes [33].

Another retrospective analysis identified FGFR alterations in 7% (745/10,582) of GC cases [34]. FGFR2 amplifications are more common in microsatellite-stable (MSS) and TP53 mutant, or MSS/epithelial-mesenchymal transition (EMT) subtypes, according to the Asian Cancer Research Group (ACRG) classification [35]. As per TCGA classification, FGFR2 amplifications are more common in the chromosomal instability (CIN) and genomically stable (GS) subtypes [12][36].

In a study of Chinese patients with GC, FGFR2 amplification was found in 4.1 percent (11/267) of GC cases, especially in the diffuse histology subtype [37]. Another study identified 20% (5/25) of GC to carry the potentially targetable FGFR3-TACC3 (F3T3) fusion [38][39].

Acquired fusions may lead to acquired resistance to FGF-directed therapy. In the case of FGFR2 inhibition of amplified GC, the development of specific fusion proteins may lead to acquired resistance to FGFR2 inhibition. An

example of this is the FGFR2-ACSL5 fusion protein, which has been demonstrated to lead to resistance by Kim et al. [40].

According to a preclinical study, another mechanism of acquired resistance to FGFR2 inhibition may be the emergence of a JHDN1D-BRAF fusion, leading to the stimulation of the RAF-MEK pathway. This finding could give a therapeutic basis for employing MEK or RAF inhibitors to prevent resistance from developing or to treat patients who have developed acquired resistance due to the JHDN1D-BRAF fusion [41].

3. A Pharmacological Overview on the Anti-FGFR Agents

FGF is a growth protein secreted from fibroblasts and stored near the basal membrane of endothelial cells. As already mentioned, the activation of the FGFR pathway can affect endothelial cell proliferation and differentiation [39], which both are important for embryonic development, wound healing and intra-tumoral angiogenesis [42]. Modulation of endothelial biology and angiogenesis in cancer is common practice since the appearance of vascular endothelial growth factor blockers (VEGFs). Anti-VEGFs are the main anti-angiogenic agents used in the management of gastrointestinal malignancies, even if the results in GC patients were under the expectations [19]. In this regard, the interest in tumor microenvironment as an active player in the process of tumorigenesis and metastatization has led to identify some new molecules that could be targeted with novel drugs. In particular, available data demonstrated that FGF-2/FGFR-2 interaction might bypass the role of the VEGF/VEGFR pathway, acting as a playmaker in the process of angiogenesis and proliferation, especially in GC [19].

Based on this background, several FGFR inhibitors are being developed. TKIs are the most common FGFR antagonists, especially for pretreated cancers with intrinsic resistance to chemotherapy and target therapy [43]. First-generation TKIs are multi-target inhibitors that include the four main isoforms of FGFR and other signaling proteins of the tumor microenvironment, such as VEGFR, KIT, and RET. The multikinase inhibition was associated with severe adverse effects in the landmark trials that limited their clinical use [20]. Since then, refinement of molecular techniques for the design of target-specific molecules and careful selection of patients have demonstrated the potential benefit of FGFR blockade in the growing portfolio of cancer drugs, especially in tumors with poor survival, such as cholangiocarcinoma [44]. A recent study showed that among patients with tumors driven by FGFR aberrations, 76% would be considered ineligible for target therapy due to currently approved indications, comprising 15 different tumor types, potentially susceptible to therapy with TKIs [45].

Among the newer molecules, erdafitinib and pemigatinib are the two TKIs with accelerated regulatory approval, decreasing cell viability by inhibiting FGFR phosphorylation and block signaling. Both medications are contingent upon FGFR alterations; therefore, they are not active in the absence of these alterations [46]. Erdafitinib is an orally active small potent TKI of FGFR1–4. In vivo data shows that it is a potent and selective pan-FGFR inhibitor, including downstream signaling, resulting in a potent anti-proliferative activity, and its intracellular lysosomal localization results in sustained pathway inhibition, with Growth Inhibition 50% (GI50 or IC50) values of 1.2, 2.5, 3.0, and 5.7 nM/L for FGFR1-4 respectively [47]. The results observed in advanced urothelial carcinoma with FGFR2 and FGFR3 genetic alterations granted it accelerated approval by regulating agencies [48].

Pemigatinib is another orally active agent that targets FGFR1, 2 and 3 with IC50 values of less than 2 nM. Pemigatinib also inhibits FGFR4 in vitro at a much higher concentration than those that inhibit FGFR1, 2, and 3. [49]. After the results of the Fight-202 trial, pemigatinib received accelerated approval by the American food and drug administration (FDA) and conditional marketing authorization by the European medicines agency (EMA) for cholangiocarcinoma harboring FGFR2 rearrangements or fusions [50].

Monoclonal antibodies have also represented a breakthrough in advanced esophagogastric and GC protocol designs. Bemarituzumab, an IgG1 antibody targeting FGFR2b ligand-binding domain, blocks ligand-dependent activation of FGFR2b by interfering with the union to FGF; it also mediates antibody-dependent cytotoxicity [51].

References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. CA Cancer J. Clin. 2021, 71, 7–33.
2. Balakrishnan, M.; George, R.; Sharma, A.; Graham, D.Y. Changing Trends in Stomach Cancer throughout the World. Curr. Gastroenterol. Rep. 2017, 19, 36.
3. Luo, G.; Zhang, Y.; Guo, P.; Wang, L.; Huang, Y.; Li, K. Global patterns and trends in stomach cancer incidence: Age, period and birth cohort analysis. Int. J. Cancer 2017, 141, 1333–1344.
4. Petrillo, A.; Smyth, E.C. 27 years of stomach cancer: Painting a global picture. Lancet Gastroenterol. Hepatol. 2019, 5, 5–6.
5. Tan, P.; Yeoh, K.-G. Genetics and Molecular Pathogenesis of Gastric Adenocarcinoma. Gastroenterology 2015, 149, 1153–1162.e3.
6. Peek, R.M., Jr.; Blaser, M.J. Helicobacter pylori and gastrointestinal tract adenocarcinomas. Nat. Rev. Cancer 2002, 2, 28–37.
7. Tramacere, I.; Negri, E.; Pelucchi, C.; Bagnardi, V.; Rota, M.; Scotti, L.; Islami, F.; Corrao, G.; La Vecchia, C.; Boffetta, P. A meta-analysis on alcohol drinking and gastric cancer risk. Ann. Oncol. 2011, 23, 28–36.
8. Smyth, E.C.; Verheij, M.; Allum, W.; Cunningham, D.; Cervantes, A.; Arnold, D.; ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2016, 27 (Suppl. 5), v38–v49.
9. Muro, K.; Van Cutsem, E.; Narita, Y.; Pentheroudakis, G.; Baba, E.; Li, J.; Ryu, M.-H.; Zamaniah, W.I.W.; Yong, W.-P.; Yeh, K.-H.; et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: A JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann. Oncol. 2019, 30, 19–33.

10. Wagner, A.D.; Syn, N.L.; Moehler, M.; Grothe, W.; Yong, W.P.; Tai, B.C.; Hol, J.; Unverzagt, S. Chemotherapy for advanced gastric cancer. Cochrane Database Syst. Rev. 2017, 8, Cd004064.
11. Körfer, J.; Lordick, F.; Hacker, U.T. Molecular Targets for Gastric Cancer Treatment and Future Perspectives from a Clinical and Translational Point of View. Cancers 2021, 13, 5216.
12. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014, 513, 202–209.
13. Wang, J.; Xiu, J.; Baca, Y.; Battaglin, F.; Arai, H.; Kawanishi, N.; Soni, S.; Zhang, W.; Millstein, J.; Salhia, B.; et al. Large-scale analysis of KMT2 mutations defines a distinctive molecular subset with treatment implication in gastric cancer. Oncogene 2021, 40, 4894–4905.
14. Salem, M.E.; Puccini, A.; Xiu, J.; Raghavan, D.; Lenz, H.-J.; Korn, W.M.; Shields, A.F.; Philip, P.A.; Marshall, J.L.; Goldberg, R.M. Comparative Molecular Analyses of Esophageal Squamous Cell Carcinoma, Esophageal Adenocarcinoma, and Gastric Adenocarcinoma. Oncology 2018, 23, 1319–1327.
15. Van Cutsem, E.; Bang, Y.J.; Feng-Yi, F.; Xu, J.M.; Lee, K.W.; Jiao, S.C.; Chong, J.L.; López-Sanchez, R.I.; Price, T.; Gladkov, O.; et al. HER2 screening data from ToGA: Targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 2015, 18, 476–484.
16. Bang, Y.-J.; Van Cutsem, E.; Feyereislova, A.; Chung, H.C.; Shen, L.; Sawaki, A.; Lordick, F.; Ohtsu, A.; Omuro, Y.; Satoh, T.; et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 2010, 376, 687–697.
17. Petrillo, A.; Smyth, E.C. Biomarkers for Precision Treatment in Gastric Cancer. Visc. Med. 2020, 36, 364–372.
18. Chao, J.; Fuchs, C.S.; Shitara, K.; Tabernero, J.; Muro, K.; Van Cutsem, E.; Bang, Y.-J.; De Vita, F.; Landers, G.; Yen, C.-J.; et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA Oncol. 2021, 7, 895–902.
19. Gambardella, V.; Fleitas, T.; Tarazona, N.; Papaccio, F.; Huerta, M.; Roselló, S.; Gimeno-Valiente, F.; Roda, D.; Cervantes, A. Precision Medicine to Treat Advanced Gastroesophageal Adenocarcinoma: A Work in Progress. J. Clin. Med. 2020, 9, 3049.
20. Liu, F.-T.; Li, N.-G.; Zhang, Y.-M.; Xie, W.-C.; Yang, S.-P.; Lu, T.; Shi, Z.-H. Recent advance in the development of novel, selective and potent FGFR inhibitors. Eur. J. Med. Chem. 2019, 186, 111884.

21. Roskoski, R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol. Res. 2019, 151, 104567.
22. Roy Burman, D.; Das, S.; Das, C.; Bhattacharya, R. Alternative splicing modulates cancer aggressiveness: Role in EMT/metastasis and chemoresistance. Mol. Biol. Rep. 2021, 48, 897–914.
23. Holzmann, K.; Grunt, T.; Heinzle, C.; Sampl, S.; Steinhoff, H.; Reichmann, N.; Kleiter, M.; Hauck, M.; Marian, B. Alternative Splicing of Fibroblast Growth Factor Receptor IgIII Loops in Cancer. J. Nucleic Acids 2011, 2012, 950508.
24. Raju, R.; Palapetta, S.M.; Sandhya, V.K.; Sahu, A.; Alipoor, A.; Balakrishnan, L.; Advani, J.; George, B.; Kini, K.R.; Geetha, N.P.; et al. A Network Map of FGF-1/FGFR Signaling System. J. Signal Transduct. 2014, 2014, 962962.
25. Itoh, N.; Ornitz, D.M. Evolution of the Fgf and Fgfr gene families. Trends Genet. 2004, 20, 563–569.
26. Del Piccolo, N.; Sarabipour, S.; Hristova, K. A New Method to Study Heterodimerization of Membrane Proteins and Its Application to Fibroblast Growth Factor Receptors. J. Biol. Chem. 2017, 292, 1288–1301.
27. Ferguson, H.R.; Smith, M.P.; Francavilla, C. Fibroblast Growth Factor Receptors (FGFRs) and Noncanonical Partners in Cancer Signaling. Cells 2021, 10, 1201.
28. Ong, S.H.; Guy, G.R.; Hadari, Y.R.; Laks, S.; Gotoh, N.; Schlessinger, J.; Lax, I. FRS2 Proteins Recruit Intracellular Signaling Pathways by Binding to Diverse Targets on Fibroblast Growth Factor and Nerve Growth Factor Receptors. Mol. Cell. Biol. 2000, 20, 979–989.
29. Arkun, Y.; Yasemi, M. Dynamics and control of the ERK signaling pathway: Sensitivity, bistability, and oscillations. PLoS ONE 2018, 13, e0195513.
30. Mossahebi-Mohammadi, M.; Quan, M.; Zhang, J.-S.; Li, X. FGF Signaling Pathway: A Key Regulator of Stem Cell Pluripotency. Front. Cell Dev. Biol. 2020, 8, 79.
31. Mandal, S.; Bandyopadhyay, S.; Tyagi, K.; Roy, A. Recent advances in understanding the molecular role of phosphoinositide-specific phospholipase C gamma 1 as an emerging onco-driver and novel therapeutic target in human carcinogenesis. Biochim. Biophys. Acta Rev. Cancer. 2021, 1876, 188619.
32. Helsten, T.; Schwaederle, M.; Kurzrock, R. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: Biologic and clinical implications. Cancer Metastasis Rev. 2015, 34, 479–496.

33. Gu, W.; Yang, J.; Wang, Y.; Xu, J.; Wang, X.; Du, F.; Hu, X.; Guo, H.; Song, C.; Tao, R.; et al. Comprehensive identification of FGFR1-4 alterations in 5 557 Chinese patients with solid tumors by next-generation sequencing. Am. J. Cancer Res. 2021, 11, 3893–3906.
34. Sun, Y.; Li, G.; Zhu, W.; He, Q.; Liu, Y.; Chen, X.; Liu, J.; Lin, J.; Han-Zhang, H.; Yang, Z.; et al. A comprehensive pan-cancer study of fibroblast growth factor receptor aberrations in Chinese cancer patients. Ann. Transl. Med. 2020, 8, 1290.
35. Cristescu, R.; Lee, J.; Nebozhyn, M.; Kim, K.-M.; Ting, J.C.; Wong, S.S.; Liu, J.; Yue, Y.G.; Wang, J.; Yu, K.; et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat. Med. 2015, 21, 449–456.
36. Kuboki, Y.; Schatz, C.A.; Koechert, K.; Schubert, S.; Feng, J.; Wittemer-Rump, S.; Ziegelbauer, K.; Krahn, T.; Nagatsuma, A.K.; Ochiai, A. In situ analysis of FGFR2 mRNA and comparison with FGFR2 gene copy number by dual-color in situ hybridization in a large cohort of gastric cancer patients. Gastric Cancer 2017, 21, 401–412.
37. Matsumoto, K.; Arao, T.; Hamaguchi, T.; Shimada, Y.; Kato, K.; Oda, I.; Taniguchi, H.; Koizumi, F.; Yanagihara, K.; Sasaki, H.; et al. FGFR2 gene amplification and clinicopathological features in gastric cancer. Br. J. Cancer 2012, 106, 727–732.
38. Lee, S.J.; Hong, J.Y.; Kim, K.; Kim, K.-M.; Kang, S.Y.; Lee, T.; Kim, S.T.; Park, S.H.; Park, Y.S.; Lim, H.Y.; et al. Detection of Fusion Genes Using a Targeted RNA Sequencing Panel in Gastrointestinal and Rare Cancers. J. Oncol. 2020, 2020, 4659062.
39. Costa, R.; Carneiro, B.A.; Taxter, T.; Tavora, F.A.; Kalyan, A.; Pai, S.A.; Chae, Y.K.; Giles, F.J. FGFR3-TACC3 fusion in solid tumors: Mini review. Oncotarget 2016, 7, 55924–55938.
40. Kim, S.Y.; Ahn, T.; Bang, H.; Ham, J.S.; Kim, J.; Kim, S.T.; Jang, J.; Shim, M.; Kang, S.Y.; Park, S.H.; et al. Acquired resistance to LY2874455 in FGFR2-amplified gastric cancer through an emergence of novel FGFR2-ACSL5 fusion. Oncotarget 2017, 8, 15014–15022.
41. Zhou, Y.; Wu, C.; Lu, G.; Hu, Z.; Chen, Q.; Du, X. FGF/FGFR signaling pathway involved resistance in various cancer types. J. Cancer 2020, 11, 2000–2007.
42. Nienhüser, H.; Schmidt, T. Angiogenesis and Anti-Angiogenic Therapy in Gastric Cancer. Int. J. Mol. Sci. 2017, 19, 43.
43. Touat, M.; Ileana, E.; Postel-Vinay, S.; André, F.; Soria, J.-C. Targeting FGFR Signaling in Cancer. Clin. Cancer Res. 2015, 21, 2684–2694.
44. Facchinetti, F.; Hollebecque, A.; Bahleda, R.; Loriot, Y.; Olaussen, K.A.; Massard, C.; Friboulet, L. Facts and New Hopes on Selective FGFR Inhibitors in Solid Tumors. Clin. Cancer Res. 2019, 26, 764–774.

45. de Almeida Carvalho, L.M.; de Oliveira Sapori Avelar, S.; Haslam, A.; Gill, J.; Prasad, V. Estimation of Percentage of Patients with Fibroblast Growth Factor Receptor Alterations Eligible for Off-label Use of Erdafitinib. JAMA Netw. Open. 2019, 2, e1916091.
46. Weaver, A.; Bossaer, J.B. Fibroblast growth factor receptor (FGFR) inhibitors: A review of a novel therapeutic class. J. Oncol. Pharm. Pract. 2020, 27, 702–710.
47. Perera, T.P.; Jovcheva, E.; Mevellec, L.; Vialard, J.; De Lange, D.; Verhulst, T.; Paulussen, C.; Van De Ven, K.; King, P.; Freyne, E.; et al. Discovery and Pharmacological Characterization of JNJ-42756493 (Erdafitinib), a Functionally Selective Small-Molecule FGFR Family Inhibitor. Mol. Cancer Ther. 2017, 16, 1010–1020.
48. Loriot, Y.; Necchi, A.; Park, S.H.; Garcia-Donas, J.; Huddart, R.; Burgess, E.; Fleming, M.; Rezazadeh, A.; Mellado, B.; Varlamov, S.; et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N. Engl. J. Med. 2019, 381, 338–348.
49. Liu, P.C.C.; Koblish, H.; Wu, L.; Bowman, K.; Diamond, S.; DiMatteo, D.; Zhang, Y.; Hansbury, M.; Rupar, M.; Wen, X.; et al. INCB054828 (pemigatinib), a potent and selective inhibitor of fibroblast growth factor receptors 1, 2, and 3, displays activity against genetically defined tumor models. PLoS ONE 2020, 15, e0231877.
50. Vogel, A.; Sahai, V.; Hollebecque, A.; Vaccaro, G.; Melisi, D.; Al-Rajabi, R.; Paulson, A.S.; Borad, M.J.; Gallinson, D.; Murphy, A.G.; et al. LBA40—FIGHT-202: A phase II study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA). Ann. Oncol. 2019, 30, v876.
51. Xiang, H.; Chan, A.G.; Ahene, A.; Bellovin, D.I.; Deng, R.; Hsu, A.W.; Jeffry, U.; Palencia, S.; Powers, J.; Zanghi, J.; et al. Preclinical characterization of bemarituzumab, an anti-FGFR2b antibody for the treatment of cancer. mAbs 2021, 13, 1981202.