Precision Oncology for Hepatocellular Cancer: Slivering the Liver by FGF19–FGFR4–KLB Pathway Inhibition

Vivek Subbiah¹ and Sumanta K. Pal²

Summary: This issue reports two studies, one by Hatlen and colleagues and the other by Kim and colleagues, that detail the drug-development journey of the FGF19–FGFR4 inhibitor fosofomib (BLU-554), from identification of the drug to preclinical validation studies to finally the results of the proof-of-principle first-in-human phase I trial of this potent and selective, type I irreversible inhibitor of FGFR4. Moreover, Hatlen and colleagues also report a resistance mechanism acquired after therapy that targets selective FGFR4 inhibition, which validates FGF as a specific target in hepatocellular cancer.

See related article by Hatlen et al., p. 1686 (9).
See related article by Kim et al., p. 1696 (8).

O sliver of liver, Get lost! Go away!
You tremble and quiver, O sliver of liver
—"A Sliver of Liver"
Myra Cohn Livingston, 1926–1996

The identification of oncogenic activation of tyrosine kinases, such as mutations in the EGFR or BRAF genes, rearrangements of the NTRK genes, and mutations/rearrangements of RET, has enabled the development of targeted treatments for such pathway-aberrant cancers. However, such advances have had a limited impact on patients with hepatocellular carcinoma (HCC), the cancer with the second highest mortality in the world, with 700,000 deaths worldwide recorded every year. Patients with HCC have yet to derive meaningful durable benefit from selective biomarker-driven targeted therapy in this era of precision oncology (1). One major challenge in HCC has been absence of "druggable" alterations; that is, genes reported to be frequently mutated in HCC such as the alterations; that is, genes reported to be frequently mutated in HCC such as the TERT promoter, TP53, and CTNNB1 (β-catenin), have all remained formidable as targets with no effective drug (1). Additional aberrations identified through the efforts of The Cancer Genome Atlas include LZTR1, EEF1A1, SF3B1, SMARCA4, ALB, APOB, and CPS1, in addition to well-characterized driver oncogenes such as CCND1, FGFR1 (11q13.3), MYC (8q24.21), MET (7q13.2), VEGFA (6p21.1), and MCL1 (1q21.3; ref. 1). This wide variability in aberrations combined with the lack of effective drugs targeting them have resulted in a dearth of biomarker-driven drug therapy options in HCC. In fact, the four nonselective VEGF-based multikinase inhibitors (sorafenib, regorafenib, lenvatinib, and cabozantinib) that have been approved by the FDA in HCC are in use without a biomarker to guide this therapy selection. Furthermore, understanding of the response and resistance mechanisms to these multikinase inhibitors has yet to be elucidated. Immune checkpoint inhibitors indicated for HCC confer very modest activity, and more than ten nonspecific, phase III trials in all patients with HCC have failed to meet the primary end-point, warranting an urgent biomarker-driven therapy (2).

CHALLENGES OF DRUG DEVELOPMENT IN THE FGFR PATHWAY

The family of FGFs regulates multiple biological processes, including cell proliferation, migration, differentiation, apoptosis, metabolism, and angiogenesis. Consequently, aberrant activation of FGFR signaling has been implicated in several malignancies. The FGFR tyrosine kinase family consists of four members, FGFR1–4, which are activated through 22 different FGF ligands, highlighting the complexities, both known and unknown, of this pathway, as evidenced by the variable success of more than 20 compounds (Table 1) that have been in development to target FGFR (3–6). Several FGFR inhibitors that have entered early-phase trials have been limited by their nonselectivity and side effects from pan-FGFR inhibition, mainly from the on-target toxicity of hyperphosphatemia, leading to frequent treatment interruptions and dose reductions and thereby loss of efficacy (4). Indeed, in the landmark study of the FGFR inhibitor erdafitinib (Balversa) in FGFR3-mutant bladder cancer, nearly half of the patients had treatment-related adverse events of grade 3 or higher; nonetheless, given the confirmed response rate of 40% with a median overall survival of 13.8 months, erdafitinib became the first-ever biomarker-based drug to be approved in bladder cancer and the first-in-class FGFR inhibitor to receive approval (7). On the basis of observed toxicities, most FGFR inhibitor trials recommend mitigation strategies for these electrolyte imbalances, such as maintaining a low-phosphate
Table 1. Small-molecule FGFR inhibitors in clinical development and their measured in vitro IC$_{50}$ values compared with BLU-554 (fisogatinib)

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>FGF4 measured IC$_{50}$ (nmol/L, in vitro)</th>
<th>Measured IC$_{50}$ (nmol/L, in vitro)</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNJ-42756493 (erdafitinib, Balversa)*</td>
<td>5.7</td>
<td>FGFR1: 1.2</td>
<td>Janssen</td>
</tr>
<tr>
<td>BLU-554 (fisogatinib)</td>
<td>5</td>
<td>FGFR1: 6.24</td>
<td>Blueprint Medicines</td>
</tr>
<tr>
<td>BLU-9931</td>
<td>3</td>
<td>FGFR1: 591</td>
<td>Blueprint Medicines</td>
</tr>
<tr>
<td>H3B-6527</td>
<td>&lt;1.2</td>
<td>FGFR1: 320</td>
<td>H3 Biomedicine, Eisai Incorporation</td>
</tr>
<tr>
<td>PRN1371</td>
<td>19.3</td>
<td>FGFR1: 0.6</td>
<td>Principia Biopharma</td>
</tr>
<tr>
<td>TAS-120 (futibatinib)</td>
<td>8.3</td>
<td>FGFR1: 3.9</td>
<td>Taiho Oncology</td>
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<tr>
<td>INCB054828 (pemigatinib)</td>
<td>30</td>
<td>FGFR1: 0.4</td>
<td>Incyte Pharmaceuticals</td>
</tr>
<tr>
<td>AP24534 (ponatinib)</td>
<td>7.7</td>
<td>FGFR1: 2.2</td>
<td>Ariad Pharmaceuticals</td>
</tr>
<tr>
<td>ARQ 087 (derazantinib)</td>
<td>34</td>
<td>FGFR1: 4.5</td>
<td>ArQule</td>
</tr>
<tr>
<td>BIBF 1120 (nintedanib)</td>
<td>610</td>
<td>FGFR1: 69</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>PD166866</td>
<td>N/A</td>
<td>FGFR1: 52.4</td>
<td>Pfizer</td>
</tr>
<tr>
<td>PD173074</td>
<td>N/A</td>
<td>FGFR1: 22–25</td>
<td>Pfizer</td>
</tr>
<tr>
<td>NVP-FGF401</td>
<td>1.1</td>
<td>N/A</td>
<td>Novartis</td>
</tr>
<tr>
<td>NVP-BGJ398 (infigratinib)</td>
<td>60</td>
<td>FGFR1: 0.9</td>
<td>Novartis</td>
</tr>
<tr>
<td>Dovitinib (CHIR258, TKI258)</td>
<td>N/A</td>
<td>FGFR1: 1.4</td>
<td>Novartis</td>
</tr>
<tr>
<td>LYS2874455</td>
<td>6</td>
<td>FGFR1: 2.8</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>AZD4547</td>
<td>165</td>
<td>FGFR1: 0.2</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Debio-1347 (CHS183284)</td>
<td>290</td>
<td>FGFR1: 9.3</td>
<td>Debiopharm International</td>
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<td>BAY1163877 (rogaratinib)</td>
<td>33</td>
<td>FGFR1: 12–15</td>
<td>Bayer</td>
</tr>
<tr>
<td>E-3810 (lucitanib)</td>
<td>&gt;1,000</td>
<td>FGFR1: 17.5</td>
<td>Clovis Oncology</td>
</tr>
</tbody>
</table>

*Balversa is the first FGFR kinase inhibitor approved by the FDA. Balversa (erdafitinib) received accelerated approval from the FDA for the treatment of adults with locally advanced or metastatic urachal carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations, and who have progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.
diet that excludes products like cheese, ice cream, chocolate, fast foods, colas, yogurt, and meats, which likely can have major implications for most patients’ way of life and, one can argue, quality of life in those with advanced cancer. In the quest for FGFR selectivity, and to limit off-target toxicities such as those associated with concurrent VEGFR2 inhibition, several observations were made—drugs that selectively target FGFR without VEGFR2 demonstrated a loss of FGFR4 pathway inhibition. This finding presented a new need to develop a selective FGFR4 inhibitor so that the lack of VEGFR2 activity does not affect the clinical outcomes regarding disease control, especially in FGFR4-driven cancers.

This issue of Cancer Discovery presents critical findings on the FGF19–FGFR4 inhibitor fisogatinib (BLU-554), a potent and selective, type I irreversible inhibitor of FGFR4. First, Kim and colleagues (8) report the identification, preclinical validation, and complete clinical data from the first-in-human phase I trial of fisogatinib. Then, Hatlen and colleagues (9) report their findings on the novel acquired mechanisms of resistance identified within the kinase domain of FGF19 in two patients on the aforementioned phase I trial who progressed on fisogatinib. Furthermore, they go on to demonstrate in vitro evidence of overcoming this resistance by using a pan-FGFR inhibitor that reaffirms continued aberrant FGFR4 signaling despite the mutations in the kinase domains. With the background of the developmental therapeutic challenge in both HCC and the FGFR pathway, it is commendable that the authors have pursued a tricky target in a challenging disease with very few therapeutic options and have demonstrated a validated biomarker-based approach for this target.

FGFR4 AND FGF19 PATHWAY

Located in chromosome 5, human FGFR4 is a protein-coding gene containing three immunoglobulin-like domains (D1–D3), a transmembrane domain, and an intracellular kinase domain that binds specific ligands (10). Functionally, it is involved in normal physiologic processes including bile-acid biosynthesis and is predominantly expressed in liver tissue. FGF19 ligand binds to FGFR4 with high affinity. FGF19 amplification is associated with development of cirrhosis and HCC. FGFR4 is regulated using its coreceptor KLB (a transmembrane protein). FGF19/FGFR4/KLB activation leads to the formation of FGFR receptor substrate 2 (FRS2) and GRB2 complex, activating the RAS–RAF–MAPK and PI3K–AKT pathways.

The authors here developed a highly potent selective oral FGFR4 inhibitor with companion IHC assay to identify aberrant FGF19 expression as a surrogate marker of pathway activation. Next, they elegantly translated this to a first-in-human phase I trial in patients with advanced HCC to assess safety and preliminary clinical activity of fisogatinib together with the validation of FGF19 IHC as a predictive biomarker of response in advanced HCC. Fisogatinib demonstrates an acceptable toxicity profile with early evidence of antitumor activity in patients with FGF19–IHC-positive HCC regardless of the underlying risk factor for HCC (such as hepatitis B, hepatitis C, nonalcoholic steatohepatitis, and others) and prognostic factors.

ACQUIRED RESISTANCE PARADIGM IN FGFR4, AND NEXT STEPS

The initial clinical benefit seen with select targeted therapies in oncology is often diminished by the eventual, seemingly inevitable development of acquired resistance. Therefore, as critical as it is to identify a novel drug to target an aberration, so too is the almost immediate effort to identify the emerging mechanisms of resistance and to formulate a therapeutic strategy to overcome them in real time. In their study, Hatlen and colleagues studied patients who developed disease progression on fisogatinib, identified mutations in the gatekeeper (V550) and hinge-1 (C552) residues of FGF4 that confer resistance to fisogatinib in the clinical setting, and validated those mechanisms of resistance in vitro and in vivo. Of the 7 patients who had imaging evidence of response per RECIST, 2 (29%) showed evidence of on-target resistance. Hatlen and colleagues went on to demonstrate that LY2874455, a gatekeeper-agnostic FGFR inhibitor, overcomes this resistance to fisogatinib in both in vitro and in vivo models. This finding further validates the theory that cancers with acquired resistance to selective FGFR4 inhibitors still maintain the FGF19–FGFR4–KLB pathway dependency.

Now, with this validation of the FGF19–FGFR4–KLB axis as a target in HCC, biomarker-driven precision oncology has arrived for this deadly cancer and undoubtedly become the subject of future investigation. What are the next steps? It is logical to move fisogatinib in the multikinase inhibitor-naive setting in HCC to see if there would be better efficacy and delayed acquired resistance. Next is how to use combination therapies in these patients to maximize the success of treatments in HCC. Given the nonoverlapping side effects of immune checkpoint inhibitors, and given the role of immune checkpoint inhibitors in HCC, concurrent development of combination trials is warranted. FGFR4 inhibition may be the first step to slivering liver cancer by identifying subsets within HCC identified and consequently targeted by their molecular aberrations. Oh! Liver cancer, “Get lost! Go away!”

Disclosure of Potential Conflicts of Interest

V. Subbiah is a consultant at Incyte, Novartis, and Helsin; is a scientific advisory board member for R-Pharma US, LOXO Oncology/Eli Lilly, and Medimmune; reports receiving commercial research grants from Blueprint Medicines, LOXO Oncology/Eli Lilly, Pharmamar, D3, Pfizer, Multivir, Agenum, AbbVie, Alfa-sigma, Agenys, Boston Biomedical, Idera Pharmaceuticals, Bayer, Inhibra, Exelixis, Medimmune, Altum, Dragonfly Therapeutics, Takeda, Roche/Genentech, GlaxoSmithKline, Nanocarrier, Vegenics, Northwest Biotherapeutics, Bergehealth, Incyte, and Fujifilm; and has received other remuneration from ASCO and ESMO. S.K. Pal is a consultant at Aveo, Eisai, Novartis, Exelixis, Ipsen, Pfizer, Astellas, BMS, Roche, and Genentech. No other potential conflicts of interest were disclosed.

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REFERENCES

Correction: Precision Oncology for Hepatocellular Cancer: Slivering the Liver by FGF19–FGFR4–KLB Pathway Inhibition

In the original version of this article (1), “FGFR4” was incorrectly spelled as “FGF4” in the title, and “FGFR4” and “FGF19” were incorrectly spelled as “FGF4” and “FGFR19” in the Summary and the section titled “Acquired Resistance Paradigm in FGFR4, and Next Steps.” The latest online HTML and PDF versions of the article have been corrected. The authors and publisher regret the error.

REFERENCE

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