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EDITORIAL

Development of Fibroblast Growth Factor Receptor Inhibitors: Kissing Frogs to Find a Prince?

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Fibroblast growth factor (FGF) and fibroblast growth factor receptor (FGFR) are important regulators of a variety of biologic functions, including cellular proliferation, differentiation, migration, angiogenesis, wound healing, and survival. The FGF protein family comprises 18 ligands that signal through four transmembrane tyrosine kinase receptors (FGFR1-4).[1] A fifth receptor, FGFR5 (or FGFRL1), can bind FGF, but it lacks a tyrosine kinase domain.[2] Dysregulation of FGFR has been implicated in the development of many neoplasms and can occur through a variety of mechanisms, including gain-of-function mutations with constitutive kinase activation, chromosomal translocations with ligand-independent signaling, altered splicing, and gene amplification, which leads to receptor overexpression.[1,3] Abnormalities in FGF and the FGFR pathway have been associated with progression of a wide spectrum of malignancies including myeloma, breast, endometrial, genitourinary, and gastric cancers.[2] For example, amplification of the 8p12 loci which codes FGFR1 is detected in approximately 10% of breast cancers,[4] FGFR2-activating mutations and amplifications are seen in 12% of endometrial cancers,[5] and FGFR3 mutations can be seen in approximately 12% of bladder cancers.[6] In addition, FGFs have been implicated in tumor angiogenesis and may mediate drug resistance to both conventional chemotherapy and anti–vascular endothelial growth factor (VEGF) therapy.[2]

Initial efforts in targeting FGFRs with small-molecule tyrosine kinase inhibitors (TKIs) have been tempered by challenges in the drug development process, which illustrates the complexities of developing drugs that target uncommon genomic alterations in tumors, as well as poor tolerability mainly related to nonspecificity and off-target effects. Multiple pharmaceutical companies are at different stages of pursuing FGFR blockade, mostly using small-molecule TKIs, but other approaches using monoclonal anti-FGFR antibodies and FGF trapping molecules are also being investigated. Early trials involved nonselective multitargeted TKIs that exhibit only modest bioactivity against FGFR and have wide-spectrum off-target inhibition against other tyrosine kinases, including VEGF receptors (VEGFRs). For example, dovitinib (TKI258) showed activity against FGFR1-3, VEGFR1-3, PDGFR-B, FLT-3, KIT, RET, and CSF1R,[7] and lucitanib (E3810) is a potent inhibitor of VEGFR1-3, FGFR1-2, and CSF1R.[8] Other nonselective FGFR inhibitors have been investigated (eg, nintedanib [BIBF1120], ponatinib [AP24534], brivanib [BMS-582664], lenvatinib [E7080], ENMD-2076, and orantinib [TSU-68]) and although they have some bioactivity against FGFR, their toxicity profiles (eg, hypertension and proteinuria) have been largely related to VEGFR inhibition. More recently, selective potent FGFR TKIs (eg, JNJ-42756493, BGJ398, AZD4547, LY287445, and TAS120) are being investigated with high in vitro kinase activity and specificity against FGFR1, FGFR2, and FGFR3 (enzymatic concentration that causes 50% inhibition [IC_{50}], < 10 nmol/L) in the hope of having a more tolerable safety profile by reducing off-target effects. Of interest, selective FGFR inhibitors cause blockade of FGF23 release from the bone, acting as an on-target effect in normal tissues. The resultant modulations of serum phosphate, FGF23, and vitamin D could potentially be used as biomarkers of effective FGFR inhibition.[9] The multitude of companies investigating FGFR inhibition need to be put in context with the difficulties of identifying patients with FGFR aberrations. In an early trial of dovitinib, molecular screening failure rates were high, and of the 243 patients with breast cancer who had their tumor samples analyzed for FGFR1 aberrations, only 25 were eligible for the FGFR1 amplified cohort.[10] Similarly, in a study by Helsten et al[11] that used Clinical Laboratory Improvement Amendments–approved next generation sequencing, only 343 of 4,853 patients who underwent molecular screening carried FGFR aberrations, primarily amplifications and activating missense mutations. Given limited resources and patients, the early drug development pathway for uncommon molecular aberrations should be scrutinized to determine whether multiple competing first-generation compounds should even be developed or whether investigation of this pathway should move forward only when more selective and potent lead candidates with minimal off-target effects are identified. Having multiple first-generation compounds that ultimately undergo attrition is an inefficient process for advancing targeted therapeutics.

It is in this context that Tabernero et al[12] reported the results of a phase I trial of the selective FGFR inhibitor JNJ-42756493 in patients with advanced solid tumors. JNJ-42756493 is a potent, oral, pan-FGFR inhibitor with IC_{50} values in the low nanomolar ranges against FGFR1-4 that exhibits minimal activity against other kinases, including VEGFR. Although the initial recommended phase II dose (RP2D) of single-agent JNJ-42756493 was 9 mg per day, the authors declared 10 mg administered on an intermittent schedule (7 days on/7 days off) as the ultimate RP2D on the basis of its more favorable toxicity profile and the attainment of biologic relevance via pharmacokinetic simulation of preclinical efficacy data. Although blood-based pharmacodynamic assessment (eg, hyperphosphatemia) supported their RP2D, these are not validated biomarkers of target inhibition in the tumor or

of optimal biologic activity, and hence their influence on the final dose should be considered cautiously. Notably, preliminary efficacy was seen mostly in patients with FGFR dysregulated tumors treated at 9 mg or more per day or at 12 mg intermittently, whereas none of the eight patients treated on the 10-mg intermittent dosing schedule achieved objective response. However, response evaluation was limited by small sample size and the mixture of molecularly selected and unselected tumor types.[12] There is insufficient information to deduce whether chronic lower doses versus intermittent higher doses of JNJ-42756493 would achieve more effective FGFR pathway inhibition. In the ideal setting, phase I studies identify an RP2D by taking into account in totality multiple relevant parameters, including toxicity, pharmacokinetics, pharmacodynamics, and preliminary efficacy data. In reality, this decision is not always clear-cut at the completion of phase I studies, as in the example of the trial reported by Tabernero et al[12] wherein the optimal dose and schedule for JNJ-42756493 remain uncertain. That study represents an illustrative example of a drug that should be tested in a randomized phase II trial setting for further refinement of its RP2D.[13] Such randomized trials enable a thorough assessment of two (or more) doses or schedules to pick the combination most likely to succeed in further evaluations.[14]

Tabernero et al[12] should be commended for their significant effort in investigating the best dose and schedule to move forward with JNJ-42756493. In addition, the customized grading of relevant toxicities such as hyperphosphatemia and nail changes based on expert consensus is novel and highlights the tailoring required when classification by the Common Terminology Criteria for Adverse Events is insufficient. Conversely, the inclusion of food effect assessments and the reporting of late or delayed adverse events,[15] if any, would help guide long-term administration of this oral agent. Furthermore, pharmacodynamic data from tumor biopsies obtained during the dose confirmation phase are not currently available, although there are suggestions of phospho-ERK reduction and FGFR pathway inhibition in post-treatment tumor samples in two patients enrolled during dose escalation.

Despite what appears to be a clear signal of biologic activity, FGFR inhibition in molecularly enriched populations presents many logistical challenges because aberrations in this pathway are present only in limited patient populations, and they require screening efforts that are not routinely performed in diagnostic laboratories. To date, there is no uniformity in the molecular procedures for detection of FGFR aberrations, nor is there a precise delineation of the alterations responsible for pathway addiction.[9] For example, in situ hybridization scoring techniques for characterizing FGFR1-2 amplification vary in trials reported to date.[9] Although ligand amplification may predict those more likely to benefit,[10] the heterogeneity in published definitions makes it difficult to assess given the lack of standardized measurement. Molecular screening for rare genomic alterations to a designated clinical trial can be inefficient. A broader screening effort under the auspices of a genotype-drug match program will allow patients to have seamless passage into histology agnostic basket trials or any other trials for which they are eligible.[16] Such a process can potentially identify multiple actionable mutations and thus will increase drug accessibility especially for those with uncommon aberrations. In addition, this would speed up the drug development pathway while minimizing screening failures associated with preassigned clinical trials. Linkage to data sharing cooperations should be encouraged to gain maximum knowledge and avoid duplicative trials in the context of finite financial resources and patients.[17]

Many unanswered questions remain in the clinical development of FGFR inhibitors. For example, does a developmental path remain for nonspecific FGFR inhibitors, given their lack of therapeutic index observed thus far? Although preliminary evidence demonstrates that specific FGFR blockade with newer generation compounds such as JNJ-42756493 has a manageable tolerability profile with promising biologic activity, there may still be a rationale for using multitargeted TKIs to preempt the emergence of resistant or escape pathways. The optimal strategies for combining FGFR inhibition with other anticancer agents requires further research. To date, patients are being enriched for tumors harboring specific FGFR mutations and amplifications presumed to be highly addicted to this pathway. However, patients are not being screened for other mechanisms that may be important in the promotion of carcinogenesis such as autocrine and paracrine overexpression. As exemplified by the drug development path of FGFR inhibitors, identification of the best-in-class compounds and the most sensitive patient populations is not always straightforward in the era of genomics. A unified molecular screening approach with direct linkage to target-drug matching, as well as data sharing on a global scale, are essential for making progress.

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