Drug Development

Major finding: The VEGFR juxtamembrane (JM) domain is a key determinant of VEGFR kinase inhibitor activity.

Concept: Type IV kinase inhibitors stabilize the JM domain in an autoinhibitory conformation.

Impact: Type IV inhibitors can inhibit VEGFR kinase with high levels of efficiency and selectivity.

REGULATORY DOMAIN CONFORMATIONS CORRELATE WITH VEGFR INHIBITOR EFFICACY

The VEGF receptor (VEGFR) family of receptor tyrosine kinases (RTK) has emerged as a therapeutic target in renal cell carcinoma (RCC) and other cancers, but the clinical efficacy and safety of small-molecule VEGFR inhibitors that have been approved for RCC varies significantly. VEGFR constructs containing only the catalytic kinase domain largely guided the design of these small-molecule inhibitors, but increasing evidence points to a role of the juxtamembrane (JM) domain in VEGFR kinase regulation and inhibitor potency. McTigue and colleagues therefore evaluated how a VEGFR construct including both the catalytic and JM domains (plus-JM) interacts with approved VEGFR kinase inhibitors. Crystal structures of plus-JM in complex with axitinib, pazopanib, sorafenib, sunitinib, and tivozanib revealed that, although each inhibitor similarly forced the aspartate-phenylalanine-glycine (DFG) segment of the activation loop to adopt an inactive "out" conformation, the VEGFR inhibitors had different effects on the JM domain, with axitinib, pazopanib, and sunitinib inducing an autoinhibitory JM "in" conformation and sorafenib and tivozanib sterically displacing the JM into an "out" conformation. VEGFR inhibitors that stabilized a JM-in conformation (termed type IV kinase inhibitors to distinguish them from ATP-pocket, DFG-pocket, or allosteric inhibitors) had at least a 10-fold higher binding affinity for the plus-JM construct than a construct lacking the JM domain (minus-JM). Additionally, the potencies of cell-based VEGFR inhibition were generally matched more closely by binding affinities for the plus-JM rather than the minus-JM construct. Moreover, plus-JM binding efficiency was significantly correlated with increased selectivity for VEGFR family kinases in a kinase screen and with longer progression-free survival in RCC clinical trials. Collectively, these findings provide insight into the underlying causes of the variable efficacy of VEGFR inhibitors and underscore the importance of using physiologically relevant target constructs in early stages of drug development to decrease the chances of failure in clinical testing. ■

McTigue M, Murray BW, Chen JH, Deng YL, Solowiej J, Kania RS. Molecular conformations, interactions, and properties associated with drug efficiency and clinical performance among VEGFR TK inhibitors. Proc Natl Acad Sci U S A 2012 Sept 17 [Epub ahead of print].

Clinical Trials

Major finding: The combination of dabrafenib and trametinib is safe and effective in *BRAF*-mutant melanoma.

Clinical Relevance: Secondary skin cancers were less common after combination therapy than with monotherapy.

Impact: MEK inhibitors can delay the emergence of acquired resistance to BRAF inhibition.

COMBINED BRAF AND MEK INHIBITION IMPROVES OUTCOME IN METASTATIC MELANOMA

Blockade of MAPK signaling through targeted inhibition of BRAF or its downstream effector MEK has been associated with improved progression-free and overall survival in patients with metastatic melanomas harboring activating BRAF V600 mutations. However, patients commonly experience disease progression due to MAPK reactivation or other resistance mechanisms, and some patients treated with BRAF inhibitors develop secondary keratoacanthomas or cutaneous squamous cell carcinomas due to paradoxical MAPK pathway activation. Flaherty and colleagues tested whether combined use of a BRAF inhibitor (dabrafenib) and a MEK inhibitor (trametinib) would circumvent MAPK reactivation and prevent the development of acquired resistance and secondary skin cancers in patients with *BRAF*-mutant melanoma. The safety and pharmacokinetic activity of combination dabrafenib and trametinib therapy were evaluated in a phase I dose-escalation trial of 85 patients. There were no adverse drug interactions, and the maximum tolerated dose combination was not reached. In an open-label phase II trial, 162 patients were randomized to receive either dabrafenib plus trametinib or dabrafenib monotherapy. Strikingly, the progression-free survival was 9.4 months in the combination group compared with 5.8 months in the dabrafenib monotherapy group, and 76% of patients on combination therapy had a complete or partial response whereas only 54% of patients on dabrafenib monotherapy responded. Furthermore, the incidence of cutaneous squamous cell carcinomas was 19% in the dabrafenib monotherapy group compared with only 7% in the combination group. Patients treated with dabrafenib and trametinib experienced more frequent fevers, chills, nausea, and vomiting than patients on dabrafenib monotherapy, but these adverse effects were manageable. Together, these findings show that combined use of BRAF and MEK inhibitors is safe and may improve clinical outcome in patients with *BRAF*-mutant metastatic melanoma. ■

Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012 Sept 29 [Epub ahead of print].