ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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B-RAF Validation in Melanoma

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H&O What is B-RAF and what role does it play in melanoma?

NR B-RAF, along with A-RAF and C-RAF, comprises the RAF family of serine/threonine kinases that act upstream of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) in response to growth signals. RAF is the main link between RAS and the MAPK pathway and when it is activated it phosphorylates MEK, which in turn phosphorylates and activates ERK.

B-RAF is an oncoprotein encoded by the B-RAF gene that is involved in the signaling of growth factor receptors. B-RAF is mutated in approximately 60% of melanomas, many thyroid cancers, and small but significant percentages of other cancers. In melanoma, B-RAF is a driver mutation in the tumor. In tumors in which the gene is mutated, the activity of the protein is most likely required for their continued growth. B-RAF mutation is present in the common type of melanoma. Tumor cells with B-RAF mutation are sensitive to inhibition of MEK, which causes downregulation of cyclin D, induction of p27, hypophosphorylation of Rb, and G1 cell cycle arrest.

Ninety-eight percent of B-RAF mutations in melanoma are mutations at codon 600, replacing a valine with an aspartate (V600E). The mutation of V600E is an early event and, on its own, does not predict the development of melanoma, as it is present in 80% of primary melanomas and nevi.

N-RAS, a member of the RAS family, is mutated in approximately 24% of melanomas. N-RAS and B-RAF mutations appear to be mutually exclusive in melanomas, suggesting that they activate a common pathway of improtance in the development of this disease.

H&O How has the discovery of this mutation helped melanoma treatment?

NR The general consensus in the field is that genes that are mutated in the cancer are often required for maintenance of the malignant phenotype and are therefore important therapeutic targets. The discovery of the B-RAF mutation has been very important to melanoma research. It is estimated that there will be 8,650 deaths from melanomas in the United States in 2009. The understanding is that

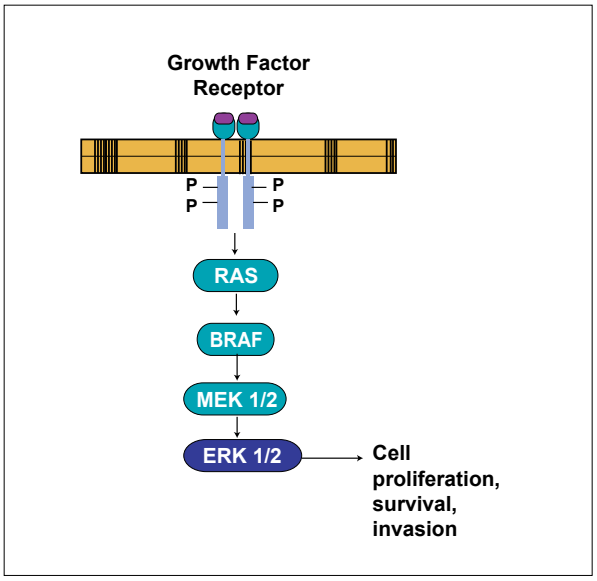

Figure 1. Ras-Raf-MEK-ERK (MAPK) signaling pathway.
Adapted from Meler F et al. *Front Biosci*. 2005;10:2986-3001.

activation of the RAS/RAF/MEK pathway is important for the development of this disease and the identification of prevalent mutations in B-RAF and N-RAS and other genes have presented new opportunities for the development of more effective therapies.

H&O What is the incidence of B-RAF mutations in the different types of melanoma?

NR Approximately 60% of melanomas originating in the skin that is not sun damaged carry B-RAF mutations. However, melanomas occurring in chronically sun-damaged skin, acral skin, and mucosal membranes carry 15% B-RAF mutations.

H&O What agents are currently under investigation in melanoma patients with BRAF mutations?

NR There are 2 types of agents inhibiting ERK signaling that are under investigation: direct inhibitors of the RAF kinase and inhibitors of the target of the RAF kinase, MEK. There have been phase II trials of MEK inhibitors that showed approximately a 13% RECIST partial response rate. At this year's annual meeting of the American Society of Clinical Oncology, Plexxikon presented results of their phase I study of PLX4032, an oral, selective RAF inhibitor. At the recent joint Congress of the European Cancer Organization and European Society of Medical Oncology, results of a phase I extension study of PLX4032 was reported by Dr. Chapman and colleagues. The study enrolled 55 patients and of these, 30 were treated at doses of 160–1120 mg twice daily. The maximum tolerated dose was determined to be 960 mg twice daily. Of the 26 patients who received 240 mg twice daily or higher, 16 were melanoma patients with B-RAF mutations. Of the 16 patients, 11 had partial response. An additional 30 melanoma patients with BRAF mutations have received the maximum tolerated dose. At the time of reporting, 22 patients were evaluable for response; 14 partial responses have been observed. Six other patients have experienced regression but did not meet the criteria for partial response. Phase II and III trials are currently being planned.

RAF265 (Novartis) is an orally bioavailable small molecule agent that targets both RAF and vascular endothelial growth factor receptor. A preclinical trial of RAF265 demonstrated inhibition in all the isoforms of RAF, as well as B-RAF V600E. A phase I study of RAF265 in locally advanced or metastatic melanoma patients is recruiting patients. Another agent, AZD6244 (AstraZeneca), is an oral, highly selective inhibitor of MEK. A phase II study comparing AZD6244 to temozolomide in patients with unresectable malignant melanoma is currently ongoing.

H&O How is B-RAF screened, and what bearing does screening have on prognosis?

NR The predominant mutation that has been reported is a single transversion in exon 15. Real time allele-specific polymerase chain reaction has been the screening method used to evaluate the presence of a mutation in this exon and in exon 11. The relevance of screening for B-RAF mutations is that many researchers believe that the RAF inhibitors currently employed will only work in mutant B-RAF disease. Screening for the mutation will not only tell us who to treat, but will also allow us to create a safer and more effective strategy for treating these patients.