BRAF Validation in Melanoma

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**H&O What is BRAF and what role does it play in melanoma?**

**EH** BRAF, along with A-RAF and C-RAF, comprises the RAF family of serine/threonine kinases that act upstream of the MEK1/2 kinases in response to RAS signals. RAF is the main link between RAS and the MAPK pathway and when it is activated it phosphorylates and in turn activates MAPK/ERK kinase (MEK 1/2). BRAF is an oncoprotein encoded by the BRAF gene that is involved in signaling of growth factor receptors. BRAF is mutated in as many as 60% of melanomas, many thyroid cancers, and small but significant percentages of other cancers. In melanoma, BRAF 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 the continued growth of the tumor. Sixty percent if BRAF mutation is present in the common type of melanoma, which is associated with sporadic sun exposure; however, there is no evidence that UV radiation is causing BRAF mutations. Ninety-eight percent of BRAF 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.

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

**EH** The general consensus in the field is that understanding what genes are mutated in a cancer will tell us what is responsible in large part for the development of the cancer and will provide us with targets of therapy, the inhibition of which may have a positive therapeutic effect on the tumor. The discovery of the BRAF mutation has been very important to melanoma research, as melanoma accounts for less than 5% of skin cancer cases but is responsible for a large majority of skin cancer deaths. It is estimated that 68,720 new melanomas will be diagnosed in the United States in 2009. The RAS/RAF/MEK target and the identification of mutations in BRAF and NRAS and other genes have presented new opportunities for development of less toxic, more targeted therapeutic modalities.

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

**EH** There are 2 types of agents inhibiting BRAF that are under investigation: direct inhibitors of the RAF kinase and inhibitors of the target of the RAF kinases, the MEK kinase. MEK is a principal target for inhibition because it only has 2 known substrates, ERK1/2. There have been phase II trials of MEK inhibitors that showed approximately a 13% RECIST partial response rate, with more patients responding than reaching RECIST criteria. [AU: what is the name of this drug, can you provide a bit more detail on the study] 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 and highly selective compound that targets BRAFV600E mutated patients with melanoma. The study enrolled 54 patients, the majority of which had metastatic melanoma (n=49); patients with thyroid, rectal, and ovarian carcinoma were also enrolled. Five of the 7 patients with BRAF V600E mutation treated with more than 240 mg twice daily had tumor regres-
sion up to 83%; 2 of 4 patients with unknown V600E status had tumor regression up to 50%; and 2 BRAF wild-type patients had progressive disease. All 7 patients with tumor regression were progression free at the time of reporting. The drug appeared to be well tolerated. None of the nonmutated patients had any response. At the recent ECCO/ESMO meeting, a phase I study of PLX4032 determined the maximum tolerated dose and observed anti-melanoma activity in almost all patients treated at this dose. Phase II and III trials are 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 BRAF 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 BRAF screened and what bearing does screening have on prognosis?

**EH** [AU: Dr. Rosen, can you describe some of the screening methods that are utilized and provide some more info on how BRAF affects prognosis] The relevance of screening for BRAF mutations is that many researchers believe that the RAF inhibitors currently employed will only work in mutant BRAF disease. [Dr. Rosen, can you clarify this. Don’t we know that the drugs only work in mutant BRAF?] Thus, in order to determine what drug should be used to treat the patient, it is necessary to screen for BRAF mutation, which will tell us who to treat.

**H&O** What is the incidence of BRAF mutations in the different types of melanoma?

**EH** Seventy percent of melanomas originating in the skin that is not sun damaged carry BRAF mutations. However, melanomas occurring in chronically sun-damaged skin, acral skin, and mucosal membranes carry 15% BRAF mutations.

**Suggested Reading**