Overcoming Metastatic Melanoma with BRAF Inhibitors

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Melanoma has the capacity to spread via the blood stream to the brain, and has been notoriously resistant to drug therapy. An activating mutation in the gene encoding BRAF is known to be responsible for half of melanomas. This article provides a review of GSK2118436 and PLX4032 as potential therapeutics for the treatment of melanomas by inhibiting oncogenic BRAF.

Melanoma is the most serious type of skin cancer which spreads throughout the body. Over 1 million cases of melanoma are diagnosed worldwide every year. Of all the solid tumors, melanoma has the greatest capacity to spread via the blood stream to the brain. Overall, 15-20% of patients with melanoma that has spread beyond the skin have brain metastases at initial diagnosis. The median progression-free survival for a patient with metastatic melanoma is less than 60 days from diagnosis of brain involvement and the median overall survival for these patients is less than 12 months (Flaherty et al., 2010).

Encouraging results from clinical studies with GSK2118436 (GlaxoSmithKline) and PLX4032 (Roche/Plexxikon), both of which target BRAF (VRAF murine sarcoma viral oncogene homologue B1) kinase, are good news for melanoma patients. BRAF is a RAS (guanine nucleotide binding protein) activated serine/threonine protein kinase that plays a central role in regulating the MAPK (mitogen-activated protein kinase) signaling pathway. This pathway normally regulates cell growth, division and differentiation, and has long been associated with human cancers due to frequent oncogenic mutations identified in RAF (rapidly growing fibrosarcoma) family members. The V600E activating mutation is most common and significantly increases the kinase activity of BRAF. Since approximately half of all metastatic melanoma patients are believed to have BRAFV600E (substitution of a valine for glutamic acid at position 600) mutation, targeted inhibition of the mutant BRAF signaling could lead to better therapy for melanoma patients (Arkenau et al., 2011).

Both GSK2118436 and PLX4032 are ATP-competitive and reversible inhibitors of BRAF with promising clinical efficacy data in melanoma patients. GSK2118436 potently inhibits BRAFV600E (IC₅₀ = 0.5 nM), BRAFV600K (IC₅₀ = 0.6 nM) and BRAFV600D (IC₅₀ = 1.9 nM), and thus possibly shows a wider range of activity with responses in V600 gene-mutant tumors (King et al., 2006; Arkenau et al., 2011). In the Phase I data presented at the ESMO 2010 meeting in Milan, GSK2118436 treatment shrank the overall size of...
brain metastases in 9 out of 10 treated patients. This was a remarkable finding, as typical responses to treatment range between 10 to 15 percent. The overall reduction in the size of brain metastases ranged from 20-100% (3 mm or larger before treatment). GSK2118436 also had an impressive 60% response rate for melanomas outside of the brain. In addition, GlaxoSmithKline has started Phase III trials of its BRAF inhibitor GSK2118436 and MEK (dual-specificity mitogen-activated protein kinase) inhibitor GSK1120212 for advanced or metastatic melanoma patients. However, these results still need to be viewed with caution since, so far, these results have been from early clinical trials only and need to be confirmed in larger-sized Phase III trials.

PLX4032 was discovered utilizing a scaffold-based drug design approach to inhibit the BRAF cancer-causing mutation (V600E). PLX4032 displayed good potency for BRAF (V600E; 31 nM) and selectivity against many other kinases, including the wild-type BRAF (100 nM; Bollag et al., 2010). BRAF mutant melanoma cell strains were highly sensitive to PLX4032 with an IC$_{50}$ in the nanomolar range (60-450 nM; Tsai et al., 2008; Yang et al., 2010). It was reported that 81 percent of patients given PLX4032 had either a partial or complete shrinkage of their tumors and they stayed in remission for an average of 7 months (Flaherty et al., 2010). It is likely that PLX4302 will reach the market first, since preliminary results from a Phase III trial showed that it significantly extended survival in patients with metastatic melanoma.

In spite of the ongoing clinical success, many important questions still need to be addressed. As for example, the emergence of resistance to BRAF inhibition in melanomas is a growing concern, a pattern seen with other kinase inhibitors. Resistance develops quickly, typically within 8-12 months following treatment. Evidence is emerging regarding reactivation of MEK/ERK (extracellular signal-regulated kinase) signaling caused by N-RAS mutation and overexpression of RAF1 (VRAF leukemia viral oncogene 1) or COT (mitogen-activated protein kinase 8) to counteract the inhibition of BRAF. Other compensatory pathways may involve the activation of upstream receptor tyrosine kinases; for example, PDGFRb (platelet-derived growth factor receptor b) makes MEK activity redundant by triggering downstream effectors of cell transformation through parallel signaling pathways (Johannessen et al., 2010; Nazarian et al., 2010). Thus, new strategies will be needed to treat patients in whom resistance to BRAF inhibitors develops and rational combination therapy is one approach to overcome drug resistance. For instance, cocktail therapy using BRAF inhibitors and other kinase inhibitors, such as MEK, mTOR (mammalian target of rapamycin), PI3K (phosphatidylinositol-3-kinase) or AKT (v-akt murine thymoma viral oncogene) inhibitors will be dedicated to either prevent or delay resistance of melanoma treatment.

Another aspect to consider is a personalized healthcare approach using diagnostic markers. This needs to be validated to identify patients whose tumors carry the BRAF mutation V600 gene, as it is now routinely being done for breast cancer (HER2) and chronic myeloid leukemia (BCR-ABL). It is still challenging to discriminate between aggressive and more indolent metastatic melanomas and standardized molecular characterization on the basis of BRAF mutation in tumors will be required for better patient classification.

To conclude, the BRAF mutation has been shown to be a key driver of cancer, particularly in melanoma. Inhibitors of the BRAF mutation, such as GSK2118436 and PLX4302, are now opening the way to provide a significant survival benefit in patients with metastatic melanoma.

**Fig. 2.** Signal transduction pathways in melanoma and drug sensitivity.