

## Mechanisms of Resistance in BRAF-Mutated Melanoma

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Development and successful use of BRAF inhibitors (such as vemurafenib) in the treatment of melanoma has been a landmark accomplishment and has helped to greatly improve prognosis in select cases. Unfortunately, a complete response to BRAF inhibitors is exceptional, and the development of eventual resistance is almost certain. Research investigating this phenomenon has revealed numerous mechanisms by which melanoma circumvents therapy.

There are two basic pathways involved in the propagation of melanocytes and the development of melanoma. The first is the mitogen-activated protein kinase (MAPK) pathway, which is involved primarily in cell proliferation. The second is the PI3K/AKT/mTOR (AKT) pathway, which is primarily involved in prolonged cell survival. Studies have implicated both pathways in cell proliferation, prolonged cell survival, impaired apoptosis, and tissue invasion. BRAF is part of the RAS-RAF-MEK-ERK (MAPK) pathway, and RAS proteins may induce activating mutations in *BRAF*. *BRAF* mutations are common in melanoma, identified in up to 50% of cases, especially in melanomas that develop on non-chronically sun-damaged skin. Up to 90% of these melanomas harbor a *BRAF* mutation at codon 600, with a V600E (substitution of glutamic acid for valine) mutation most commonly identified. BRAF inhibitors demonstrate an increased affinity for the mutated forms of *BRAF* over wild-type.<sup>1</sup> While the MAPK pathway is blocked through the use of BRAF inhibitors, both MAPK and AKT pathway alterations have been implicated in resistance.

Within the MAPK pathway, aberrations in NRAS, CRAF, and MEK have been identified in previously treated melanomas.<sup>2, 3, 4</sup> Additionally, ERK activation has been described and was surmounted only when all isoforms of RAS (H, K, and NRAS) were inhibited, indicating that inhibited melanoma cells are able to switch between the different forms of RAS as needed.<sup>5</sup> ERK activation with subsequent MAPK pathway activation is also possible through a protein known as COT.<sup>6</sup>

Acquired resistance through stimulation of the AKT pathway has been described, as well, and is commonly mediated through PI3K (phosphatidylinositol-3-kinase). Two mechanisms account for this acquired resistance: upregulation of the transmembrane receptor PDGFR- $\beta$  (platelet derived growth factor receptor beta) and upregulation of the IGF-1 (insulin-like growth factor 1) transmembrane receptor.<sup>3, 5</sup>

Studies evaluating the efficacy of combination therapy are currently underway. MEK inhibitors, such as trametinib, used in combination with BRAF inhibitors have been shown to be more beneficial than either medication used exclusively as monotherapy; however, cross-resistance may be conferred with subsequent MEK inhibitor therapy

after initiation of a BRAF inhibitor.<sup>7,8</sup> Inhibitors of mTOR, such as rapamycin, used in combination with BRAF inhibitors have shown promise in vitro to overcome resistance.<sup>9</sup> Future studies will undoubtedly identify other resistance mechanisms as well as elucidate potential therapeutic strategies.

## References

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