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Targeted Therapy for Cutaneous Melanoma: Beyond \textit{BRAF}…

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Abstract
The development and regulatory approval of vemurafenib and dabrafenib for metastatic melanoma patients with activating \textit{BRAF} mutations has demonstrated that personalized targeted therapy strategies can provide significant clinical benefit in this highly aggressive disease. However, these agents are not beneficial in patients who do not have activating \textit{BRAF} mutations, who represent over half of all melanoma patients. Recent studies have demonstrated that melanomas have the highest rate of somatic mutations among the major cancers. Based on this information, additional personalized treatment strategies are now in various stages of clinical development and testing. These efforts are being guided by the lessons learned in the development of effective therapeutics for \textit{BRAF}, as well as a growing understanding of the molecular heterogeneity and drivers of this disease. (\textit{J Patient-Centered Res Rev.} 2014;1(1):12-20.)

Keywords
melanoma, targeted therapy, NRAS

Introduction
The management of patients with metastatic melanoma is evolving rapidly. A sentinel event in this evolution was the discovery of point mutations in the \textit{BRAF} gene, which was published in 2002.\textsuperscript{1} This landmark paper reported that somatic mutations that resulted in substitutions for the valine at the 600 position of the \textit{BRAF} protein (now commonly referred to as \textit{BRAF} V\textsubscript{600} mutations) were detected in over half of the melanomas in that study. These mutations cause constitutive and markedly increased (>50-100X) activity of the \textit{BRAF} protein, which is a serine-threonine kinase in the RAS-RAF-MAPK signaling pathway [Figure 1]. Subsequent large single-center studies and meta-analyses of clinical specimens demonstrated that the prevalence of \textit{BRAF} V\textsubscript{600} mutations is \textasciitilde40-45\% in cutaneous melanomas in patients.\textsuperscript{2,3} The discovery of the high prevalence of activating \textit{BRAF} mutations in melanoma strongly implicated activation of the RAS-RAF-MAPK signaling pathway as a critical factor in the pathogenesis of this disease. More importantly, this discovery led to the rapid and successful development of targeted therapies that provide marked clinical benefit in metastatic melanoma patients with \textit{BRAF} V\textsubscript{600} mutations. As described elsewhere in this issue, vemurafenib (2011), dabrafenib (2013), and trametinib (2013) have each been approved by the FDA for the treatment of metastatic melanoma patients with activating \textit{BRAF} V\textsubscript{600} mutations.\textsuperscript{4,6} Combined with the regulatory approval of ipilimumab in 2011, these results have dramatically altered the treatment landscape for patients with this highly aggressive disease.\textsuperscript{7,8}

The clinical results achieved with vemurafenib, dabrafenib, and trametinib in metastatic melanoma patients with \textit{BRAF} V\textsubscript{600} mutations provide the proof-of-concept that the identification and inhibition of molecular drivers in this disease can have significant clinical impact. However, these agents have only demonstrated significant clinical activity and regulatory approval in melanoma patients with \textit{BRAF} V\textsubscript{600} mutations. Over half of cutaneous melanoma patients do not have such mutations, and their prevalence is much lower in other clinical subtypes of melanoma.\textsuperscript{9} The prevalence of \textit{BRAF} V\textsubscript{600} mutations is 10-15\% in acral lentiginous melanomas, \textasciitilde5\% in mucosal melanomas, and they are not found in uveal melanomas. Unexpectedly, preclinical studies have shown that treatment with \textit{BRAF} V\textsubscript{600} mutation-specific inhibitors (i.e. vemurafenib, dabrafenib) paradoxically activates the MAPK pathway and accelerates tumor growth in melanomas without activating \textit{BRAF} mutations.\textsuperscript{10-12} Thus, these agents are not an option for many patients with metastatic melanoma.

The understanding of the molecular pathogenesis of melanoma is now increasing rapidly due to the emergence of data from broad molecular profiling studies. In particular, recent whole-exome sequencing analyses have provided multiple new insights into the molecular events and diversity that are present in melanomas [Figure 2].\textsuperscript{13,14} These and other studies have implicated many additional potential therapeutic targets for melanoma, a number of which are now leading to new clinical trials for patients without \textit{BRAF} V\textsubscript{600} mutations.
Point mutations in *NRAS* are the second most frequent activating oncogenic mutations in melanoma. Overall, recurrent hotspot mutations in *NRAS* are detected in ~20% of cutaneous melanomas. The majority (80%) of these mutations result in substitutions at the Q61 position of the NRAS protein, while the rest (20%) cause substitutions at the G12/G13 positions. These mutations are essentially mutually exclusive with BRAF V600 mutations in treatment-naive melanomas. In our study of ~700 melanoma patients who underwent mutation testing, BRAF V600 mutations and NRAS mutations were present concurrently in <1% of the tumors tested. Of note, mutations of NRAS are a known mechanism of resistance to BRAF inhibitors, and they are detected in 20-25% of BRAF V600 mutation (+) melanomas after disease progression on selective BRAF inhibitors. Retrospective analyses of cohorts of melanoma patients with early- and late-stage disease support that the presence of an activating NRAS mutation is associated with worse clinical outcomes, including shorter survival. Thus, the development of effective therapeutic strategies for melanomas with NRAS mutations is a high priority in melanoma research. The mutual exclusivity of NRAS mutations and BRAF V600 mutations is likely attributable to the fact that both of these events activate signaling in the RAS-RAF-MAPK pathway. In cells with BRAF V600 mutations, the mutant BRAF proteins form homodimers in the cytoplasm that activate downstream MEK and ERK signaling largely independently of other proteins. In contrast, cells without BRAF V600 mutations trigger activation of the pathway through a multi-protein complex that includes RAS proteins and dimers of different RAF proteins, including CRAF.
BRAF, and ARAF. Thus, while the FDA-approved BRAF inhibitors are not an option for melanomas with NRAS mutations, other inhibitors against the MAPK pathway may be effective.

Sorafenib is a small molecule inhibitor of multiple kinases. While sorafenib was initially investigated in melanoma primarily as a therapeutic strategy for tumors with BRAFV600 mutations, it is a more potent inhibitor of CRAF (IC50 6 nmol) than it is of either wild-type (22 nmol) or mutant (38 nmol) BRAF proteins. As preclinical studies support that NRAS is more dependent upon CRAF than other RAF isoforms to activate the RAS-RAF-MAPK pathway, sorafenib may be effective in melanomas with activating NRAS mutations. This hypothesis is supported by a recent analysis of the results of the ECOG 2603 trial, which was a randomized trial of paclitaxel and carboplatin (TC) with or without sorafenib in treatment-naïve metastatic melanoma patients. The analysis of the entire treatment population demonstrated that sorafenib did not significantly improve the overall response rate (ORR), PFS, or overall survival (OS), similar to the results reported in a randomized trial in previously-treated metastatic melanoma patients. However, among the 39 patients with activating NRAS mutations, the ORR was 5.6% for patients treated with TC, while the ORR for patients who also received sorafenib was 22.7% (odds ratio 4.26, 95% confidence interval 0.36 – 49.74). In contrast, minimal difference in clinical response rate was observed for patients with activating BRAF mutations (15.6% with TC, 19.2% with TC and sorafenib), or in patients with no activating mutation in BRAF or NRAS (16.7% and 20%).

Figure 2. Landscape of mutations, amplifications and deletions in cutaneous melanoma. The figure shows the somatic mutations, amplifications and deletions of the genes indicated on the left side of the chart. Each column reflects the findings in one patient (total = 121 patients). The number of somatic mutations detected by whole-exome sequencing is shown at the top of the graph; the relative percentage of each type of substitution observed in each patient is shown at the bottom. The genes were selected based on the finding of statistically significant event rates in whole-exome sequencing, and/or by previous data implicating a role in melanoma (“Selected Focal Amplifications and Deletions”). (Reprinted from Hodis E, Watson IR, Kryukov GV, et al. A Landscape of Driver Mutations in Melanoma. Cell. 2012;150(2):251-63, with permission from Elsevier.)
MEK inhibitors are another available strategy to inhibit the RAS-RAF-MAPK pathway. The phase I trial of the MEK inhibitor trametinib included 9 patients with known NRAS mutations, none of whom achieved an objective response. More promising results were observed with MEK162, which is another potent inhibitor of MEK1/2. In an open-label phase II study of 30 metastatic melanoma patients with activating NRAS mutations, RECIST-criteria clinical responses were observed in 6 patients (20%), while multiple other patients had minor responses. While the response rate was promising, the median duration of the response was only 7.6 weeks, and the overall median progression-free survival (PFS) was 7.9 weeks. A randomized phase III trial comparing the efficacy of MEK162 to chemotherapy (dacarbazine) opened for enrollment in 2013 (NCT01763164). Inhibitors of ERK1/2, which are kinases downstream of MEK in the RAS-RAF-MAPK pathway, have demonstrated efficacy in preclinical models of both BRAF- and RAS-mutant cancers. Clinical trials are currently ongoing to determine their safety and efficacy in patients (NCT01358331).

Despite the clinical responses observed with single agents targeting the MAPK pathway, it is likely that the effective treatment of melanomas with NRAS mutations will require combinatorial approaches. Experiments in multiple tumor types have shown that mutant RAS proteins utilize additional pathways to mediate their oncogenic effects. Such pathways include signaling through the PI3K-AKT pathway, cytoskeletal proteins (i.e. RAC, RALGDS), and phospholipase C (PLC). As many different inhibitors against the PI3K-AKT pathway have been developed, most clinical efforts to date have focused on the effects of combining those agents with MAPK pathway inhibitors. While such combinations have shown efficacy in preclinical models, to date little clinical activity has been observed, albeit in the setting of phase I trials. Notably, it remains unclear if the doses of the PI3K-AKT and MAPK pathway inhibitors that have been tolerated in such combinations achieve sufficient inhibition of their targets to produce clinical benefit.

A new strategy for NRAS-mutant melanomas is to combine MEK inhibitors with CDK4 inhibitors. This strategy is based predominantly on findings from experiments performed in a genetically engineered mouse model (GEMM) of melanoma. In this model, melanomas are rapidly and reliably induced in mice expressing NRAS in melanocytes under the control of a doxycycline-inducible promoter. Importantly, the tumors are established by giving the mice doxycycline, cessation of doxycycline causes complete loss of NRAS expression and all tumors resolve. As this model recapitulates the effects of complete inhibition of NRAS, it provided a way to compare the effects of MEK inhibitors to identify the critical cellular pathways and/or functions that they fail to inhibit. This strategy demonstrated that while MEK inhibitors slow tumor growth and induce cell death, they did not achieve equivalent anti-proliferative effects as complete NRAS inhibition. A number of molecular approaches implicated CDK4 as a key node and target that could overcome this deficiency and complement MEK inhibition. In the NRAS GEMM model, and in an NRAS-mutant patient-derived melanoma cell line, the combination of a MEK inhibitor and a CDK4 inhibitor produced not only a significant regression of tumor size, but 33% of the mice achieved complete tumor responses. Based on this data, open and planned clinical trials are evaluating the safety and efficacy of MEK inhibitors and CDK4 inhibitors in metastatic melanoma patients with activating NRAS mutations (i.e. NCT01781572).

Non-V600 BRAF Mutations and Other Alterations in the RAS-RAF-MAPK Pathway

While substitutions at the V600 position represent approximately 95% of the mutations detected in melanoma, mutations at more than 15 other positions in BRAF have been identified. Some non-V600 BRAF mutations that are detected in melanoma patients cause comparable activation of the kinase activity of BRAF comparable to V600 mutations. However, many cause only moderate activation, and others actually decrease catalytic activity. Interestingly, the mutations that do not increase BRAF’s kinase activity still cause increased activation of signaling through the RAS-RAF-MAPK pathway due to conformational changes that promote dimerization with other RAF family members. Notably, while BRAFV600 mutations are mutually exclusive with NRAS mutations, non-activating BRAF mutations are often detected in tumors with NRAS mutations.

Isolated case reports support that MAPK pathway inhibitors may be an effective strategy in at least some patients with non-V600 BRAF mutations. A study by Dahlman and colleagues reported the dramatic response of a melanoma patient who had a BRAFV597S mutation treated with the MEK inhibitor TAK-733. Experiments in melanoma cell lines supported that this mutation conferred increased sensitivity to MEK inhibition. A patient with a BRAFV597S mutation had a partial response (60% tumor reduction) of >2 years duration in the phase I trial of trametinib. Another patient in that trial had a G469A substitution in BRAF, and that patient achieved a minor response. Preclinical studies have...
also demonstrated that sorafenib can inhibit the growth of melanoma with non-activating BRAF mutations in vitro and in vivo. A durable (>4 years) complete response to dasatinib has also been reported in a non-small cell lung cancer patient with an inactivating BRAF mutation. Preclinical studies demonstrated that the expression of inactivating BRAF mutations conferred sensitivity to dasatinib, whereas BRAFV600 mutations caused resistance. A clinical trial with dasatinib for patients with inactivating BRAF mutations is currently open for enrollment (NCT01514864).

In addition to mutations, the BRAF gene locus can be involved in chromosomal translocations that result in fusions with other genes. Such fusions have been identified as rare events in prostate, thyroid, and gastric cancers, and in a melanocytic nevus. More recently, fusions of BRAF with other genes have been identified in a small number of melanomas that do not have driver mutations in either BRAF or NRAS. Enforced expression of some of the fusions caused increased activation of RAS-RAS-MAPK signaling, which could be inhibited by treatment with a MEK inhibitor. Multicenter clinical trials are now in development for patients with BRAF fusions and non-V600 mutations to evaluate the efficacy of MEK inhibitors in this patient population.

Whole-exome sequencing studies have revealed that almost all melanomas have at least one genetic aberration in the RAS-RAF-MAPK pathway. These mutations include likely activating mutations in HRAS, MEKI, and MEK2, and loss-of-function mutations in NF1 (a negative regulator of RAS proteins). The high prevalence of these events supports the hypothesis that the RAS-RAF-MAPK pathway likely plays a role in virtually all cutaneous melanomas. These findings also support the rationale to include inhibitors of the RAS-RAF-MAPK pathway in combinatorial strategies even in patients without detectable mutations in BRAF or NRAS.

Cell Cycle Regulators

The critical need for the disruption of cell cycle control in melanoma was implicated initially by studies of the genes that are associated with familial melanoma. Approximately 10% of melanomas are familial (≥3 affected individuals in a family). The most common causes (~40%) of familial melanoma are the presence of germline loss-of-function mutations or deletions of the CDKN2A gene. Due to alternative splicing mechanisms two cell cycle regulators (P16INK4A and P14ARF) are encoded by this CDKN2A. Most functional studies in melanoma have focused on P16INK4A, as some mutations in CDKN2A detected in patients do not affect the function of P14ARF. P16INK4A normally inhibits the function of the complex of CDK4 (or CDK6) with CyclinD1 (CCND1), which otherwise promotes cell cycle progression by phosphorylating RB1. Mutations in CDKN2A are the second most common germline mutation found in familial melanoma. These mutations affect the residue in the CDK4 protein that mediates the binding of P16INK4A, thus blocking this interaction from occurring, and reinforcing the significance of loss of P16INK4A function in melanoma.

While familial melanomas are rare, whole-exome sequencing analysis of melanomas has demonstrated that somatic alterations in CDKN2A, CDK4 and CCND1 are extremely common in cutaneous melanomas. As shown in Figure 2 from the study by Hodis et al., which included both whole-exome sequencing and focused copy number analysis of genes previously implicated in melanoma, deletions of CDKN2A were detected in almost 40% of the examined samples, and mutations were identified in 19%. These alterations were found in melanomas with activating BRAF mutations and with NRAS mutations, and in tumors without mutations in either gene. As P16INK4A function can also be lost epigenetically by gene methylation, which was not evaluated in this study, loss of this cell cycle regulator is among the most common events detected in melanomas. The study also revealed that amplifications of the genes encoding CDK4 and CyclinD1 are enriched in cutaneous melanomas that do not have mutations in either BRAF, NRAS or NF1. While not identified as significant events in this study, other studies have also reported the detection of somatic mutations in CDK4.

The high prevalence of somatic alterations in cell cycle regulators suggests that agents that target this cellular process may have a role in melanoma. As described above, CDK4 has already been implicated as a combinatorial target with MEK inhibitors in melanomas with NRAS mutations. In addition, preclinical testing of human melanoma cell lines with the CDK4 inhibitor palbociclib demonstrated a correlation between the presence of alterations in CDKN2A, CDK4 and CCND1 with increased sensitivity to the agent. Palbociclib previously demonstrated an impressive and statistically significant improvement in PFS when combined with the hormonal agent letrozole (median 26.1 versus 7.5 months with letrozole alone) in patients with metastatic breast cancer at safely tolerated doses. Several other CDK4 inhibitors are in various stages of clinical testing. Multiple trials are now open or will open soon to determine the clinical efficacy of CDK4 inhibition as single-agents and in combinations in patients with metastatic melanoma.
KIT Mutations and Amplifications

Mutations in the KIT receptor tyrosine kinase (RTK) are the most common somatic event detected in gastrointestinal stromal tumors (GIST).47 The mutations detected in GIST are generally short insertions or deletions that affect key regulatory domains in the KIT protein and cause constitutive activation of its tyrosine kinase activity. Small molecule inhibitors of KIT, such as imatinib, have demonstrated significant clinical activity in GIST, and they are now the standard of care for the treatment of this disease.48,49 Thus, the discovery of KIT mutations in melanoma in 2006 generated tremendous excitement.50 While the mutations in KIT in melanomas generally affect the same regions as those that are observed in GIST, most frequently they are point mutations that result in single base substitutions.51 Amplification of KIT has also been observed in melanoma, both in wild-type and mutated alleles of the gene.

Mutations in KIT are relatively rare in melanomas that arise on skin characterized by intermittent sun exposure.52 However, some studies have suggested an increased prevalence of these mutations in melanomas with evidence of chronic sun damage.50,53 KIT mutations (10%) and amplifications (25%) are also relatively frequent in acral lentiginous melanomas, which arise from skin on the palms of the hands, the soles of the feet, and the nailbeds. Multiple case reports have demonstrated impressive and durable clinical responses in metastatic melanoma patients with KIT mutations treated with approved KIT inhibitors.51 These responses stand in contrast to the lack of responses observed in three previous phase II trials of imatinib in unselected metastatic melanoma patients, which reported only one clinical response. More recently, the results of three clinical trials have been reported for imatinib in metastatic melanoma patients with confirmed mutations and/or amplifications of the KIT gene.54-56 The trials reported clinical response rates of 16% to 29% with imatinib. These results demonstrate that KIT inhibitors can have clinical benefit in metastatic melanoma patients with KIT alterations. However, it remains unclear why many of the patients enrolled in these trials did not respond, and why the response rate even in this molecularly selected population is much lower than that observed in GIST patients with KIT mutations (70-80%). Each study included molecular analyses to elucidate the melanoma patients most likely to benefit from imatinib. A recurring finding was that many of the patients who responded had mutations that have been observed frequently in melanoma (i.e. L597P, K642E), although not all patients with those mutations responded. The studies have also demonstrated that the presence of a mutation in KIT is critical, as no patients with KIT amplification alone responded. One study suggested that patients whose tumors had both mutation and amplification of KIT were most likely to benefit from imatinib.55 Another study reported that the presence of concurrent mutations in NRAS, which were detected in 4 of 24 evaluable patients, predicts lack of response.54 Additional studies are ongoing to understand the correlates of sensitivity and resistance, and to define the activity of other KIT inhibitors in this population. Combinatorial strategies are also being investigated.

Other Targets and Novel Mutations in Cutaneous Melanoma

The PI3K-AKT pathway can be activated in cancer many different ways.57 In melanoma, the pathway appears to be activated most frequently and potently by loss of function of the tumor suppressor PTEN, although rare (1-3% prevalence) mutations in PIK3CA and AKT have also been observed.58 PTEN is a lipid phosphatase that antagonizes the activity of PI3K; loss of PTEN function results in constitutive activation of downstream components of the pathway, particularly AKT. Loss of PTEN expression is detected in 10-30% of melanomas.59 While loss of PTEN is largely mutually exclusive with NRAS mutations, it is observed both in melanomas with activating BRAF mutations and in melanomas that have wild-type BRAF and NRAS.15,60,61 There are many different classes of inhibitors targeting different components of the PI3K pathway. Preclinical studies have shown that AKT inhibitors are most potent in tumors that have loss of PTEN function.62,63 Thus, AKT inhibition may be a strategy that is particularly well-suited to melanomas with PTEN loss. Other studies support that tumors that have loss of PTEN are selectively dependent upon the β-isofrom of PI3K (PIK3CB).64,65 Consistent with this biochemical finding, preclinical studies have shown a positive correlation between loss of PTEN and sensitivity to selective inhibitors of PI3Kβ.66 Phase I trials of two different PI3K-selective inhibitors are currently enrolling patients (NCT01673737, NCT01458067).

While the PI3K-AKT pathway has been implicated in many cancers, melanoma sequencing analyses have also identified new molecular targets and mechanisms. Both large whole-exome sequencing studies of cutaneous melanomas identified recurrent point mutations in the RAC1 gene, which encodes a protein that is involved in cytoskeleton dynamics and cellular motility.13,14 A recurrent mutation that results in a P29S substitution was detected in 4-9% of cutaneous melanomas, making it the most commonly expressed hotspot mutation in melanoma after mutations in BRAF and NRAS. Initial functional studies showed that enforced expression
of the RAC1 P29S protein caused increased proliferation, migration, and RAS-RAF-MAPK pathway activation. Studies are ongoing to identify and test the therapeutic potential of RAC1 inhibitors. Unexpectedly, analysis of the data from whole genome sequencing of melanomas also identified two recurrent hotspot mutations in the promoter region of the TERT gene. This gene encodes telomerase, an enzyme which is essential for maintaining chromosome length through multiple cycles of cell division. Both mutations that were identified (C228T and C250T) caused increased transcription of the TERT gene due to the creation of new binding sites for transcription factors. Impressively, these mutations were detected in 50 of 70 melanomas (71%), making them more common than either BRAF or NRAS mutations. The therapeutic potential and significance of TERT mutations is currently unknown.

Conclusions and Future Directions
The field of melanoma is being transformed by multiple advances that have been made in both the laboratory and the clinic. It is now clear that somatic mutations in melanoma are extremely common and important events in this disease. This information has already been successfully exploited for patients with BRAFV600 mutations, as there are now both approved and experimental therapies that have demonstrated significant clinical efficacy in that molecularly-defined subtype of melanoma. While there is considerable research ongoing to identify strategies that will increase the degree and duration of clinical benefit of BRAF inhibitors, there is also growing momentum for the development of effective strategies for many of the other mutations that are found in this disease. As described above, clinical trials are now ongoing or in development for cutaneous melanoma patients with NRAS, KIT, and non-activating BRAF mutations. In addition, the discovery that ~80% of uveal melanomas have hotspot mutations in genes (GNAQ, GNA11) that regulate the activity of G-protein coupled receptors has led to new clinical trials for patients with that disease as well. Based on the lessons learned in the development of targeted therapies for BRAFV600 mutations, many clinical studies in melanoma patients include planned analyses to identify molecular features that predict sensitivity or resistance. As effective strategies are identified, there is also strong evidence to support the collection of biopsies from progressing lesions to rapidly identify and develop rational combinatorial strategies.

While much of the development of personalized approaches for patients with metastatic melanoma has focused on targeted therapy combinations, there are also opportunities to examine the benefit of other treatment modalities. In parallel to the described advances in targeted therapies, there have recently been multiple breakthroughs in the use of immunotherapy for melanoma. Interestingly, there is growing evidence that the pathways that are activated in tumor cells by somatic mutations can regulate the ability of the immune system to recognize and kill tumors. Mutations may also predict which patients benefit from immunotherapies, and may even create novel antigens that the immune system can recognize. Thus, there is a strong rationale to perform integrated analyses of both oncogenic networks and the immune system in clinical studies in melanoma moving forward, and to evaluate combinatorial approaches of these agents. Similar to earlier findings with immunotherapy, it is also possible that targeted therapies may synergize with other therapeutic approaches, such as radiation. Thus, while melanoma remains an aggressive and challenging disease, the progress that has been made on multiple fronts supports the new-found optimism that continued research will lead to additional clinically significant advances in the years to come.

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Conflicts of Interest
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References
Discov. models of acquired resistance to BRAF and MEK inhibitors.


