



Published in final edited form as:

*J Invest Dermatol.* 2015 August ; 135(8): 1929–1933. doi:10.1038/jid.2015.14.

## Targeted therapies in melanoma: Translational research at its finest

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### Abstract

The therapeutic landscape for advanced melanoma has expanded in recent years. This expansion has largely been driven by investigational work in melanoma tumor biology and immunology that has been successfully translated to the clinical setting. Molecular evidence generated through benchside experimentation identified BRAF and MEK as key molecular targets in melanoma. This commentary will highlight this work and provide a rationale for the continued importance of translational work in the field of targeted melanoma therapies.

### Introduction

Recent progress in melanoma drug development highlights the critical impact that translational research plays in advancing patient care. Prior to 2011, dacarbazine, interleukin (IL)-2, and interferon (IFN) $\alpha$ -2b were the only Food and Drug Administration (FDA) approved treatment options for metastatic melanoma. These early therapies resulted in poor and inconsistent overall response rates (~10–15% (Eggermont and Kirkwood, 2004)). A renaissance in melanoma therapeutics occurred with the recognition that molecular aberrations in the mitogen-activated protein kinase (MAPK) pathway (Figure 1) were present in a majority fraction of melanomas. (Davies *et al.*, 2002) These investigations resulted in the vigorous pursuit of small molecule kinase inhibitors and the eventual FDA approval of 3 novel MAPK pathway inhibitors for the treatment of advanced melanoma (Figure 1). Although key insights into immune checkpoint blockade have generated a similar number of recent immunotherapeutic breakthroughs (Brahmer *et al.*, 2012; Hamid *et al.*, 2013; Hodi *et al.*, 2010), this commentary will focus on the development of molecular targeted therapies.

Melanoma arises from the activation, or inactivation, of genes that regulate critical cellular functions including proliferation, cell cycle regulation, survival, angiogenesis, and cell migration. Efforts to systematically codify these changes have uncovered molecularly

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#### Conflict of Interest

The authors state no conflict of interest.

discrete subsets of melanoma (Curtin *et al.*, 2005). For instance, melanomas arising in the context of non-chronic sun-damaged (CSD) skin are associated with BRAF and NRAS mutations while lesions that arise from mucosal and acral surfaces are linked to KIT alterations (Curtin *et al.*, 2005). Moreover, some melanomas that lack NRAS or BRAF mutations harbor deleterious lesions in NF1 or amplifications of CCND1 and CDK4 (Lin *et al.*, 2008), which are downstream mediators of cell cycle progression in the MAPK pathway (Figure 1). These data suggests that inasmuch as melanomas ought to be classified histologically, molecular subtyping may provide a more pragmatic approach as specific therapies targeting receptor tyrosine kinases, downstream kinases, and other signaling molecules become available. Table 1 highlights key clinical trials that have expanded the treatment landscape of melanoma with targeted therapies.

## BRAF inhibition

The rationale for targeting BRAF is evident since the Val-600-Glu mutation in the BRAF kinase domain is the single most common mutation in cutaneous melanoma (Davies *et al.*, 2002). This substitution constitutively activates BRAF and its attendant downstream MAPK pathway effectors such as MEK (Figure 1). Although 50% of melanomas harbor the BRAF V600E mutation, nearly 80% of benign nevi also contain the identical mutation (Pollock *et al.*, 2003). Thus, it is an early genetic lesion that is neither necessary nor sufficient to fully induce melanoma. Preclinical work demonstrated that BRAF knockdown reduced tumor formation in murine xenograft models, and selective small molecule inhibitors of RAF suppressed BRAF-mutant melanoma cell lines (Hoeflich *et al.*, 2006; Joseph *et al.*, 2010). These translational studies show that BRAF is a well-validated target, and set the stage for the development of BRAF inhibitors for clinical use.

Early studies targeting RAF employed sorafenib, a multi-kinase inhibitor that has activity against BRAF and CRAF, but resulted in little to no clinical activity as monotherapy (Eisen *et al.*, 2006; Ott *et al.*, 2010). *Selective* BRAF inhibitors (i.e. those agents that specifically target mutant BRAF over wildtype BRAF), however, demonstrated impressive results in melanoma. The small molecule inhibitors vemurafenib and dabrafenib selectively bind the active conformation of BRAF and inhibit signal transduction between BRAF and MEK. A phase III trial, BRIM-3, of vemurafenib versus dacarbazine as first-line therapy for BRAF V600E mutated metastatic melanoma demonstrated improved median progression free survival (PFS; 5.3 vs 1.6 months) and better overall survival (OS; 84% vs 64%) at 6 months in the vemurafenib versus dacarbazine groups, respectively (Chapman *et al.*, 2011). The most commonly detected toxicities of vemurafenib included cutaneous eruptions, arthralgias, photosensitivity reactions, and cutaneous squamous cell carcinomas that were observed in 26% of patients. These results led to the FDA approval of vemurafenib (Zelboraf) in August 2011 for the treatment of unresectable BRAF V600E mutant melanoma.

Another phase III trial, BREAK-3, compared dabrafenib to dacarbazine in the treatment of patients with unresectable, metastatic, BRAF V600E mutation positive melanoma. BREAK-3 demonstrated similarly impressive results as BRIM-3. Patients in the dabrafenib arm had improved median PFS when compared to those in the dacarbazine arm, 5.1 versus

2.7 months, respectively, with a hazard ratio (HR) for progression of 0.30 (95% CI 0.18 – 0.51;  $p < 0.0001$ ) (Hauschild *et al.*, 2012). However, one important distinction between the 2 trials is that the primary endpoint for BREAK-3 was PFS, whereas the co-primary endpoint for BRIM-3 was PFS and OS. Dabrafenib also demonstrated remarkable efficacy in the treatment of intracranial metastases (Long *et al.*, 2012). Though vemurafenib and dabrafenib appear to have similar efficacy with respect to overall response rates, patients in the vemurafenib trials had higher rates of cutaneous squamous cell carcinomas, 18 – 25%, when compared to those in the dabrafenib trials, 6 – 11% (Chapman *et al.*, 2011; Hauschild *et al.*, 2012). BREAK-3 led to the FDA approval of dabrafenib (Tafinlar) in May of 2013 for the treatment of unresectable melanoma harboring BRAF V600E.

## MEK inhibition

Solit *et al.* reported early pre-clinical results that melanoma sensitivity to MEK inhibition was also correlated with the presence of the BRAF V600E mutation (Solit *et al.*, 2006). Thus, pharmacologic attenuation of MEK signaling represents another possible approach for BRAF-mutated tumors. Exome sequencing of metastatic melanoma specimens identified somatic mutations in MEK1 and MEK2 as potential clinically significant aberrations, characterizing MEK1 and MEK2 mutations in 8% of melanomas (Nikolaev *et al.*, 2012). Moreover, pharmacological MEK blockade completely abrogated tumor growth in BRAF mutant xenografts (Solit *et al.*, 2006). These data provided the rationale for a phase III trial, METRIC, which compared trametinib, a small molecule selective MEK1/2 inhibitor, to chemotherapy (dacarbazine or paclitaxel) in the treatment of patients with BRAF V600E/K mutant positive metastatic melanoma. Compared with patients receiving chemotherapy, patients treated with trametinib demonstrated significant improvement in median PFS (1.5 versus 4.8 months; HR 0.45; 95% CI 0.33 – 0.63;  $p < 0.001$ ) and 6-month OS (67% versus 81%; HR 0.54; 95% CI 0.32 – 0.92;  $p = 0.01$ ), despite being permitted to crossover to trametinib. Though cutaneous eruptions were observed as an adverse effect in 87% of patients, trametinib treatment was minimally associated with the development of cutaneous squamous cell carcinomas. Other toxic effects such as diarrhea and peripheral edema occurred in 35% and 27% of patients, respectively (Flaherty *et al.*, 2012b). Trametinib (Mekinist) gained FDA approval in May 2013 for the first-line treatment of patients with unresectable, BRAF V600E/K mutant positive melanoma.

## Combination BRAF and MEK inhibition

Despite the impressive levels of tumor shrinkage observed in BRAF mutant melanoma patients treated with small molecule BRAF inhibitors, responses are typically short-lived with a PFS of approximately 7 months (Chapman *et al.*, 2011; Hauschild *et al.*, 2012). Importantly, molecular studies characterized a number of potential mechanisms of resistance and demonstrated that combined BRAF and MEK inhibition effectively abrogated resistance mediated by MEK1 mutations, BRAF truncation, and acquired NRAS mutations (Paraiso *et al.*, 2010; Poulikakos *et al.*, 2011; Wagle *et al.*, 2011). In order to “over-suppress” MAPK signaling, a phase I/II trial demonstrated that combination dabrafenib and trametinib at full monotherapy doses improved response rate (76% vs 54%,  $p = 0.03$ ) and PFS (10.5 versus 5.6 months; HR 0.39; 95% CI 0.25 – 0.52;  $p < 0.001$ ) when compared to dabrafenib alone,

respectively (Flaherty *et al.*, 2012a). Based on these results, both dabrafenib and trametinib received accelerated FDA approval in January of 2014 for use in the treatment of patients with metastatic melanoma with a BRAF V600E/K mutation. Three recent phase III trials corroborated these early results. The combination of vemurafenib and the MEK inhibitor cobimetinib improved PFS (9.9 versus 6.2 months; HR 0.51; 95% CI 0.39 – 0.68;  $p < 0.001$ ) and OR (68% versus 45%;  $p < 0.001$ ) when compared to vemurafenib alone (Larkin *et al.*, 2014). In another expanded study, the combination of dabrafenib and trametinib improved PFS (9.3 versus 8.8 months, HR 0.75; 95% CI 0.57 – 0.99;  $p = 0.03$ ) and OR (67% versus 51%,  $p = 0.002$ ) when compared to dabrafenib alone (Long *et al.*, 2014). The much anticipated trial of the combination dabrafenib and trametinib demonstrated improved PFS (11.4 vs 7.3 months, HR 0.56, 0.46 – 0.69;  $p < 0.001$ ) and OS (72% vs 65%, HR 0.69; 0.53 – 0.89,  $p = 0.005$ ) when compared to vemurafenib as monotherapy (Robert *et al.*, 2014). Consistent with earlier studies, combination treatment led to lower rates of cutaneous squamous cell carcinoma formation compared to BRAF monotherapy. Thus, at this juncture, dual BRAF and MEK inhibition is quickly emerging as a standard-of-care for BRAF V600E mutated melanomas.

## Looking forward

Indeed, molecular targeted therapy has proven successful in the treatment of melanoma. Future directions include optimizing the currently available drugs for maximal clinical benefit and also the identification of novel therapeutic targets in melanoma. The above discussion highlights the significant clinical benefit of selective BRAF inhibitors and the eventual relapse that occurs in patients treated with this modality. Combination therapy targeting BRAF and MEK is one potential avenue to abrogate this resistance that has been explored clinically. Work in human melanoma xeno-graft models suggests another approach to delay BRAF inhibitor resistance. These studies demonstrate that vemurafenib-resistant melanoma cells maintain dependency on BRAF V600E signaling via BRAF V600E overexpression. Intriguingly, the vemurafenib-resistant tumors in this model demonstrate dependency on vemurafenib for continued proliferation, such that cessation of the drug leads to tumor regression (Das Thakur *et al.*, 2013). This suggests that a pulsed dosing strategy may forestall eventual vemurafenib-resistant tumors. As novel targeted therapies for melanoma emerge, one key clinical challenge will be developing optimal therapeutic regimens or combinations of therapies that will provide the most durable clinical response.

Inasmuch as the ideal treatment regimen of the existing melanoma drugs are being investigated, therapies targeting novel melanoma targets are in development. Given the genetic diversity of melanoma cells, there exist other attractive therapeutic targets including PI3K, CDK4, ERK, NF1, PPP6C, BCL-2, HSP90, mTOR, PDGF, Notch, MITF, and RAC1. Pre-clinical studies have begun to lay a foundation for further efforts to confirm clinical relevance.

## PTEN/PI3K

Molecular aberrations in the PI3K pathway play an important role in the pathogenesis of melanoma (Figure 1). The tumor suppressor PTEN negatively regulates PI3K signaling and has emerged as the dominant genetic target in the PI3K pathway for melanoma therapies.

PTEN mutations were found in 40% of melanoma cell lines and 10% of primary melanomas (Guldberg *et al.*, 1997; Tsao *et al.*, 1998b). Moreover, PTEN forced expression of PTEN in PTEN-deficient melanoma tumor cells abrogate activation of the downstream PI3K effector molecule AKT and cell growth (Robertson, 2005). Mouse models have suggested that PTEN dysregulation acts in concert with BRAF V600E to promote melanoma tumorigenesis and that targeting both MEK and the PI3K pathway in these mice inhibits tumor growth (Dankort *et al.*, 2009). These data strongly implicate PTEN and the PI3K pathway in the development of melanoma. Clinical trials targeting the PI3K pathway in combination with inhibiting the MAPK pathway in melanoma are currently underway (Table 2).

## CDK4/6

Inappropriate CDK4/6 activity can result from rare activating mutations of CDK4 (Tsao *et al.*, 1998a; Zuo *et al.*, 1996), or more commonly, loss of p16 (Figure 1). Knock-in mice expressing CDK4 mutations display enhanced melanoma in response to carcinogen exposure (Sotillo *et al.*, 2001). Thus, small molecule inhibitors targeting CDK4/6 may also be an effective strategy to target the cell cycle, and several agents are currently in clinical trials (Table 2).

The development of novel targeted therapeutic interventions in the treatment of advanced melanoma demonstrates the importance of translational studies. Characterization of the molecular aberrations present in different subsets of melanoma cells has driven the development of therapies targeted specifically at mutations proven to contribute to melanomagenesis. Pre-clinical and clinical efforts have led to the recent approval of a number of therapeutic agents that have improved the PFS and OS of advanced melanoma patients. Despite these successes, there remains much work to be done to characterize and exploit other molecular targets, to overcome resistance and adverse effects associated with the recently approved agents, and to evaluate how best to combine these new interventions to maximal benefit. The “bench to bedside” model provides an effective and efficient means to achieve these goals.

## Acknowledgments

Mentorship during the writing of this work was supported in part by the National Institutes of Health (K24 CA149202 to H.T.).

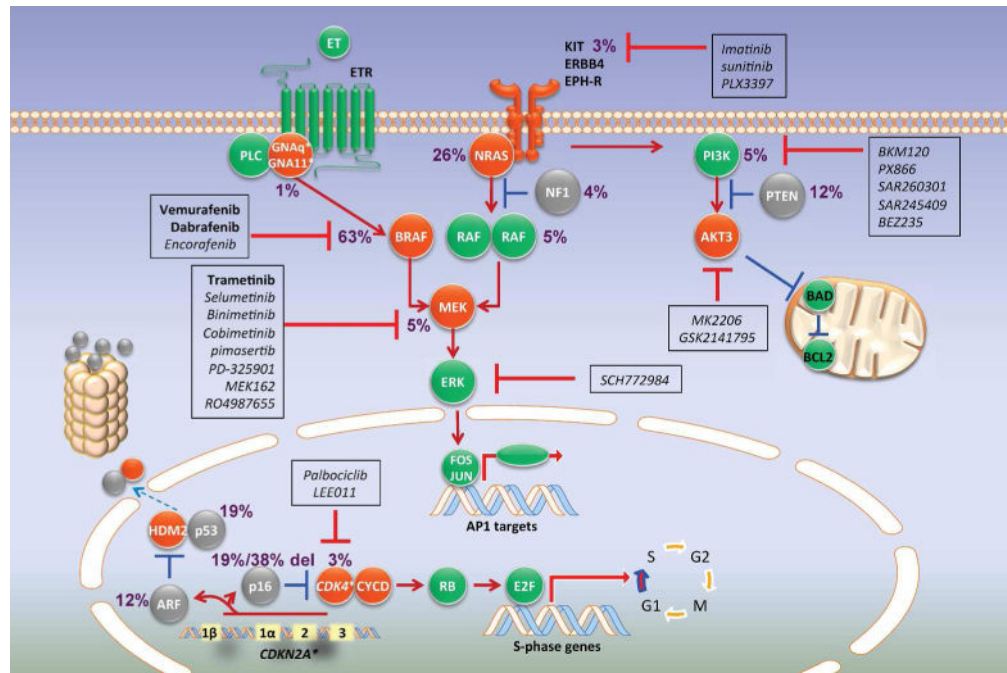
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**Figure 1.**

Molecular targeting of the mitogen-activated protein kinase (MAPK), PI3K, and CDK4 pathways and the associated mutation rates of potential molecular targets in advanced melanoma (Hodis *et al.*, 2012). Activation of a receptor tyrosine kinase such as c-KIT results in the propagation of signal via the MAPK pathway leading to activation of RAS, RAF, MEK and ERK. This ultimately results in the gene expression and promotes cellular proliferation and survival. Mutated BRAF bypasses this ordered pathway and stimulates constitutive signaling, making it a prime target for vemurafenib and dabrafenib. Trametinib targets the downstream effector molecule MEK. Dysregulation of the PI3K pathway promotes melanoma progression. Small molecule inhibitors of the PI3K pathway are being clinically tested in combination with MAPK pathway inhibition. Similarly, CDK4 is an attractive candidate molecule to target in melanoma and is the focus of multiple clinical trials. Red=activated; gray=inactivated; green=normal function. Drugs (shown in boxes) that have been approved (bold), or in trial (non-bold, italics), are indicated.



**Table 1**

Table of key clinical trials in targeted melanoma therapy.

Trial Name	Experimental agent	Control agent	Tumor response (experimental; 95% CI vs control; 95% CI)	PFS (experimental vs control)	OS (experimental vs control)
BRIM-3	vemurafenib (N = 337)	dacarbazine (N = 338)	48%; 42 – 55 vs 5%; 3 – 9	5.3 vs 1.6 months (HR 0.26; 0.20 – 0.33; p < 0.001)	84% vs 64% (HR 0.37; 0.26 – 0.55; p < 0.001)
BREAK-3	dabrafenib (N = 187)	dacarbazine (N = 63)	50%; 42.4 – 57.1 vs 6%; 1.8 – 15.5	5.1 vs 2.7 months (HR 0.30; 0.18 – 0.51; p < 0.0001)	Not statistically significant (HR 0.76; 0.48–1.21)
METRIC	trametinib (N = 214)	dacarbazine or paclitaxel (N = 108)	22%; 17 – 28 vs 8%; 4 – 15	4.8 vs 1.5 months (HR 0.45; 0.33 – 0.63; p < 0.001)	81% vs 67% (HR 0.54; 0.32 – 0.92; p = 0.01)
COMBI-d	dabrafenib + trametinib (N = 211)	dabrafenib (N = 212)	67%; 60 – 73 vs 51%; 45 – 58	9.3 vs 8.8 months (HR 0.75; 0.57 – 0.99; p = 0.03)	93% vs 85% (HR 0.63; 95% CI 0.42 – 0.94; p = 0.023)
coBRIM	vemurafenib + cobimetinib (N = 247)	vemurafenib (N = 248)	68%; 61 – 73 vs 45%; 38 – 51	9.9 vs 6.2 months (HR 0.51; 0.39 – 0.68; p < 0.001)	81% vs 73% (HR 0.65; 0.42 – 1.00; p = 0.046)
COMBI-v	dabrafenib + trametinib (N = 352)	vemurafenib (N = 352)	64%; 59 – 69 vs 51%; 46 – 57	11.4 vs 7.3 months (HR 0.56; 0.46 – 0.69; p < 0.001)	72% vs 65% (HR 0.69; 0.53 – 0.89; p = 0.005)

**Table 2**

Table of combined melanoma targeted therapies in progress.

Clinical trial number	Description
NCT01512251	BKM120 (PI3K inhibitor) + vemurafenib in BRAF V600E/K advanced melanoma
NCT01616199	PX866 (PI3K inhibitor) + vemurafenib in advanced melanoma
NCT01363232	Safety and pharmacodynamics of BKM120 (PI3K inhibitor) + MEK162 (MEK1/2 inhibitor) in advanced solid tumors
NCT01673737	Phase I/Ib trial of SAR260301 (PI3K inhibitor) +/- vemurafenib in advanced cancers
NCT01820364	LGX818 (RAF inhibitor) + MEK162, BKM120, LEE011, BGJ398, or INC280 in advanced BRAF melanoma
NCT02065063	Safety, anti-cancer activity, and pharmacodynamics of trametinib + palbociclib (CDK4/6 inhibitor) in solid tumors
NCT01777776	Safety and efficacy of LEE011 (CDK4/6 inhibitor) + LGX818 (RAF inhibitor) in BRAF melanoma
NCT01826448	Phase Ib trial of PLX3397 (Kit inhibitor) + vemurafenib in BRAF melanoma
NCT01928940	Japanese Phase I/II trial of GSK2118436 (dabrafenib) + GSK1120212 (trametinib) in BRAF solid tumors and cutaneous melanoma
NCT01433991	E7050 (cMET + VEGF inhibitor) + E7080 (VEGF inhibitor) in glioblastoma or advanced melanoma
NCT01909453	LGX818 (RAF inhibitor) +/- MEK162 (MEK1/2 inhibitor) vs vemurafenib in BRAF melanoma
NCT01701037	Dabrafenib +/- trametinib before surgery in advanced melanoma that can be removed surgically
NCT01562899	MEK162 (MEK1/2 inhibitor) + AMG479 (IGFR-1 mAb) in solid tumors
NCT01519427	Selumetinib (MEK inhibitor) + MK2206 (AKT inhibitor) in advanced melanoma that failed vemurafenib or dabrafenib
NCT01271803	Vemurafenib + GDC0973 (MEK inhibitor) in BRAF advanced melanoma
NCT01380818	MEK inhibitor + PI3K/mTOR inhibitor in advanced solid tumors
NCT01781572	Phase Ib/II trial of LEE011 (CDK4/6 inhibitor) + MEK162 (MEK1/2 inhibitor) in NRAS melanoma