The Intersection of Immune-Directed and Molecularly Targeted Therapy in Advanced Melanoma: Where We Have Been, Are, and Will Be

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Abstract
In three years, four drugs have gained regulatory approval for the treatment of metastatic and unresectable melanoma, with at least seven other drugs having recently completed, currently in, or soon to be in phase III clinical testing. This amazing achievement has been made following a remarkable increase of knowledge in molecular biology and immunology that led to the identification of high-valued therapeutic targets and the clinical development of agents that effectively engage and inhibit these targets. The discovery of either effective molecularly targeted therapies or immunotherapies would have led to dramatic improvements to the standard-of-care treatment of melanoma. However, through parallel efforts that have showcased the efficacy of small-molecule BRAF and MAP–ERK kinase (MEK) inhibitors, as well as the immune checkpoint inhibitors, namely ipilimumab and the anti-PD1/PDL1 antibodies (lambrolizumab, nivolumab, MPDL3280), an opportunity exists to transform the treatment of melanoma specifically and cancer generally by exploring rational combinations of molecularly targeted therapies, immunotherapies, and molecular targeted therapies with immunotherapies. This overview presents the historical context to this therapeutic revolution, reviews the benefits and limitations of current therapies, and provides a look ahead at where the field is headed. Clin Cancer Res; 19(19); 5283–91. ©2013 AACR.

Introduction
Melanoma is a deadly disease that is rising in incidence. In 2013, an estimated 76,000 new cases and 9,400 deaths are expected in the United States (1). Still, despite these stark numbers, there is great optimism in the melanoma research and treatment communities due to a number of breakthroughs that are transforming the way this disease is being treated. To highlight the dramatic progress being made to treat patients with melanoma, it is very possible that for the second time in 3 years, the number of therapies approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced melanoma will double in a 12-month period (Fig. 1). These advances have been the result of extraordinary scientific discovery combined with robust clinical and translational efforts. What follows is an overview of the past, current, and near future states of melanoma therapeutics and an introduction to the topics covered in this Clinical Cancer Research Focus section.

Immunotherapy and Melanoma
Melanoma has long been considered a malignancy that has a complex and unique interaction with the immune system. The first description of immune infiltrates in primary tumors was made decades ago, as was the definition of the prognostic significance of these infiltrates (2, 3). Further interactions between the immune system and melanoma have been posited as the explanation of two fascinating phenomena: (i) the long latency from primary melanoma resection of early-stage disease to the development of widespread metastases and (ii) the spontaneous regression of metastatic melanoma in a small number of patients (4, 5). Because of these findings and beliefs, immunotherapy has a long history in the treatment of melanoma starting with injections of immune stimulants (i.e., Bacillus Calmette-Guérin), moving to treatment with mediators of immune responses (i.e., cytokines) with or without “educated” immune effectors such as primed T lymphocytes (adoptive cell transfer), and more recently, monoclonal antibodies that target critical immune checkpoints and thereby lead to T-lymphocyte (T-cell) activation (6–11).

Cytokine therapy
In the early days of tumor immunology, it was evident that T-cell activation, in particular cytotoxic T-lymphocyte (CTL) activation, was required (12). Although the understanding of how T cells become active has evolved over the past four decades, one of the first major discoveries was that
a number of substances were produced and secreted by immune cells and could interact with receptors on other immune cells as well as tumor cells (13–15). The substances known as cytokines were initially grouped as one of two types, type 1 associated with CTL activation (so-called cellular immunity) and type 2, associated with antibody formation (so-called humoral immunity; ref. 16). Interestingly, these two types of cytokines were typically antagonistic, such that type 1 cytokines would inhibit humoral immunity and type 2 cytokines would inhibit cellular immunity. Not surprisingly, a number of type 1 cytokines were tested as antineoplastic therapies for melanoma, among other malignancies; only IFN-α-2B (IFN2B) and interleukin-2 (IL-2) showed sufficient benefit to support regulatory approval for melanoma (17).

High-dose IFN2B is approved for the adjuvant treatment of patients with intermediate- to high-risk melanoma (defined as American Joint Committee on Cancer stage IIIB, IIC, IIIA, IIIB, and IICC) based on data that showed an improvement in relapse/disease-free survival (RFS) and overall survival (OS; ref. 18). Since this initial report, a number of studies have been conducted with high-dose IFN2B showing a consistent improvement in RFS, yet not necessarily in OS (19). Similar data have been seen with pegylated IFN2B, an agent that received FDA approval in 2011 (20). Although the data with IFN2B led to its FDA approval as an adjuvant therapy for patients with intermediate- and high-risk melanoma, given its toxicity profile and underwhelming efficacy, its use in this setting is more by default due to a lack of more promising options than an endorsement of its effectiveness.

High-dose IL-2 is a highly toxic therapy that leads to a capillary leak syndrome associated with hypotension/shock, massive fluid retention, and renal failure necessitating that it be given in an inpatient, intensive-care level setting (8, 21). Its use is associated with a 16% to 23% response rate, with 5% to 10% of patients treated achieving a durable response that can last for decades (8, 22). Given the high toxicity and low response rate, IL-2 is only given in a small number of centers, although the potential for decades-long response is compelling and the reason why this therapy is still considered for highly selected and motivated patients.

**Adoptive immunotherapy**

Another therapy associated with long-term remissions is adoptive T-cell therapy (23). This involves the harvesting of tumor-infiltrating lymphocytes (TIL) from metastatic tumors, ex vivo expansion, and administration with IL-2 following nonablating lymphodepleting chemotherapy (24). In a small series of patients, this has resulted in complete remissions in up to 40% of cases, even when other immunotherapies have failed (24, 25). This approach remains investigational but is being explored at an increasing number of centers. In addition, further manipulations or genetic modifications of TILs (new culture conditions, altered cytokine secretion) and coadministration with other immune cells (i.e., natural killers cells or dendritic cells) and/or vaccines are being explored (26–30). Alternatively, tumor reactive T cells for clinical administration are also being engineered from peripheral blood by the introduction of receptors specific for tumor-associated antigens. And, most recently, the potential for molecularly targeted therapy to augment tumor infiltrates and enhance effector T-cell function following administration is being explored (reviewed by Kwong and colleagues in this issue; ref. 31).

**Immune checkpoint inhibition**

Over the past three decades, the complexities of immune activation, and T-lymphocyte activation specifically, have been elucidated. Although cytokines play an important role in directing immune effectors, the process of T-cell activation requires two major signals: (i) T-cell receptor (TCR) recognition of antigen in the context of MHC expressed on a professional antigen-presenting cell (APC) and (ii) costimulation in the form of TCR interactions between the T cell and the APC (32–34). This second step of costimulation involves a number of so-called "checkpoints" that regulate whether this process occurs or not (35). The two checkpoints that have garnered the most attention to date are the CTL antigen 4 (CTLA4) and the program death 1 (PD1) molecule.

CTLA4 is a surface protein on T cells that interacts with the APC membrane-bound costimulatory molecules, B7-1 (CD80) and B7-2 (CD86), and functionally competes with the T-cell costimulatory molecule CD28 (35, 36). After its identification as a potent, negative regulator of T-cell activation, it became an attractive target for monoclonal antibody therapy (37). Ipilimumab is a fully humanized monoclonal antibody that binds and inhibits CTLA4 function, thereby releasing a critical brake to T-cell costimulation (10). The preclinical discoveries of CTLA4 and its role in T-cell costimulatory regulation and subsequent clinical development of ipilimumab offer an amazing example of translational research, as ipilimumab was the first agent to be proven to prolong OS in patients with metastatic melanoma and the first agent since IL-2 to achieve FDA approval.
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for this treatment indication (10, 38). Clinical activity of ipilimumab has also been associated with the induction of serious immune-mediated adverse events, most prominently colitis, implying a broad role for CILA4 in suppressing autoimmunity. Notably, an agonist CD28 antibody proved to induce a life-threatening cytokine release syndrome and highlights the delicate balance of immune cell activation/inactivation that must be respected in designing safe and effective immune checkpoint–targeted therapies (39).

A second example of the increased knowledge of immune checkpoint biology leading to clinical improvement is the development of antagonists of PD1 and one of its ligands, PDL1. Following chronic T-cell activation, the inhibitory receptor PD1 is induced on T cells, and expression of one of its ligands, PDL1, on tissue-based macrophages and tumor cells can offer protection from immune destruction (40). As a result, targeting either PD1 or PDL1 offers an opportunity to disable a major mechanism of tumor-mediated immune evasion. The clinical development of monoclonal antibodies that inhibit either PD1 or PDL1 is under way and the results of early-stage clinical trials of the PD1 antibodies, nivolumab and lambrolizumab, as well as the PDL1 antagonists, MDX-1107 and MPDL1-3280, are impressive. Tumor responses (at least 50% appearing to be durable) are seen in a sizable minority of patients, whereas toxicity seems to be less prominent as compared with ipilimumab (11, 41–44).

In addition to the oncogenic mutations that lead to hyperactivation of the MAPK pathway (BRAF, NRAS, CKIT, NF1, and GNAQ/GAQL1), a number of other genes may be altered in melanoma and serve to complement the primary oncogenic mutations described above. In particular, abnormalities of genes involved in cell-cycle regulation, including cyclin-dependent kinases (CDK), CDK inhibitors [such as P16INK4a (CDKN2A)], and cyclin D are seen in more than 70% of the patients (reviewed in detail by Sheppard and McArthur in this CCR Focus section; refs. 59, 60). Also, the function of the negative regulator of the PI3K pathway, PTEN, is either lost or impaired in up to 30% of cases (61, 62). This is most commonly seen in a subset of patients with BRAF mutations, thereby allowing for unregulated signaling of both the MAPK pathway, via BRAF mutation, and the PI3K pathway, through PTEN loss of function (52, 63).

**Molecular classification of melanoma**

The MAPK pathway is almost always overexpressed in melanoma and is constitutively activated through genetic aberrations, most commonly via specific point mutations, in the great majority of the cases (Fig. 3). The most common of these genetic aberrations is mutation at the 600 position of BRAF (V600), present in 40% to 50% of melanomas (49, 50). Mutations of the N-isoform of RAS are found in another 15% to 25% of cases and tend to occur at either position 12 or 61 (51). NRAS and BRAF mutations are mutually exclusive (the co-occurrence rate is <<1%), lead to hyperactivation of the MAPK pathway, and are associated with a worse prognosis than are melanomas with wild-type NRAS and BRAF (52, 53). A loss-of-function mutation in the tumor suppressor gene, neurofibromatosis 1 (NF1), was recently identified in approximately 10% to 15% of cases and also is associated with abnormal MAPK signaling (54). When mutated, NF1 is no longer capable of keeping RAS in its inactive RAS-GDP form and thus leads to constitutive activation of RAS and the pathways downstream (55). Genetic mutations or amplifications are seen in other genes leading to upregulation of the MAPK pathway as well. These include cKIT mutations, seen in less than 1% of all melanomas, although in upwards of 10% to 30% of acral or mucosal melanomas, and mutations in small G-protein subunits called GNAQ and GNA11 that are present in more than 80% of ocular melanomas, though rarely seen in other melanoma subtypes (56–58).

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**Molecular Signaling and Melanoma**

In parallel to the amazing developments in the field of immunotherapy, there has been a remarkable advancement in the understanding of the molecular biology of tumor cells. Perhaps the most profound discovery, as it relates to the field of targeted therapy development, is the identification that tumors generally, and melanoma specifically, co-opt and then become dependent upon a small number of signal transduction pathways to stimulate cell-cycle progression and angiogenesis, prevent apoptosis, and abrogate host defense responses. In melanoma, the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways are the two major pathways that mediate growth and survival signals (Fig. 2; refs. 46, 47). The role of the PI3K pathway is reviewed in detail by Kwong and Davies in this CCR Focus section (48).

**MAPK inhibition and resistance**

With the first description of oncogenic BRAF mutations in melanoma, efforts were made to identify and develop clinical inhibitors of both BRAF specifically and the MAPK pathway in general. The initial targeted therapy studies in melanoma were with agents that are now considered non-specific inhibitors of BRAF, sorafenib and RAF265, and lower potency inhibitors of MAP–ERK kinase (MEK)-1/2, such as selumetinib, PD-325901, and CI-1040 (64–72). It is important to note that these studies were open to any patient with melanoma independent of mutational status. Thus, these trials were doomed for failure as the agents were not able to inhibit the MAPK pathway sufficiently at tolerable doses, and the patients treated were not preselected to include only those most likely to benefit. Mechanisms of resistance to these agents were impossible to determine given the fact that the pathway was suboptimally inhibited and thus few patients received benefit.

**BRAF-directed therapy in BRAF mutants.** The first so-called targeted therapy to show substantial efficacy in
melanoma was vemurafenib (73). In the initial phase I study, it was determined early that only patients with oncogenic (i.e., V600) mutations experienced clinical benefit and that almost every one of these patients had some evidence of tumor regression with treatment. Furthermore, responses occurred early with improvement of symptoms within days and near complete 2[18F]fluoro-2-deoxy-D-glu-
cose positron emission tomography (FDG-PET) responses within 2 weeks from the onset of therapy. A subsequent phase II study confirmed the remarkable response dynamics and frequency of vemurafenib, and a phase III study confirmed that vemurafenib conferred a survival advantage compared with chemotherapy (50, 74). A second, potent, and specific mutant BRAF inhibitor, dabrafenib, has been associated with very similar clinical efficacy as vemurafenib and joined it as the second BRAF inhibitor to achieve FDA approval (75). A third such BRAF inhibitor, LGX818, has shown responses at every dose level tested (76).

Although the advantages of BRAF inhibitor therapy are the rapid onset and high frequency of responses, the disadvantage is the limited duration of clinical benefit (74, 75). Specifically, BRAF inhibitor treatment is associated with a progression-free survival (PFS) of only 5 to 7 months as a result of the development of cellular resistance over this relatively short period of time. The mechanisms of this resistance can be subdivided into those that can be
predicted on the basis of pretreatment analysis of tumors and those that clearly were not identified at baseline but rather developed as a result of selective pressure placed upon the tumor cells by BRAF inhibitor treatment.

A number of identifiable pretreatment factors have been described as being associated with either a poorer response and/or a shorter PFS to BRAF inhibitor treatment. These include stromal hepatocyte growth factor (HGF) production, BCL2A1 [an antiapoptotic B-cell leukemia 2 (BCL-2) family member] expression, activation of cyclin D1, and loss of PTEN (77–81). It is interesting that each of these examples is associated with critical regulation of growth, survival, or cell-cycle regulation: the activation of the PI3K pathway (stromal HGF production leads to CMET activation of the pathway; PTEN loss leads to dysregulation of the pathway), resistance to apoptosis (BCL2A1), or cell-cycle progression (cyclin D1; Fig. 2).

Acquired resistance to BRAF inhibitors, defined here as the development of cellular resistance by a mechanism not identified in pretreatment tumors, is associated with reactivation of the MAPK pathway approximately two thirds of the time (82). One of the first described mechanisms of resistance (MOR) to BRAF inhibitors was the upregulation of receptor tyrosine kinases (RTK) such as insulin-like growth factor receptor 1 (IGF-R1), platelet-derived growth factor (PDGF), as well as HER3 that can signal through PI3K or the MAPK pathway by activating the C isoform of RAF (83–86). Although BRAF inhibitors potently inhibit BRAF, a mutant isoform that signals through a constitutively active kinase in a monomeric form, they paradoxically facilitate RAF dimerization, thereby leading to activation of the MAPK pathway (87, 88). This so-called “BRAF inhibitor paradox” explains how RTK activation upstream of RAF can reactivate the MAPK pathway through CRAF homo- or heterodimerization and how other MORs to BRAF inhibitor therapy activate the pathway. For example, concomitant mutation of NRAS and BRAF is seen in more than 20% of the resistance samples driving MAPK signaling, and an alternative splice variant of BRAFV600E that can dimerize in the context of BRAF mutation emerges in 20% to 25% of the resistance samples; loss of NF1 leading to NRAS activation has also been described (86, 89, 90). In addition, other MORs that do not rely on paradoxical activation also are seen and include increased expression of BRAFV600D, downstream oncogenic mutation of MEK, and alternative MAPK activation (COT) leading to activation of MEK (refs. 91–94; MORs are summarized in Fig. 4).

MEK-directed therapy. The clinical development of more selective MEK1/2 inhibitors, such as trametinib and MEK162, has led to the proof of principle that MEK is a legitimate target in melanoma, both in BRAF-mutant melanoma and, to a lesser degree, in BRAF wild-type melanoma (harboring NRAS or NF1 mutations; refs. 95, 96). In fact, trametinib has recently been FDA approved for the treatment of BRAF-mutant metastatic melanoma based on a randomized phase III study showing that treatment with trametinib is associated with a survival advantage compared with conventional chemotherapy (response rate (RR) 22%, PFS 4.8 months, 6-month OS 81% for trametinib vs. RR 8%, PFS 1.5 months, 6-month OS 67% for chemo; ref. 96). MEK162 has also shown clinical efficacy in both BRAF- and NRAS-mutant melanoma in a phase II study (BRAF mutants: RR 20%, PFS 3.6 months; NRAS mutants: RR 20%, PFS 3.7 months; ref. 97). A phase III study is under way to explore
whether MEK162 is more effective than chemotherapy in NRAS-mutant melanoma (NCT01763164). Finally, selumetinib was shown to have modest efficacy in patients with uveal melanoma. In a randomized, phase II study, treatment with selumetinib was associated with a two-fold improvement in PFS compared with patients who received chemotherapy, though notably, OS was not different in the two treatment groups (98). On the basis of the results of all of these studies, it seems clear that MEK inhibition is associated with modest benefit (20% RR, PFS 4–5 months) in subsets of patients with melanoma and will have a role as a single agent in the treatment of this disease. The MORs of single-agent MEK inhibitor therapy have not been well elucidated.

**The future of targeted therapy in melanoma**

It is important to acknowledge that targeted therapy in melanoma remains in its infancy. Only 4 years have passed since initial clinical data with vemurafenib were presented. During this time, the collective knowledge about both mechanisms of action and resistance of BRAF and MEK inhibitor therapy has grown nearly exponentially. As these data have emerged, so too have clinical trial ideas using BRAF and MEK inhibitor therapy as the backbone to combinatorial regimens that have been rationally designed from our scientific understanding of how these agents change tumor cells.

The first example of this second wave of trials focusing on combination regimens is a phase I/II combination of dabrafenib and trametinib (99). It was predicted that reactivation of the MAPK pathway would occur in the setting of BRAF inhibitors (82). Therefore, inhibition of the pathway downstream of BRAF by targeting either MEK or extracellular signal-regulated kinase (ERK) was considered as an approach that might lead to further clinical benefit, and perhaps more remarkably, improvement in severity of toxicity. Interestingly, the sequential administration of a BRAF inhibitor followed by a MEK inhibitor is ineffective and exposes patients to the potential toxicities seen with each single agent, yet concurrent treatment with both agents is associated with an improvement in RR, response depth (i.e., greater maximal response), response duration, and PFS, and a reduction in toxicity severity (99, 100). This peculiar safety signal is based on the fact that BRAF inhibitors paradoxically activate the MAPK pathway through facilitation of RAF dimerization (87, 88). As discussed above, many MORs to BRAF inhibitors emerge as a result of this phenomenon, however, the toxicity of BRAF inhibitors is also likely explained by this. Namely, BRAF inhibitor toxicity is likely a result of upregulation of the MAPK in nonmelanoma cells; the best-described example is the development of squamous cell carcinomas of the skin secondary to RAS mutations in skin cells (101). This phenomenon is seen at a much lower frequency with the treatment of BRAF-mutant melanoma with MEK inhibitors (99). Therefore, in BRAF-mutant cells, BRAF and MEK inhibitors both inhibit the pathway leading to augmented inhibition but exert differential effects on the MAPK pathway in non-BRAF–mutant cells such as squamous cells of the skin, leading to an attenuation of toxicity. There are now two additional phase I combinations of BRAF plus MEK inhibitors showing similar improvements in efficacy and abrogation of toxicity severity (102, 103). Phase III studies of each of these combinations are under way (NCT01689519; NCT01597908; NCT01584648) or being planned. It is expected that over the coming 5 years, triple and quadruple drug regimens will be studied in the clinic to treat BRAF-mutant melanoma with the BRAF and MEK inhibitor combination at the core.

In NRAS-mutant melanoma, it is anticipated that two events will occur in the near future that will hopefully lead to the dramatic improvement in how these patients are treated. First, a phase III study of MEK162 (NCT01763164) has been launched to determine the efficacy of this agent compared with chemotherapy. If successful, regulatory approval would be expected. Second, a number of combination regimens are expected on the basis of preclinical data showing that a number of agents may augment MEK inhibitor toxicity in patients with NRAS-mutant melanoma (104, 105). Two examples are the combination of a MEK inhibitor with a CDK4/6 inhibitor (NCT01781572) and a combination of a MEK inhibitor with an HDM2 antagonist, though many more doublet and triplet combinations are expected in the near future.

**Grand unification: the intersection of MAPK inhibition and immunotherapy**

When ipilimumab and vemurafenib were approved by the FDA within months of each other in 2011, a great deal of advocacy was directed toward the makers of each drug to support a combination trial. It turns out that there is actually a compelling rationale to combine BRAF inhibitors with immunotherapies that goes beyond the fact that they are both effective in patients with melanoma. In particular, emerging evidence suggests that oncogenic BRAF is immunosuppressive (106, 107). Furthermore, treatment with MAPK inhibitors is associated with enhanced expression of melanocytic antigens, antigen recognition by T cells, and an influx of CTLs (108–112). These findings offer compelling evidence for the development of combined targeted and immune therapies, although based on the early attempts at combining BRAF inhibitors with checkpoint inhibitors, clinical trials may not be so simple. As an example, the phase I trial of vemurafenib plus ipilimumab was closed because of toxicity concerns, namely a high rate of severe hepatic toxicity (113). Still, a number of trials have opened exploring various BRAF-directed therapies (single agent, BRAF inhibitor plus MEK inhibitor combinations, etc.) with checkpoint inhibitors and cytokines alike. The great hope is that the ideal combination will be identified that will be associated with a very high rate of durable clinical response and no untoward toxicity.

**Conclusions/Future Directions**

From the bleakness of the recent past to the great promise of the near future, the development of melanoma therapeutics has always relied on a strong connection with hardcore molecular biology and immunology laboratories to drive the clinical progress. This is more important than ever as critical issues remain about the ideal sequences and
combinations of the various agents that have proven pre-clinical and clinical efficacy.

Disclosure of Potential Conflicts of Interest

K.T. Flaherty is a consultant/advisory board member of GlaxoSmithKline, Roche/Genmtech, and Novartis. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: R.J. Sullivan, K.T. Flaherty
Development of methodology: R.J. Sullivan

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