Targeting KIT for Treatment Of Advanced Melanoma

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This is a remarkable time for melanoma research and treatment. Before this year, approved agents available for the treatment of metastatic melanoma were limited to dacarbazine (DTIC) and interleukin-2 (IL-2), with benefits achieved in only a small minority of patients treated with either drug. In 2011, however, two new agents, ipilimumab (Yervoy™) and vemurafenib (Zelboraf™), were approved, with each showing a demonstrable survival advantage in patients with advanced disease.

Ipilimumab, an antibody targeting cytotoxic T-lymphocyte associated antigen 4 (anti-CTLA-4), may be beneficial in all patients irrespective of tumor genotype.1,2 In contrast, it is clear that vemurafenib, a small molecule inhibitor with specificity for mutant BRAF harboring a substitution of glutamic acid for valine at position 600 (V600E), is only effective in patients whose tumors carry such a mutation.3 The clinical success of vemurafenib was dependent upon the discovery of driver mutations in BRAF in 45 percent of melanomas and limiting the inclusion of patients in clinical trials of this agent to those with BRAF-mutant tumors.

Recurrent alterations of other key melanoma oncogenes leading to constitutive activation of growth-signaling pathways have also been identified. In some cases, the tumor is dependent upon one or more of these mutations for survival. Targeting such alterations in select cases may achieve significant benefits.

From the Editors

It has been a watershed year in melanoma therapy, with FDA approval of two new drugs for advanced melanoma. The most dramatic clinical responses have been to BRAF targeted therapy, which capitalizes on the discovery of a specific driver mutation present in many melanomas, and was discussed in detail in the last issue of The Melanoma Letter.

Other driver mutations are now being targeted in tumor-directed therapies. One such mutation found in a subset of melanoma patients involves cKit. Targeting the cKit mutation offers similar hopes of controlling metastatic melanomas that harbor the defect. In the lead story in this issue, Dr. Richard Carvajal shares with us current knowledge on the use of imatinib and other developing drugs as targeted therapy for melanomas harboring the cKit driver mutation.

On the other side of the equation, it has long been appreciated that the immune system plays an important role in preventing and controlling cancer. Harnessing the immune system to treat cancer has been the goal of immunotherapists for decades, and therapies like IL-2 and adoptive T cell transfer have demonstrated encouraging evidence of the principle that even patients with advanced metastatic cancer can be cured with immunotherapy.

Unfortunately, these immunotherapies are associated with considerable toxicity and are applicable for only a small minority of patients. A recent breakthrough in melanoma immunotherapy was the approval of ipilimumab (Yervoy), an immune checkpoint blockade inhibitor, which
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clinical benefits potentially comparable to those observed with BRAF targeting. Such is the hope for KIT.

Identification of KIT as a Melanoma Oncogene

KIT is a transmembrane receptor tyrosine kinase normally expressed on hematopoietic progenitor cells, mast cells, primordial germ cells, the interstitial cells of Cajal (the gastrointestinal stromal tumor [GIST] cells of origin), and melanocytes. Binding of its ligand, stem cell factor, results in activation of downstream signaling pathways including the MAPK, PI3K/AKT, and JAK/STAT pathways. Intracellular signaling through KIT plays a critical role in melanocyte development. Loss of function alleles leads to defects in melanocyte migration, survival, proliferation, and differentiation.

Initially, KIT was considered a possible melanoma tumor suppressor gene. It was observed that melanomas lost KIT expression with progression to more advanced stages, suggesting that loss of KIT might, in part, lead to tumor progression. Constitutive activation of KIT in primary melanocytes led to decreased proliferation, and expression of KIT in melanoma cell lines without native KIT expression led to the induction of cell-cycle arrest and apoptosis, findings that also supported the tumor suppressor hypothesis. It was not until the discovery of activating KIT mutations in several distinct clinical subgroups of melanoma that investigators began to take another look at KIT.

Bastian and colleagues identified the existence of several distinct molecular subtypes of melanoma, each with a corresponding clinical subgroup and each characterized by a unique frequency of key genetic alterations. While KIT mutations or amplification were not observed in melanoma arising from non-chronically sun-damaged skin (non-CSD), these changes were observed in 29 percent of mucosal, 18 percent of acral, and 23 percent of CSD-melanomas. The KIT mutations identified included activating mutations in the juxtamembrane domain similar to those found in GIST, a disease known to be dependent upon KIT activation. Preclinical work demonstrated the constitutive activation of KIT kinase activity in mutant cells not observed in KIT wild-type cells. Exposure of mutant, but not wild-type, cells to clinically available KIT inhibitors led to down-regulation of multiple downstream mediators, resulting in cell cycle arrest, induction of apoptosis, and a reduction of cell proliferation.

Exposure of mutant, but not wild-type, cells to clinically available KIT inhibitors led to down-regulation of multiple downstream mediators, resulting in cell cycle arrest, induction of apoptosis, and a reduction of cell proliferation.

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is more broadly applicable and has had significant life-extending benefits.

Along with immunotherapy for advanced disease, there have been decades of research in adjuvant immunotherapy. The concept is to treat patients without clinical evidence of disease who are nonetheless at very high risk of developing distant metastases; the hope is to forestall or prevent this from happening. Typically, these patients have been surgically rendered ‘free of disease’ by removal of lymph node metastases or thick primary melanomas. The only FDA-approved immunotherapy for these patients is interferon, the most broadly and extensively tested adjuvant therapy for melanoma. The varied formulations, doses, and timing of interferon in multiple clinical trials make interpretation of the data a bit challenging. In this issue of *The Melanoma Letter*, Drs. Ahmad A. Tarhini and John Kirkwood present an excellent review and summary of these many trials, including the latest information on the recently FDA-approved pegylated version of interferon.

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From Bench to Bedside

Identification of these oncogenic KIT mutations led to the hypothesis that KIT targeting would be an effective treatment strategy for melanomas driven by such alterations. Indeed, dramatic tumor responses achieved with imatinib mesylate or dasatinib, two small molecule inhibitors of KIT, were observed, including cases of two patients with melanoma arising from the anorectal mucosa, one harboring an exon 13 K624E mutation and one harboring a seven-codon duplication of exon 11. Both were treated with imatinib. A third case of melanoma arising from the vaginal mucosa and harboring an exon 11 L576P mutation significantly responded to dasatinib.

These reports are all the more remarkable given the negative results of three completed phase II studies of imatinib for patients with advanced melanoma.9-11 These studies were initiated before the identification of KIT mutations in melanoma and enrolled primarily patients with the more common melanomas arising from non-CSD skin not associated with KIT aberrations. In this molecularly unselected patient population, imatinib was ineffective, with only one response observed among the 62 evaluable patients enrolled across these three trials. Interestingly, the patient who achieved a durable, near-complete response had an acral melanoma. Although his tumor was characterized by a KIT splice site mutation in exon 15, the significance of the resulting aberrant protein is unknown. While negative, these studies are not inconsistent with the hypothesis that KIT inhibition in the proper genetic context is an effective therapy for advanced melanoma. Rather, they support the hypothesis that KIT inhibition in molecularly unselected patients is ineffective.

Three additional phase II clinical trials of imatinib in advanced melanoma patients were subsequently initiated to assess the efficacy of KIT inhibition in melanomas harboring KIT aberrations, with a KIT alteration required for eligibility. Of the 25 evaluable patients treated in a study led by Memorial Sloan-Kettering Cancer Center (MSKCC), two achieved complete responses lasting 94 weeks (ongoing) and 95 weeks, two achieved durable partial responses lasting 53 weeks and 89 (ongoing) weeks, and two achieved transient responses lasting 12 and 18 weeks.
The overall durable response rate was 16 percent; however, significant clinical benefit in terms of disease control was also observed in patients with stable disease.

Similar findings were observed in the other studies. Guo, et al reported a 23.3 percent response rate in 43 evaluable patients, with a median progression-free survival of nine months for those achieving a response or disease stability, and a median overall survival of 15 months. At the 2009 International Melanoma Congress held in Boston, MA, Hodi, et al provided an interim report on a study led by the Dana-Farber Cancer Institute, revealing a 25 percent RECIST (Response Evaluation Criteria In Solid Tumors) response rate in the 20 evaluable patients treated. All five responses were observed in patients whose tumors harbored KIT mutations. Of the 10 patients whose tumors harbored KIT amplification without a mutation, no responses were observed; however, two such patients achieved stable disease lasting six to seven months.

Mutations in KIT, unlike those in BRAF, are widely distributed over the coding region (See Figure 1), raising the possibility that not all mutations are equally relevant functionally. Many KIT mutations identified in melanoma have not previously been reported and are present only in individual cases, suggesting that some mutations represent passenger mutations rather than true driver alterations. Interestingly, all six responses in the MSKCC study occurred in tumors with L576P or K642E mutations, the most common mutations found in melanoma. Similarly, in the study by Guo, et al, nine of the 10 patients who achieved a response to therapy had melanoma harboring a mutation in exons 11 or 13 of KIT, while only one of three patients whose tumors harbored amplified KIT alone achieved a response.

These observations suggest that by utilizing more selective molecular criteria, we may be better able to identify those patients who will benefit from imatinib. Only those tumors truly dependent upon a constitutively active KIT signaling pathway will likely be susceptible to KIT inhibition, and the development of biomarkers permitting the reliable identification of these KIT-driven tumors is critical.

<table>
<thead>
<tr>
<th>KIT Exon Number</th>
<th>Associated Protein Domain</th>
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<td>Exon 9 (n = 3/48; 6%)</td>
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<td>Exon 17 (n = 5/48; 10%)</td>
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<td>Exon 18 (n = 9/48; 19%)</td>
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<td>A829P (n = 1) L831P (n = 1) P838L (n = 1) S840I (n = 1) Y846C (n = 1) S850G (n = 1) V852I (n = 1) L859P (n = 1) L862P (n = 1)</td>
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Figure 1. Schematic representation of the KIT tyrosine kinase receptor and mutation frequency

This diagram shows the distribution and frequency of mutations observed in a phase II trial of imatinib in patients with melanoma harboring a mutation or amplification of KIT. Five immunoglobulin-like domains are located in the extracellular domain and serve as the binding site for the KIT ligand. The juxtamembrane autoinhibitory domain serves to maintain the kinase domains in an inhibited state unless the receptor is bound by ligand.12
Future Directions

While significant benefit is achieved with imatinib in a subset of patients whose tumors harbor KIT aberrations, evaluation of other inhibitors is warranted. The spectrum of activity of each inhibitor for specific KIT mutations or affected domains is unique, thus the sensitivity of a melanoma to a particular inhibitor may differ depending on its KIT mutation. Trials of sunitinib, sorafenib, nilotinib, dasatinib and masatinib in patients with advanced melanoma are ongoing (See Table 1).

A randomized phase III trial of nilotinib versus DTIC in KIT mutant melanoma was initiated in 2010; however, due to challenges with accrual of patients with this uncommon genetic subset of melanoma, the study (the Tassigna Efficacy in Advanced Melanoma, or TEAM, Trial) was recently modified to a single-arm phase II trial of nilotinib alone. Unfortunately, the implications of this modification upon potential drug approval by the US Food and Drug Administration, should the study be positive, is currently unclear.

Conclusions

Further work is necessary to elucidate mechanisms of primary and secondary resistance to KIT inhibition in order to optimize KIT-targeted therapy for this patient population. Evaluation of the sequential use of different KIT inhibitors (a strategy of proven benefit in GIST) in KIT-driven melanoma resistant to one agent is under way. Finally, studies combining KIT inhibitors with chemotherapy, immunotherapy, and other “targeted” agents in an effort to improve outcomes are in development or ongoing.

With our increasing knowledge of the biological heterogeneity of melanoma, we are making significant strides in developing effective therapies for this disease; however, this success is dependent upon tumor genotyping. Prospective screening for specific alterations, such as KIT mutations or amplification, will permit us to select specific targeted therapies for genetically appropriate patients, and allow continued improvement in clinical outcomes for those with advanced disease.

Table 1. Trials of Inhibitors Targeting KIT

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<th>Agent(s)</th>
<th>Lead Site/Sponsor</th>
<th>NCT Number</th>
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</table>

Table 1. Trials of Inhibitors Targeting KIT

References

New Adjuvant Peg-IFN: What Does Its FDA Approval Mean?

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To date, immunotherapy has been associated with the only long-term durable clinical benefits for patients with high-risk or advanced melanoma. Until recently, the only immunotherapy treatments approved by the US Food and Drug Administration (FDA) were adjuvant therapy with high-dose interferon-alpha2b (IFNα2b), approved in 1996 for high-risk resected melanoma, and high-dose interleukin-2 (IL-2), approved in 1998 for patients with metastatic disease. In 2011, however, two new immune agents received regulatory approval: ipilimumab, aka Yervoy™ (for metastatic unresectable melanoma), and pegylated interferon-alfa 2b (Peg-IFN), aka Sylatron™ for adjuvant therapy of node-positive resected melanoma.

The Significance of Marshaling the Immune Response

This progress has emerged from the continually increasing understanding of immune processes and their relationship to melanoma. Over the years, the significance of host immunity in melanoma therapy had been suggested by reports of spontaneous regression of disease and pathological evidence of lymphoid infiltrates in primary melanoma associated with tumor regression. In addition, T cell infiltrates have been suggested to be of prognostic value in primary melanoma.1,2 and in regional nodal metastases have been associated with clinical benefits in patients treated with neoadjuvant IFNα2b.3,4,5 Moreover, the use of immunotherapy in the adjuvant disease-free setting is supported by the observation that host immune responses differ qualitatively (Th1 effector T cell versus Th2 tolerant T cell) between early and advanced disease settings. Patients in the adjuvant setting exhibit Th1-polarized immune responses that may be more susceptible to immunologic interventions.5,7 Notably, while IFNα at high dosage has shown a limited clinical impact in the management of metastatic disease, it demonstrated the first significant impact upon melanoma relapse and survival in the adjuvant therapy setting.

The High-Dose IFNα2b Regimen

Adjuvant therapy with high-dose IFNα2b (HDI) for surgically resected high-risk cutaneous melanoma has been tested in three phase III US national cooperative group studies (E1684, E1690, and E1694, all focused upon resected AJCC stage IIB and III melanoma) and one Eastern Cooperative Oncology Group (ECOG) randomized phase II trial (E2696, focusing upon resected AJCC stages IIB, III, and IV). The HDI regimen consists of an induction phase administered intravenously at 20 MU/m²/d for five consecutive days out of seven every week for four weeks followed by a maintenance phase given subcutaneously at 10 MU/m²/d every other day three times each week for 48 weeks.

E1684 and E1694 demonstrated significant survival prolongation for the HDI regimen compared with observation or a vaccine that proved to be ineffective. E1684 showed median relapse-free survival (RFS) of 1.72 years in the HDI arm versus 0.98 in the observation arm [stratified log-rank one-sided p-value (P₁) = 0.0023], and median overall survival (OS) of 3.82 years in the HDI arm versus 2.78 (P₁ = 0.0237) for observation only.8

The HDI regimen also demonstrated prolonged survival compared to the GMK vaccine that was selected as the most promising vaccine candidate at the time (E1694 in 1995).9 In E1694, significant differences emerged in both trial efficacy endpoints at a median follow-up interval of 16 months where HDI provided significant RFS benefit (hazard ratio [HR] = 1.47; P = 0.0015) and OS benefit (HR = 1.52; P = 0.009) compared with GMK. A similar benefit was observed in the intent-to-treat analysis of RFS (HR = 1.49) and OS (HR = 1.38).9

The second cooperative group trial testing HDI, E1690, has provoked more questions than other trials: E1690 was conducted in part before and in part after FDA approval of HDI (based on E1684 results), and was associated with consistent crossover of patients from the observation-assigned arm to treatment with HDI at nodal relapse. This trial showed differences in terms of RFS but not OS. In the intent-to-treat analysis of RFS, treatment with HDI was associated with a statistically significant benefit compared with observation (HR = 1.28; P = 0.025).10 Observation patients who crossed over to HDI at regional nodal recurrence (stage IIB patients) had not been required to undergo lymphadenectomy prior to study entry as in E1684, and analysis of the post-relapse impact of HDI demonstrated a large benefit that could have confounded the survival analysis.10 The analysis of each of these studies was updated in a pooled analysis of survival and relapse-free outcomes up to April 2001.11 The pooled analysis demonstrated that IFNα2b prevents relapse up to intervals of 20 years, although this analysis (which included the observation-controlled trials E1684 and E1690 but not E1694) did not yield compelling evidence of an impact upon
OS, despite the positive survival results of the two randomized US Cooperative Group and Intergroup studies (E1684 and E1694). This is not surprising, given that the larger of the two observation-controlled trials included in the pooled analysis (E1690) did not show an OS benefit for HDI.

A meta-analysis of 12 randomized trials of adjuvant IFNα in high-risk melanoma patients estimated a highly significant reduction in the odds of recurrence in treated patients compared to observation only patients. Further, it demonstrated evidence of increased benefit with increasing IFN dose and a trend toward increased benefit with increasing total dose. However, it found no statistically significant OS benefit.12 A subsequent larger meta-analysis of 13 randomized trials reported that IFNα reduced the risk of recurrence or death by 13 percent (OR 0.87, 95% CI 0.81–0.93 for RFS; p=0.0001) and the risk of death by 10 percent (OR 0.90, 0.84–0.97 for OS; p=0.008) compared with observation or vaccination. It did not define an optimal (high, intermediate, or low) dose of interferon.13 The latest and largest meta-analysis of 14 adjuvant randomized clinical trials estimated that IFNα therapy was associated with a significant improvement in disease-free survival (HR for disease recurrence: 0.82; 95% CI: 0.77–0.87; P < .001) and improved OS (HR for death: 0.89; 95% CI: 0.83–0.96; P = .002). However, this meta-analysis again did not clarify an optimal dose or duration for IFNα.14

Peg-IFNα

The covalent attachment of polyethylene glycol (PEG) polymer chains to a drug or therapeutic protein can mask the agent from the host’s immune system, reducing immunogenicity and antigenicity, and thereby increasing the size in solution of the agent, which prolongs its circulatory time by reducing renal clearance. The EORTC (European Organization for Research and Treatment of Cancer) 18991 trial that is the pivotal study of Peg-IFN theorized that prolonged treatment may be necessary for the anti-angiogenic benefits of IFN, citing prior studies (EORTC 18952 and French Melanoma COG) where the authors concluded that the effects of IFN on RFS are rapidly lost after discontinuation of treatment.15,16 The 18991 trial authors hypothesized that prolonged weekly self-administered adjuvant pegylated IFN might improve the benefit-toxicity ratio for patients with resected stage III melanoma. This study compared observation with treatment utilizing maximally tolerable doses of pegylated IFNα2b (Peg-IFNα) for an intended five years in patients with resected stage III melanoma (TxN1–2M0).17

The pooled analysis demonstrated that IFNα2b prevents relapse up to intervals of 20 years, but did not yield compelling evidence of an impact upon overall survival.

Peg-IFNα was administered at six µg/kg/week during the first eight weeks, followed by three µg/kg/week maintenance therapy for up to five years. This trial showed significant benefit in the primary endpoint of RFS, with a median RFS of 34.8 months for peg-IFNα compared with 25.5 months for the observation only group (HR: 0.72; 99% CI: 0.46–1.13) and OS (HR: 0.59; 99% CI: 0.35–0.97). A prospective EORTC 18081 trial plans to compare Peg-IFNα with observation in patients with ulcerated primary tumors > 1 mm. Patients with stage III N2 disease showed no benefit from adjuvant peg-IFNα in any endpoint.

Conclusions

There is now wide overall agreement that RFS is significantly improved with IFNα2b as reported in all three US Cooperative Group trials testing HDI (E1684, E1690, E1694) and in the multiple lower-dose IFN trials summarized in the three aforementioned meta-analyses. OS benefits have been significant only in the independent observation-controlled and vaccine-controlled trials of HDI (E1684 and E1694). An OS benefit was also noted in the two largest meta-analyses, by Wheatley, et al13 and Mocellin, et al.14 For peg-IFNα as tested in EORTC 18991, patients with gross nodal metastases (N2) derive no benefit. Therapeutic benefits appear to be confined to the N1 population with microscopic nodal disease and greatest in patients with microscopic nodal disease who have an ulcerated primary tumor. The prolonged regimen of up to five years of treatment as originally planned is hard to achieve, and the median duration of therapy as reported in the EORTC 18991 trial was little over one year. On the other hand, peg-IFNα has a weekly, relatively convenient dosing schedule requiring less frequent administration that may be attractive to patients unwilling to receive the standard high-dose regimen.
The future direction of melanoma adjuvant therapy is to identify biomarkers that define the subpopulations of patients who benefit from IFN, and to build on recent successes with CTLA4-blocking antibodies (ipilimumab [BMS-Medarex]), which have shown promising durable clinical activity as monotherapy in patients with metastatic melanoma. Randomized controlled trials are currently under way testing ipilimumab versus placebo (EORTC 18071) and versus standard HDI (US Intergroup E1609) in the adjuvant arena for melanoma, but no data are expected for several years. MAGE-A3 (melanoma-associated antigen A3) vaccine as adjuvant therapy is under evaluation,

The trial showed significant benefit in recurrence-free survival, with median RFS of 34.8 months for peg-IFNα compared with 25.5 months for observation only. No significant improvement was found in overall or distant metastasis-free survival.

following promising EORTC phase I-II studies in which the expression of MAGE-A3 has been found in 66 percent of patients with melanoma. MAGE-A3 is given with a potent TLR-9 (toll-like receptor 9) agonist vaccine adjuvant (Cpg). The trial requires the expression of the vaccine antigen in the tumor tissue, and employs the evaluation of a predictive gene signature that may be associated with antitumor efficacy of the vaccine.15,16

The high-risk surgically resected stages provide a great opportunity for curing melanoma by targeting microscopic residual disease at an earlier stage and in a less compromised host. The future of adjuvant therapy appears very promising, building upon unprecedented advances in the management of metastatic disease derived from continuously deepening understanding of melanoma molecular biology and host immunity.

References

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