Abstract

Angiogenesis is a hallmark of melanoma progression. Antiangiogenic agents have been infrequently tested in patients with advanced melanoma. Experience with most other cancers suggests that single-agent chemotherapy or angiogenic inhibitors is unlikely to have substantial clinical antitumor activity in melanoma. It is more likely that combinations of antiangiogenic agents with either chemotherapy or other targeted therapy will be needed to produce significant clinical benefit. In melanoma, numerous cellular pathways important to cell proliferation, apoptosis, or metastases have recently been shown to be activated. Activation occurs through specific mutations (B-RAF, N-RAS, and PTEN) or changes in expression levels of various proteins (PTEN, BCL-2, NF-kB, CDK2, and cyclin D1). Agents that block these pathways are rapidly entering the clinical setting, including RAF inhibitors (sorafenib), mitogen-activated protein kinase inhibitors (PD0325901), mammalian target of rapamycin inhibitors (CCI-779), and farnesyl transferase inhibitors (R115777) that inhibit N-RAS and proteasome inhibitors (PS-341) that block activation of nuclear factor-kB (NF-kB). It will be a challenge to evaluate these agents alone, in combination with each other, or with chemotherapy in patients with melanoma. Trials with large populations of biologically ill-defined tumors run the risk of missing clinical antitumor activity that is important for a particular yet-to-be-defined subset of patients. To rationally and optimally develop these targeted agents, it will be critical to adequately test for the presence of the presumed cellular target in tumor specimens and the effect of therapy on the proposed target (biological response). Investigators in this field will need to carefully plan these trials so that at the end of the day, we learn from both the failures and successes of targeted therapy.

Empirical use of chemotherapy and/or immunotherapy in the treatment of patients with melanoma has successfully shown that the majority of melanomas are resistant to most agents. Recent scientific investigations have highlighted genetic alterations and biological processes that seem to be critical to melanoma cell survival and resistance to standard therapy. Investigators are at a point where these advances in our understanding of melanoma biology can be used to influence future therapeutic investigation. The remarkable efficacy of targeted agents (imatinib, trastuzumab, and erlotinib) and antiangiogenic agents (bevacizumab and sorafenib) in other cancers, together with the limited success associated with more conventional approaches, has made this shift in the investigational paradigm imperative for melanoma (1–5).

Figure 1 displays our current understanding of the various pathways critical to melanoma biology. It is now appreciated that melanomas have “unique” defects that include loss of regulatory functions or the gain of proliferative or antiapoptotic functions that are no longer under normal regulatory control (6–8). One critical targetable pathway is the mitogen-activated protein kinase (MAPK) pathway (9). Efforts to target this pathway are the subject of other reviews in this supplement. Consequently, this review will focus on other potential therapeutic targets (Table 1). For example, melanomas have been shown to express cell surface receptors for growth factors that mediate their signals through tyrosine kinases (10). These receptors include platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor 1 (EGFR1 or ErbB1), and c-kit, which are expressed in melanoma at various stages of progression (11–16). In addition, chemokines (CXCL1 and CXCL8) can also function as growth factors for melanoma (17–23). These proteins bind to their surface receptors on the tumor surface and mediate their effects downstream through the constitutively activated nuclear factor-kB (NF-kB) complex (7, 24–28). Activated NF-kB is a critical central regulator of a number of genes involved in antiapoptosis, proliferation, angiogenesis, and even additional chemokine production through a positive feedback loop (29–32).

There is also a strong therapeutic rationale for attempting to inhibit several important signaling pathways simultaneously in patients with melanoma. Evidence exists that inhibition of
either NF-κB or the MAPK pathway may be more effective if done in combination. In addition, simultaneous inhibition of both the MAPK pathway and the phosphatidylinositol 3-kinase (PI3K)/Akt (mammalian target of rapamycin) pathways may also offer therapeutic advantages over inhibiting either pathway alone. Even attempts to block both RAS and RAF, which are components of a common pathway, may prove to be more effective at shutting down the critical MAPK pathway and produce more robust clinical activity.

Finally, the important role of angiogenesis in melanoma and its inhibition may provide a basis for effective cancer treatment (32–35). The success of antiangiogenic therapy with bevacizumab, primarily in combination with chemotherapy, shows that targeting the tumor vasculature even in the presence of less than optimal chemotherapy can be an effective strategy (36). This review will describe results of recent investigations with targeted therapy and antiangiogenic therapies in melanoma and the potential targets and agents likely to be central to future clinical trials.

Targeting of Cell Surface Receptors (EGFR, PDGFR, and c-kit)

It is known that melanoma expresses a number of growth factor receptors (22). Evidence exists for the presence of ligands for these growth factor receptors within the tumor milieu (37, 38). Receptor expression changes with disease progression. Some studies show an increase in EGFR expression with disease progression (12, 13), whereas others have shown that c-kit expression decreases (11). In particular, triggering of the c-kit receptor leads to microphthalmia-associated transcription factor expression that can ultimately induce increased expression of BCL-2 (39). Fisher et al. have shown an important role in melanoma pathogenesis for microphthalmia-associated transcription factor, the melanocyte master regulator, in acting as a lineage-specific oncogene (40). Microphthalmia-associated transcription factor can be amplified in some cases of melanoma (40). Limited evidence exists that inhibitors of EGFR, c-kit, or PDGFR produce significant antimalignant effects in preclinical models. Activating mutations or translocations of these receptors had not been reported in melanoma as in chronic myelogenous leukemia, gastrointestinal stromal tumors, and non-small cell lung cancer (1–4, 41). Recent reports of mucosal and acral melanomas with mutations in c-kit are being claimed but not published. Nonetheless, the presence of c-kit, PDGFR, and EGFR on the surface of at least some melanomas along with a few reports of preclinical efficacy encouraged the cautious exploration of these agents in patients with melanoma. The trials had two-stage designs to prevent large numbers of patients from receiving ineffective therapy (10, 37–39, 42).

An imatinib phase 2 study enrolled 26 melanoma patients non with mucosal primary (43). Patients experienced significant grade 3 and 4 toxicity. No objective clinical responses were seen among the 25 evaluable patients. The median time to progression was 54 days, and median overall survival was 200 days. No patient was progression free at 6 months. Paraffin-embedded tumor specimens from 15 patients were tested by immunohistochemistry for expression of imatinib-responsive kinases. Three tumors had moderate (++) and five had weak (+) immunohistochemical staining for c-kit. Five tumor samples had weak (+) staining for PDGFR-α and PDGFR-β. This level of c-kit and/or PDGFR-α or PDGFR-β expression was lower than previously reported. Furthermore, such expression did not seem to influence clinical outcome. Based on the poor results in this study, it was concluded that imatinib is inactive as single-agent therapy for metastatic melanoma. This may need to be reevaluated in a group of patients more likely to have c-kit mutation or amplification.

Another trial in patients with advanced melanoma targeted the EGFR. EGFR is a type 1 receptor tyrosine kinase involved in cellular differentiation and proliferation that is dysregulated in many cancers (44). EGFR expression has been reported in melanocytic lesions (12, 13). Although a number of investigators have reported the EGFR expression to increase with tumor progression, others have shown either no expression or expression with no association with cancer progression (12, 13). More recently, genetic studies using comparative genomic hybridization or fluorescence in situ hybridization have shown the amplification of the seventh chromosome and

![Fig. 1. Activating pathways in melanoma: 10–20% of melanoma have activating mutations of N-Ras, 40–80% have activating mutations of B-Raf (great majority V600E), more than 50% have lost PTEN expression with 10% carrying PTEN mutation, majority with NF-κB activation. Additionally, melanoma can express c-kit, PDGFR, and EGFR1 receptors that could be targets for therapy.](image-url)
the 7p12 site, including the EGFR gene in a number of cases of melanoma (14–16). EGFR amplification that ranged from three to seven copies of the gene was more prevalent in tumor obtained from metastatic melanoma deposits than from early-stage disease samples. Budillon et al. reported that the EGFR tyrosine kinase inhibitor gefitinib was synergistic with IFN in blocking proliferation in five melanoma cell lines (45). In melanoma cell lines resistant to IFN, addition of gefitinib was able to inhibit growth even at lower doses of IFN.

A phase 2 trial with erlotinib at its maximum tolerated dose (150 mg/d) was done.1 It was relatively well tolerated with only acneiform rash and mild diarrhea as its major adverse effects. Fourteen patients were enrolled, with no objective responses, one mixed response, and only one patient with stable disease lasting >6 months being observed. Analysis of tumor blocks for EGFR and other ErbB family receptors are pending. More recent clinical experience has shown that responses to EGFR kinase inhibitors in non–small cell lung cancer are not related to the surface level of EGFR expression but instead to the presence of activating mutations in the receptor (3, 4). Such mutations have yet to be identified in melanoma tumors, perhaps partially explaining the disappointing results.

NF-κB Activation as a Target for Melanoma Treatment

NF-κB mediates antiapoptotic, proliferative, metastatic, and proangiogenic effects primarily through inducing gene expression of proteins critical to these activities (refs. 29–32; Fig. 2). The IκB family of cytosol proteins binds to NF-κB and prevents its translocation into the nucleus and activation of its genetic program. Proteasome inhibitors, such as PS-341, selectively and reversibly inhibit the 26S proteasome and prevent the breakdown of many regulatory proteins through the inhibition of the ubiquitination-proteasome process (46–49). One of these proteins whose breakdown is impaired is IκB. This presumably leads to NF-κB inactivation and reversal of the malignant phenotype that it regulates (46, 48, 50).

PS-341 inhibits growth of melanoma cells in vitro either alone or in combination with temozolomide (51–53). This effect was also noted in a murine xenograft melanoma model. PS-341 or temozolomide alone each inhibit tumor growth to a limited degree; however, the combination of temozolomide and PS-341 produced striking regressions of palpable human melanoma xenografts and complete remissions that lasted >200 days in some mice (53).

Although a single-arm phase 2 trial with PS-341 alone showed no single-agent clinical activity in patients with melanoma (54), these preclinical data prompted us to pursue a phase 1 clinical trial of temozolomide (administered daily by oral route for 6 weeks) in combination with PS-341 (administered i.v. on days 1, 4, 8, and 11 of a 21-day cycle). Besides defining the maximum tolerated dose, this trial also attempted to define doses that achieved the greatest degree of inhibition of NF-κB activation in peripheral blood mononuclear cells and, when feasible, in parallel tumor samples.

Nineteen patients, all with advanced melanoma, were enrolled onto this study. The maximum tolerated dose was determined to be 1.3 mg/m² of PS-341 (days 1, 4, 8, and 11 of 21 days) and 75 mg/m² daily (days 8-50) of temozolomide. Dose-limiting toxic effects (grades 3 and 4) included extreme fatigue,

---

1 Wyman KA, personal communication.
neuropathy, and rash. Although most patients were heavily pretreated, 4 of 19 patients showed some signs of tumor regression (three with moderate regression and one with partial regression). Nine of 17 patients tested showed a decline in the NF-κB activation of peripheral blood cells by electromobility shift of p65 following either PS-341 alone (day 8) or temozolomide + PS-341 (day 29). Six of 12 patients receiving 1.3 mg/m² of PS-341 showed a decline in electromobility shift p65 in the peripheral blood. 20S proteasome inhibition in blood was at 60% to 80% and was not effected by temozolomide treatment.

Nine patients underwent pretreatment tumor biopsies, and three patients underwent both pretreatment and posttreatment biopsies. At baseline, immunohistochemistry for nuclear p65 NF-κB expression was strong in nearly all the tumor specimens. Posttreatment, nuclear-translocated p65 NF-κB expression decreased in two of the three tumor specimens studied. The encouraging preliminary results have prompted the initiation of a phase 2 trial in both chemotherapy-naïve and previously treated patients, which hopes to obtain sequential biopsy specimens from nearly all patients.

**Inhibition of Multiple Signaling Pathways and Targets Simultaneously**

As mentioned previously, many pathways likely contribute to melanoma resistance to cytotoxic chemotherapy. These include the PI3K/Akt pathway (55–59), MAPK pathway, and NF-κB-mediated events (Fig. 1). Evidence exists that inhibition of both the MAPK pathway and NF-κB in combination may produce enhanced antitumor effects. For example, in patients with multiple myeloma cells, p38 MAPK inhibition can increase expression of p27 and decrease p21<sup>cip</sup> and augment PS-341 cytotoxicity against PS-341–resistant myeloma cells (60). Although PS-341 induces expression of an antiapoptotic protein, Mcl-1, as a cell survival mechanism, inhibition of the MAPK pathway can decrease expression of Mcl-1 (61). MAPK inhibition is feasible at the level of B-raf/C-raf, downstream at MAPK or even upstream at N-RAS (62–64).

Apoptosis resistance is a hallmark of melanoma, and attempts to overcome this property have included the administration of a number of new agents in development (53, 58, 64). Development of IκB kinase-β inhibitor, such as BMS-345541, will likely block NF-κB activation far more specifically and effectively than a proteasome inhibitor (65). Inhibition of mammalian target of rapamycin, a critical component of the PI3K/Akt pathway, with agents such as CCI-779 (phase 2/3) and RAD001 (phase 1/2) affords great promise (66–68). PTEN expression is either lost or the gene mutated in a number of melanomas, leading to activation of the PI3K/Akt pathway (57–59). Inhibition of both RAS and RAF with the combination of R115777 (farnesyl transferase inhibitor) and sorafenib may more effectively block the MAPK pathway than either agent alone. Downstream from RAS are several signaling pathways, including the PI3K/Akt pathway, that could simultaneously be inhibited with an agent such as R115777 (farnesyl transferase inhibitor) (69, 70). Finally, as discussed previously, inhibitors of either the C-Raf/B-Raf, such as sorafenib, or MAPK kinase, such as PD0325901, are in phase 1 and 2 clinical trials (62–64). Combined approaches are already being tested, and more are being planned, with some including antiangiogenic agents, such as bevacizumab. Some of the most promising combination approaches development are listed in Table 2. These trials are planned with an emphasis on tumor biology. Molecular characterization of the tumors before therapy (mutations, deletions, expression, and comparative genomic hybridization) and following treatment examining inhibitory effects on the target will be critical to understanding any clinical results.

**Antiangiogenic Agents**

Angiogenesis has proven to be a critical step in melanoma transformation. A number of angiogenic factors have been shown to be released by melanoma cells and/or host cells within the tumor microenvironment (33, 34). These include vascular endothelial growth factor (VEGF), PDGF, interleukin-8, and basic fibroblastic growth factor (33). Several human melanoma xenografts models show that these factors play a role in tumor progression. Antibodies to VEGF are effective at blocking tumor growth and metastasis (71). Serum levels of VEGF in melanoma patients increase with clinical stage and can be predictive of worse prognosis (35). The integrin α<sub>v</sub>β<sub>3</sub> can act as the vitronectin receptor and seems to play a critical role in melanoma growth and further metastasis (72). This integrin is specific for tumor-associated vasculature and is required for melanoma cell survival. Furthermore, α<sub>v</sub>β<sub>3</sub> blockade has produced antitumor effects in preclinical models (72).

**Sorafenib**

The initial interest in sorafenib was based on its activity as a RAF kinase inhibitor (C-RAF > B-RAF). Later, it was also found to block other receptors effectively, including VEGFR2 and PDGFRβ (62, 69). Simultaneously, clear cell renal cancers frequently driven by von Hippel-Lindau loss or mutations proved to be clinically responsive to sorafenib (73). At present, animal models and correlative human studies show that much of the in vivo effects on tumors are antiangiogenic (69). The promising results with the combination of chemotherapy (carboplatin + paclitaxel) plus sorafenib may be an example of antiangiogenic agents enhancing chemotherapy effects, similar to what has been observed in other cancers with bevacizumab (74).

---

**Table 2. Promising combinations in development for therapy of melanoma**

<table>
<thead>
<tr>
<th>Combination</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib + R115777 (farnesyl transferase inhibitor)</td>
<td>to achieve vertical blockade</td>
</tr>
<tr>
<td>Sorafenib + CCI-779</td>
<td></td>
</tr>
<tr>
<td>Sorafenib + bevacizumab (anti-VEGF)</td>
<td></td>
</tr>
<tr>
<td>R115777 (farnesyl transferase inhibitor) + bevacizumab (anti-VEGF)</td>
<td></td>
</tr>
<tr>
<td>CCI-779 + bevacizumab (anti-VEGF)</td>
<td></td>
</tr>
<tr>
<td>Molecular characterization of the tumors before therapy (mutations, deletions, expression, and comparative genomic hybridization)</td>
<td></td>
</tr>
<tr>
<td>Following treatment examining inhibitory effects on the target</td>
<td></td>
</tr>
</tbody>
</table>
Although thalidomide/revlimid (CC-5013; IMiDS) have shown important clinical effects in patients with multiple myeloma or myelodysplastic syndrome, their mechanisms of action are still unknown (75). Initially, these agents were thought to be antiangiogenic based on preclinical models. A randomized trial of an ultralow (biologically inactive) revlimid dose compared with the maximum tolerated revlimid dose was reported in the lay press, and no evidence of significant clinical activity was observed. Thalidomide has been combined with temozolomide chemotherapy in patients with melanoma. Hwu et al. have reported response rates as high as 30% for the combination of thalidomide and temozolomide in a single-center study of patients with stage IV melanoma with or without brain metastases. However, these encouraging results have not been confirmed (76, 77) by other centers or cooperative groups.

Bevacizumab Alone and with Other Agents

Bevacizumab is a humanized IgG antibody directed at the VEGF molecule (71). By blocking the ligand (VEGF), the most potent endothelial proliferating factor, angiogenesis is greatly impaired. During the past 5 years, bevacizumab has produced beneficial clinical effects in a variety of human cancers. As a single agent, it has shown benefit in patients with cytokine refractory clear cell renal cancer and some with ovarian cancer (78). However, when combined with fluorouracil plus CPT-11 or fluorouracil plus oxaliplatin for colon cancer, carboplatin plus paclitaxel for non–small cell lung cancer, or paclitaxel alone in breast cancer, significant increases in objective response rates, time to progression, and overall survival have been reported (79). Initial trials with bevacizumab in melanoma have been few due to limited access to the agent. Carson et al. evaluated a regimen of bevacizumab alone or in combination with low-dose IFN-α. Because some clinical activity was observed only in the combined therapy arm, this trial has been modified to incorporate higher doses of IFN-α. Others have proposed studying the combination of bevacizumab and erlotinib in patients with melanoma. VEGF/VEGFR and EGF/EGFR1 interact in several ways that make the combination of inhibitors attractive (80, 81).

In mice and in vitro, treatment of human tumors with EGFR inhibitors for extended periods can lead to resistance to EGFR inhibition (80). This resistance is mediated by VEGF. In vitro, EGFR1 inhibition blocks VEGF release by tumor cells and proliferation of both tumor and endothelial cells. In conditions of limiting VEGF, TGFα plays an important role in endothelial cell proliferation, survival, and sprouting (81). Simultaneous blockade of EGFR1 and VEGFR pathways results in a cooperative antitumor effect. Studies of bevacizumab and erlotinib have shown promising clinical activity in both clear cell renal carcinoma and non–small cell lung cancer (82). A trial of the combination in patients with advanced melanoma has recently been initiated with results likely to be available in 2006.

MEDI-522 (Vitaxin), Anti-αvβ3 Integrin

αvβ3 is an integrin whose ligand is vitronectin. It is expressed by a large percentage of cancers, including melanoma, but not by normal melanocytes. Proliferating endothelium of the melanoma milieu and osteoclasts can also express αvβ3. Its expression in melanoma primary lesions increases as they progress from the horizontal to vertical growth phase (72). In addition, tumors from patients with stage IV melanoma seem to express the integrin more intensely (72). The MEDI-522 antibody is a humanized form of murine antibody called LM609 that binds αvβ3, triggering antibody-dependent cellular cytotoxicity and potentially blocking tumor growth in mice by directly causing tumor cell apoptosis and impairment of tumor angiogenesis (72). Preliminary results of phase 2 studies of MEDI-522 in patients with melanoma were recently reported (83). One hundred twelve patients were randomized to either MEDI-522 alone or MEDI-522 with dacarbazine chemotherapy. Although a few patients receiving MEDI-522 and dacarbazine exhibited tumor responses, no objective responses with MEDI-522 alone occurred. Progression-free survival was short in both arms but better in the combination arm. Most unexpected was the finding that patients who took MEDI-522 alone had a median survival of >12 months, longer than the combined arm and longer than reported for most first-line regimens in patients with advanced melanoma. Whether this reflects some form of selection bias or a delayed effect of the therapy on survival alone remains to be determined.

Multitargeted Agents with Activity against VEGFR2 and Other Surface Receptors

SU011248, AG013736, and ZD6474 are all oral tyrosine kinase inhibitors that already show promise in other cancers, including clear cell renal carcinoma (84). They are effective inhibitors for the VEGFR2 receptor signaling but also block one or more other receptors. Targets for both SU011248 and AG13736 include VEGFR2, PDGF, and c-kit, whereas ZD6474 blocks both VEGFR2 and EGFR1. The ability of these agents to inhibit multiple targets makes them of interest to investigate in patients with melanoma alone, with chemotherapy, or with other targeted agents. It is anticipated that many such studies will be done in the coming years (Table 3).

The next 5 to 10 years will offer those physicians treating patients with melanoma and melanoma patients themselves an entirely new and different set of treatment options to fight this disease. We must be careful to understand these “new cancer drugs” and structure our investigations to maximize information ascertained along the way. As the biology of melanoma becomes clearer, it is hoped that this will lead to a clear path for better therapy.

Open Discussion

Dr. Atkins: A lot of the studies that you talked about were in second- or third-line melanoma patients, who have already failed chemotherapy and maybe failed chemobiotherapy or some immunotherapy. Some of these studies are proving that these patients do poorly and also have a lot of side effects from therapy. It’s probably too much to ask that a targeted single agent be effective. Can we do these studies first line?

Dr. Kirkwood: The E1696, which had 120 patients, was all second-, third-, and fourth-line therapy. The overall survival median for patients without immune response was 10.3 months.
while for people who got immune responses, it was 23.7 months.

Dr. Sosman: That’s a pretty select group of patients. My strategy initially was to be very flexible about entry criteria for a number of reasons, and none of them scientific. With time, I’ve come to believe that is suboptimal, at least in my patient population. In most of the studies being performed now, patients have undergone at most one prior therapy.

Dr. Kirkwood: I don’t know how we sensed which patients to put on this trial. It would be interesting to go back and determine the criteria. But looking at prior chemotherapy and prior radiotherapy, it didn’t seem as though people were holding back much. If that is the case, it’s a population to whom you can ask questions about immunization and non-immunization. I’m worried that we removed patients after first-line therapy, when we could potentially benefit. We need to ask meaningful questions and advance the field in that group of patients much more than we have.

Dr. Sosman: We could be picking better patients by waiting to second line, because they live through first line and they’re still in decent shape.

Dr. Atkins: When you wait for a study to open, particularly with melanoma, you often get a group of patients with significant tumor burden but still meeting the eligibility criteria. Then the natural history of their disease gets in the way of clinical response assessment and patients tolerate the side effects less well.

Dr. Sosman: You can take this approach in renal cancer.

Dr. Atkins: In renal cancer, it works the other way. If you hold patients, they do better. A group of patients whom we don’t use a lot for these type of studies, who are the ideal patients in some ways, are those with skin-only in-transit disease. It’s easy to perform biopsies to identify the target in these patients. Also use of neoadjuvant therapy was a good way to learn something about IFN and this would be even more true for these targeted agents. Is this an appropriate thing to do? Would it be approved by the institutional review boards? Could we convince patients, surgeons, and referring physicians that this would be a worthwhile effort?

Dr. Kirkwood: I think so. This is where you inform both the patient and the medical community better. There is nothing lost. The surgery wasn’t going to be curative in the first place.

Dr. Atkins: Would surgeons consider designing studies in in-transit or in neoadjuvant disease for these target agents?

Dr. Sondak: They’re absolutely appropriate settings for targeted therapy trials. Limb perfusion has enormous morbidity and, although it’s effective at achieving control in the limb, most of those people eventually die of their metastatic disease. You lose next to nothing by waiting before treating them.
Dr. Flaherty: Regarding drug development in first-line or second-line or later therapy, the issue really is that strong signals will not be missed in any line. In fact, there are circumstances where we want to identify weak signals.

Dr. Sondak: But the signals you may be looking for may not be on your computed tomography scan. They may be in a piece of tumor, and those studies looking for biologic signals should be done at an early stage in drug development.

Dr. Atkins: If there weren't any limitations between drug availability or resource availability, what agents available right now would you be most interested in testing in melanoma? What combination would you be most interested in testing? What pathway would you be most interested in blocking?

Dr. Haluska: I would hold constant inhibition of BRAF. I would look for partners that concurrently inhibit the associated pathways. The problem is that philosophy is based on knowing BRAF is mutated, and I don't know what else is mutated, so I don't know where to look. I may try rational combinations.

Dr. Flaherty: The only drug that I wish we could use in combination, which is one we're actually doing a phase 1, single-agent study on as we speak, is a good CDK-4 inhibitor.

Dr. Mier: I'd like an AKT inhibitor if it were available. I'd also like to get one of the STAT–3 inhibitor drugs.

Dr. Sosman: STAT–3 is something we haven't talked about too much. It would be a candidate to look at alone and maybe with some of the mitogen-activated protein (MAP) kinase inhibitors.

Dr. Atkins: So there are things available that could potentially block relevant pathways that are potentially available. If we could develop a better targeted therapy, how would one combine that with an immunotherapy? Does it make sense to do that? Are there certain things that one would not want to do? Are we just going to repeat the whole biochemotherapy experience over again if we start doing that?

Dr. Gajewski: Many of these signaling pathways are also critically important in T-cell activation. ROS and MAP kinase signaling are among those. In our R115777 trial in melanoma, we have analyzed T-cell activation before and after drug therapy and have preliminary data that it's blunted. There would have to be careful consideration of the way those drugs would be combined.

Dr. Slingluff: I wonder if there may be a role in giving one of these inhibitors that may actually cause lymphopenia; therefore, timing these therapies before immunotherapy would be advantageous in slowing the tumor.

Dr. Sondak: Targeted therapy, as the sole approach, is probably not the answer; even in GIST we see eventual relapse in just about everyone who responds to imatinib. If immunotherapy has a role, it might be accentuated in those patients who responded to targeted therapy but in whom some disease remained that would otherwise eventually resurface.

References


Molecular Targets in Melanoma from Angiogenesis to Apoptosis

Jeffrey A. Sosman and Igor Puzanov


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/12/7/2376s

Cited articles
This article cites 81 articles, 39 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/12/7/2376s.full.html#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/12/7/2376s.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.