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New Therapeutic Options in the Medical Management of Advanced Melanoma

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During the past 3 decades, the incidence, morbidity, and mortality of malignant melanoma have increased dramatically. Advanced melanoma has remained a disease that is for the most part incurable and has challenged all therapeutic efforts to make a dent in its natural history. Recent advances in the understanding of the molecular alterations in melanoma and in the immunologic mechanisms playing a role in this malignancy have brought hope that significant progress can be achieved, as evidenced by early encouraging clinical data. This review will summarize these recent developments and their impact on current clinical practice.

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Although current epidemiologic data suggest decreasing incidence trends for a variety of malignancies, the incidence and mortality of malignant melanoma appear to be increasing. For 2009 the American Cancer Society estimated 68,720 new cases in the United States, with 8650 deaths.[1] Unless detected at an early stage in patients, melanoma remains difficult to treat effectively. Approved treatment for patients with locally advanced disease and at high-risk of recurrence is toxic and of limited benefit.[2,3] The treatment of distant metastatic disease has been similarly frustrating, with a multitude of clinical trials yielding negative results.

The final version of the American Joint Committee on Cancer 2009 staging system for melanoma has been recently published.[4] The new database consisted of 30,946 patients with stages I, II, and III melanoma and 7972 patients with stage IV disease. The 5-year survival for patients with stage I and II disease ranged from 97% to 53% and for patients with stage III disease from 70% to 39%. For stage IV patients the 1-year survival rate ranged from 62% to 33%. The prognostic importance of the mitotic rate (expressed as mitoses/mm^2) is reflected in the fact that it now replaces level of invasion in the T1b category. In the new staging system, micrometastatic nodal disease detected by immunohistochemistry only is regarded as stage III disease.

Recent progress in the understanding of the molecular alterations as well as immunoregulatory processes in malignant melanoma have given rise to treatment approaches that have demonstrated initial positive results, triggering renewed excitement to pursue clinical investigations in melanoma.

This concise review will focus on some of these new paradigms and their current application in the treatment of melanoma. Although surgery remains the primary treatment of early melanoma and an important modality in the management of advanced melanoma, the many controversies in surgical management are out of the scope of this article, which will concentrate on nonsurgical treatment of advanced disease.

Choosing systemic treatment for locally unresectable or distant metastatic melanoma has been complicated by the lack of a clear standard of care and the fact that, until recently, therapeutic options had demonstrated little effect on survival or quality of life for most patients. However, in the last few years there has been significant progress in the main treatment modalities, including immunotherapy, chemotherapy and the new molecularly targeted approaches.

Immunotherapy

Immunotherapy has been extensively used to treat advanced melanoma; systemic treatment with cytokines and the use of a variety of tumor vaccines have been tested over the years. Most of these earlier trials have shown no significant activity and the only approved immunotherapy regimen to date remains high-dose interleukin-2 (IL-2).

A meta-analysis of patients with metastatic melanoma who received high-dose IL-2 in 8 separate trials reported an objective response rate (ORR) of 16% and a complete response in 6% of patients, with 4% remaining free of progression, therefore demonstrating durable remission of melanoma in

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this small subset of patients. Unfortunately, IL-2 treatment is associated with substantial toxicity; it is not appropriate for most patients with stage IV disease, requires staff expertise, and is quite expensive. Toxicity limits its use to patients with good organ function under careful physician monitoring. Better Eastern Cooperative Oncology Group performance status, skin, nodal, soft tissue, and lung involvement predict a better outcome.[5] Other predictive factors of response include lymphocytosis immediately after treatment, low pretreatment serum lactate dehydrogenase (LDH) levels and the development of vitiligo or hypothyroidism.[6,7] Recent studies have also suggested that the likelihood of a response to IL-2 can be predicted by specific tumor gene signatures and the levels of serum vascular endothelial growth factor (VEGF) and fibronectin.[8,9] Prospective studies of these and other putative response surrogates are clearly needed to better define the patients who will most likely benefit from IL-2−based therapy. Studies combining IL-2 with other immunotherapeutic agents, such as interferon alpha-2b,[10] granulocyte-macrophage colony stimulating factor (sargramostim),[11] histamine dihydrochloride,[12] tumor-infiltrating lymphocytes (TIL), and various vaccines have failed to demonstrate improvement in significant outcome parameters, such as overall survival (OS) or disease-free survival in randomized phase 3 trials.[13,14] However, Schwartzentruber et al[15] have recently reported the results of a prospective study that randomized 185 HLA-A0201−positive patients with metastatic melanoma to high-dose IL-2 alone or in combination with a gp100:209-217(210M) peptide vaccine. The results revealed a statistically significant doubling of both the response rate (RR) and progression-free survival (PFS) and a trend towards improved OS in the group treated with the combined regimen. Follow-up trials to confirm these results are planned.

Interferon-alpha (IFN-α) has also demonstrated modest antitumor activity in metastatic melanoma, although this agent is primarily used in the adjuvant setting.[3] The pegylated formulation of IFN, which is associated with less toxicity, demonstrated response rates of 6%-12% as first-line therapy for metastatic disease.[7] IFN-α has also been combined with chemotherapy but without significant improvement in outcomes.[16,17]

Biochemotherapy or chemoimmunotherapy has been extensively used to treat advanced metastatic melanoma. Various regimens have been tested, often by combining drugs such as dacarbazine, cisplatin, and vinblastine with IL-2 and IFN. Although initial reports from single institution suggested high response rates and prolonged survival, large randomized trials have failed to confirm a survival benefit.[18-22] Attempts to prolong responses to biochemotherapy with maintenance immunotherapy have suggested potential benefit in a phase 2 multicenter trial and this approach remains an area for further investigation.[23]

Adoptive immunotherapy for melanoma refers to the infusion of lymphocytes that have been manipulated to promote reactivity against tumor cells. These TILs are generated ex vivo from the patient's tumor cells. TILs have been used in conjunction with IL-2, and more recently their infusion has been preceded by lymphodepletion with nonmyeloablative chemotherapy and/or radiation therapy. Results in patients treated with previous lymphodepletion have been impressive, with response rates of 50% or greater being reported. However, the generation of TIL cells is cumbersome, time-consuming, and dependent on the availability of viable tumor cells, the latter frequently failing to grow in culture. Recent strategies to eliminate these impediments have focused on the genetic engineering of patients' T cells with retroviral vector insertion of the alpha and beta chains of the T-cell receptor of highly reactive T-lymphocytes previously selected for mediating in vivo tumor regression.[14,24] Another recent strategy is the infusion of expanded peptide-specific $CD4^+$ T cells cocultured with a cancer–testis antigen (NY-ESO-1) peptide-pulsed autologous mononuclear cells. Infusion of a clonal population of these $CD4^+$ T cells has resulted in complete regression of metastatic melanoma, even when a significant percentage of the tumor cells did not express NY-ESO-1, presumably through the mechanism known as antigen spreading.[25] Further trials confirming these results are eagerly awaited.

Therapeutic vaccines have also been used to treat melanoma for several decades. There are many possible vaccination strategies. Autologous or allogeneic intact tumor cells or antigen-supplemented tumor cells have been frequently used. Defined antigen vaccines include purified peptides, proteins, gangliosides, and antiidiotypes. Genetic manipulation of tumor cells, viruses, or dendritic cells transfected with cytokines or with antigen genes also constitute a major area of focus in cancer vaccine development. For a more detailed discussion of this subject, the reader is referred to recent review publications.[26] Although extensive work in this field evolves and continues, it is important to emphasize that to date all large randomized studies of vaccines in the treatment of melanoma have not met their primary endpoints. More concerning are the results of recent large randomized adjuvant clinical trials reporting inferior results for the vaccination arms.[27-29]

Other immunotherapeutic approaches are based on the concept of modifying tumor cells in vivo by transferring genes that could enhance their ability to trigger an immune response. These gene products have been transferred into tumor cells in vivo by direct injection, vector transfection or electroporation. Velimogene aliplasmid (Allovectin-7) is a plasmid/lipid complex containing the DNA sequences encoding HLA-B7 and β2 microglobulin, which together form the major histocompatibility complex, or major histocompatibility complex class I. The putative mechanisms of action of velimogene aliplasmid include an allogeneic antitumor response in HLA-B7-negative tumors, up-regulation/restoration of major histocompatibility complex class I antigenicity attributable to the expression of β2 microglobulin, and a proinflammatory effect of lipid/DNA complex. Extensive phase 2 testing has demonstrated that clinical responses are mostly local and regional, although responses in certain distant metastatic sites have been documented. A large randomized phase 3 trial of velimogene aliplasmid versus dacarbazine with the primary end point of durable response rate has completed accrual but the results are not yet available.[30] Di-

rect injection into melanoma lesions of an oncolytic herpes simplex virus type 1 encoding granulocyte-macrophage colony-stimulating factor resulted in a 28% objective response rate in a phase 2 clinical trial. A dual mechanism of action has been postulated, including a direct oncolytic effect in injected tumors and a secondary immune-mediated antitumor effect on noninjected tumors. Regression was seen in both injected and noninjected lesions and based on these preliminary results a prospective, randomized phase III clinical trial in patients with unresectable stage III and stage IV melanoma is ongoing.[31]

Intralesional injection of accessible melanoma tumors has also been reported with chemotherapeutic agents (cisplatin, bleomycin), as well as with drugs capable of generating a local immune response, including Bacille Calmette Guerin, IL-2, IFN, granulocyte-macrophage colony-stimulating factor, imiquimod, and Rose bengal (PV-10).[32-39] A phase 3 trial of PV-10 is planned.[40,41]

A promising novel immunotherapeutic strategy is based on the idea of blocking the inhibition of T-cell receptor signaling that occurs with the up-regulation of certain molecules on T cells, an intrinsic regulatory mechanism to prevent unopposed activation. One molecule that has been under intensive study is the cytotoxic T lymphocyte antigen-4 (CTLA-4). It is known that antigen presentation alone is not enough to initiate an effective immune response and that costimulatory signals are needed to activate the T cell. Stimulatory and inhibitory signals modulate the immune response. The T-cell surface molecule CD28 interacts with its ligands (B7-1/CD80, B7-2/CD81) on the surface of the antigen-presenting cells to provide a costimulatory signal that facilitates and maintains T-cell response. T-cell activation concomitantly leads to up-regulation of CTLA-4, which has a much greater binding affinity for the B7 surface molecules found on the antigen-presenting cell than CD28, thus effectively inducing T-cell anergy and inhibition of IL-2 secretion, halting T-cell activation. Inhibition of CTLA-4 by administration of anti-CTLA-4 monoclonal antibodies can shift the immune system balance toward T-cell activation, potentially resulting in tumor shrinkage.[42] Two mAb targeting CTAL-4 have been under investigation: tremelimumab and ipilimumab.

Tremelimumab (CP-675,206) is a fully human IgG2 anti-CTLA-4 mAb that has been studied in clinical trials as a single agent and in combination in patients with advanced melanoma.[43,44] The promising clinical activity of tremelimumab in phase 1 and 2 trials in advanced melanoma led to a phase 3 clinical trial in which patients with treatment-naive advanced melanoma were randomized to single-agent tremelimumab (15 mg/kg intravenously every 3 months) or standard-of-care chemotherapy with either dacarbazine or temozolomide. The primary end point was OS. The trial was halted for futility based on the recommendations of the data Safety Monitoring Board. Median survival in the tremelimumab arm was 12.02 months and in the chemotherapy arm 10.45 months, with most responses to tremelimumab being durable.[45] Additional follow-up and retrospective analyses of prognostic factors have identified a low C-reactive protein level as a prognostic surrogate for response and another phase 3 trial in this selected patient subset has been designed.

Ipilimumab (MDX-010) is a fully humanized IgG1κ monoclonal antibody against CTLA-4. Data from phase 2 studies suggest a long-term survival effect of ipilimumab monotherapy. In an analysis of 3 of these studies, with a median follow-up from 10.1 to 16.3 months and a range reaching up to 37.5 months, the 12-month survival rates were >47%, the 18-month survival rates were >34%, and the 24-month survival rates were ≥30%. Even for previously treated patients, 24-month survival rates ranged from 24% to 33%. A meaningful proportion of patients continued to survive beyond the updated follow-up period. Long-term survivors included patients with progressive disease.[46,47]

Results from a pivotal phase 3 trial with ipilimumab have been recently published.[48] A total of 676 HLA-A*0201-positive patients with unresectable stage III or IV melanoma with progressive disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100, ipilimumab alone, or gp100 alone. Ipilimumab, at a dose of 3 mg/kg, was administered with or without gp100 every 3 weeks for up to 4 treatments. This phase 3 study showed that ipilimumab, either alone or with gp100, improved OS compared with gp100 alone in previously treated patients with metastatic melanoma; more than 70% of the patients had visceral metastases, and more than 36% had elevated LDH, both of which are poor prognostic factors. The median OS in the ipilimumab-plus-gp100 group was 10.0 months compared with 6.4 months in the gp100-alone group (hazard ratio for death, 0.68; $P < 0.001$). The median OS in the ipilimumab-alone group was 10.1 months with ipilimumab alone compared with gp100 alone (hazard ratio 0.66; $P = 0.003$). OS in the ipilimumab-plus-gp100 group, the ipilimumab-alone group, and the gp100-alone group, respectively, were 43.6%, 45.6%, and 25.3% at 12 months; 30.0%, 33.2%, and 16.3% at 18 months; and 21.6%, 23.5%, and 13.7% at 24 months. The effect of ipilimumab on overall survival was independent of age, gender, baseline LDH levels, stage of disease, and previous IL-2 therapy. Ipilimumab is the first agent to improve median and long-term OS in a phase 3 study of previously treated patients with advanced melanoma.

The most common adverse events related to the study drugs were immune-related events, which occurred in approximately 60% of the patients treated with ipilimumab and 32% of the patients treated with gp100. The frequency of grade 3 or 4 immune-related adverse events was 10-15% in the ipilimumab groups and 3.0% in the gp100-alone group. The immune-related adverse events most often affected the skin and gastrointestinal tract. The most common immune-related adverse event was diarrhea, which occurred at any grade in 27%-31% of the patients in the ipilimumab groups. There were 14 deaths related to the study drugs (2.1%), of which 7 were associated with immune-related adverse events. A recent prospective phase 2 trial in patients with melanoma metastatic to the brain has shown that ipilimumab has similar activity in these patients.[49] Management guidelines with algorithms for management of immune-related ad-

verse events have been developed. They require close patient follow-up and timely administration of corticosteroids and infliximab. Although early data suggest a positive association, the relationship between immune-related adverse events and disease control/OS in patients with metastatic melanoma treated with ipilimumab remains undefined.[50,51]

Clinical experience with anti-CTLA-4 monoclonal antibodies has disclosed novel patterns of tumor response; these include the occurrence of responses weeks to months after therapy initiation. Response or stable disease may be preceded by apparent early disease progression, or may occur simultaneously with other progressing lesions within the same patient (a "mixed" response).[52] Awareness of these patterns is important to avoid early treatment discontinuation. Systematic immune-related response criteria have been developed and warrant prospective evaluation and validation.[53]

The results of a second pivotal trial that randomized treatment-naive to therapy with ipilimumab and dacarbazine versus dacarbazine and placebo and of a multinational phase 3 trial of adjuvant ipilimumab versus placebo in high-risk resected melanoma are expected in the near future.[54,55]

Anti PD1 (MDX 1106) is another monoclonal antibody that blocks the programmed death receptor-1 PD1, which is a costimulatory molecule that can also be expressed on melanoma cells and has been shown to inhibit T-cell responses.[56] Early results suggest objective responses with limited toxicity in multiple malignancies warranting further investigation of PD-1 blockade.[57] Other immune modulatory targets currently under investigation include CD137 (4-1BB) and OX40, both members of the TNFRSF4 (tumor necrosis factor receptor) superfamily.[58]

Chemotherapy

Systemic chemotherapy has been historically the most prevalent therapy modality for metastatic melanoma. The only Food and Drug Administration-approved cytotoxic agent used in this setting is the alkylating agent dacarbazine. Response rates range from 15% to 25% as a single agent in early studies, although recent data from a large randomized trial suggest a much lower ORR of approximately 7%.[59] Response duration is relatively short, and a survival advantage remains to be proven. Temozolomide is an orally available analog of dacarbazine associated with an ORR of 21%, and median response duration of 6 months in a phase 2 study in chemotherapy-naive metastatic melanoma.[60] A phase 3 trial comparing temozolomide with dacarbazine as first-line therapy showed no significant improvements in response rate (13.5% vs 12%) or median survival (7.7 vs 6.4 months).[61] A phase 3 EORTC trial comparing dose intense temozolomide to standard dacarbazine showed improved response rates (14.5% vs 10%, $P = 0.05$), but PFS and OS were similar in both arms.[62] Temozolomide has better central nervous system penetration and is preferable in the patient with brain metastases.[63] This drug has also been used in combination with radiation therapy to the brain.[64] Fotemustine is a nitrosourea that is approved for the treatment of metastatic melanoma in Europe and elsewhere; like temozolomide, it has shown activity in brain metastases.[65] Other drugs with reported single agent activity in melanoma include other nitrosoureas, cisplatin and carboplatin, vinca alkaloids and taxanes.[66,67]

Combination chemotherapy regimens that include the use of dacarbazine or temozolomide and other drugs have been investigated in countless clinical trials without proof of significant improvement in clinically relevant endpoints over single agents. Some melanomas and nevi have been reported to express estrogen receptors; hormone receptor antagonists have been tried as single agents and in combination with chemotherapy in metastatic disease. However, the clinical utility of this approach has not survived the test of randomized clinical trials.[68-70]

A new albumin-bound formulation of paclitaxel has recently demonstrated clinical activity both as a single agent as well as in combination with chemotherapy and antiangiogenic agents.[71-73] A phase 3 clinical trial comparing this agent with dacarbazine in the first line setting is under way.[74]

Other recent strategies aimed at improving the efficacy of chemotherapy by modulation of cellular pathways include but are not limited to combinations of chemotherapy with antiapoptotic agents, O^6-methylguanine-DNA methyltransferase (MGMT) depletion, inhibition of poly-(adenosine diphosphate-ribose) polymerase, antiangiogenic agents, and inducers of oxidative stress.

Melanoma cells have been found to have up-regulated Bcl-2, a pivotal antiapoptotic molecule. Enhancement of apoptosis by oblimersen, a Bcl-2 antisense drug, was suggested by significant clinical activity seen in melanoma when combined with dacarbazine in a phase 2 trial. A large randomized phase 3 trial of dacarbazine versus oblimersen plus dacarbazine in 771 patients significantly increased PFS by 1 month and the ORR, but failed to show an improvement in OS, the primary endpoint.[59,75]

The intracellular levels of the repair enzyme MGMT appear be predictive of the clinical course of melanomas treated with dacarbazine and temozolomide, with high levels being associated with poorer outcome.[76] Lomeguatrib is an inactivator of MGMT that has been tested in a phase 3 randomized trial in combination with temozolomide. Unfortunately, no clinical benefit was detected by the addition of the modulator.[77]

Preclinical data has shown that inhibition of poly-(adenosine diphosphate-ribose) polymerases, a family of DNA-repairing enzymes, sensitizes tumors, including melanoma, to chemotherapy; a synergistic effect has been demonstrated with temozolomide. Clinical data from a breast cancer trial in a subgroup of patients revealed promising activity. A phase 3 clinical trial in combination with temozolomide in previously untreated patients with metastatic melanoma is ongoing.[78-82]

Many new drugs targeting tumor angiogenesis have come into clinical practice after demonstrating clinical activity in malignancies, such as colon cancer, renal cell carcinoma, breast cancer, lung cancer, and glioblastoma multiforme. The rationale for using drugs with antiangiogenic activity in melanoma is based on extensive preclinical data. Although the single-agent activity of these drugs in melanoma is limited, combinations with chemotherapy or immunotherapy appear to be synergistic.[83-89]

A randomized phase 2 trial is evaluating carboplatin/paclitaxel chemotherapy with or without bevacizumab as first-line therapy in 214 patients with metastatic melanoma. The primary endpoint of this trial is PFS with secondary end points, including OS, ORR, and safety. In a recent report with a minimum follow-up of 1 year, a trend favoring the bevacizumab containing arm was reported for PFS and ORR. In an exploratory subgroup analysis, the combination of bevacizumab with chemotherapy resulted in improved OS in poor prognosis patients with M1c-stage disease.[90]

Elevated serum VEGF levels have been linked to immunosuppression and decreased activity of immunotherapy; conversely, lowering of VEGF levels or inhibition of VEGF receptors may result in synergistic effects. Two ongoing trials, one in metastatic melanoma (bevacizumab plus ipilimumab) and the other in metastatic renal cell carcinoma (bevacizumab plus IL-2) are investigating this hypothesis.[91,92]

Synergy of antiangiogenic drugs with chemotherapy drugs may be attributable to a variety of mechanisms, such as the normalization of blood flow allowing better access to tumor cells, additive antiangiogenic properties of certain cytotoxics, ablation by cytotoxics of immunosuppressive myeloid cells, and others.[93]

Sorafenib is a kinase inhibitor with significant activity on both B-RAF and vascular endothelial growth factor receptor (VEGFR) kinases; it is approved by the Food and Drug Administration for treatment of renal cell and hepatocellular carcinomas. Early data from phase 1 and 2 studies suggested that the addition of sorafenib to chemotherapy in patients with melanoma was associated with a higher ORR and improved PFS.[94-97] Two large phase 3 trials were conducted to test this hypothesis. In the first trial, 270 previously treated melanoma patients were randomly assigned to receive intravenous paclitaxel plus intravenous carboplatin on day 1 of a 21-day cycle followed by either placebo or oral sorafenib twice daily on days 2-19. The primary efficacy endpoint was PFS. The median PFS, RR, and OS were nearly identical in both groups. Both regimens had clinically acceptable toxicity profiles with no unexpected adverse events.[98] Recent data from a randomized intergroup trial in first line comparing carboplatin and paclitaxel with the same chemotherapy plus sorafenib, have likewise demonstrated no advantage for the addition of sorafenib. The primary endpoint was OS, and 823 patients were accrued over 34 months. After the third interim analysis, the study had crossed the futility boundary and the study was unblinded. The median OS and PFS for the chemotherapy plus sorafenib group were 11.1 and 4.9 months, whereas for the chemotherapy alone group they were 11.3 and 4.1 months. Response rates were 18% and 16%, respectively.[99] Although negative for their primary end points, the results of these 2 large studies confirmed the activity of a carboplatin and paclitaxel combination as an active therapeutic option in both first line and previously treated melanoma.

Elesclomol is an investigational first-in-class oxidative stress inducer that increases reactive oxygen species in cancer cells leading to mitochondria-induced apoptosis. A randomized phase 2 study of paclitaxel alone compared with paclitaxel plus elesclomol resulted in a statistically significant doubling of median PFS, with an acceptable toxicity profile and encouraging OS.[100] A multinational phase 3 trial of elesclomol plus paclitaxel compared with paclitaxel alone in metastatic melanoma has accrued 651 patients. The primary end point was PFS. A recent update reported the lack of a statistically significant improvement in PFS or OS. Baseline LDH was an important predictor of outcome.[101]

Novel Targeted Agents

Modern biology has advanced our understanding of the molecular make-up of melanoma. It is now clear that melanoma is not a molecularly homogenous malignancy and that several so-called driving mutations can be identified in a significant proportion of samples. More relevant are the reports of early clinical data demonstrating that treatment of melanoma with drugs that inhibit these mutated molecular targets are associated with important and sometimes major clinical responses.

The mitogen-activated protein kinase pathway plays a key role in melanoma development and is an important therapeutic target. Deregulation of this pathway may result in increased signaling activity leading to proliferation, invasion, metastasis, migration, survival and angiogenesis. Activating mutations in the *BRAF* and *NRAS* genes have been found to be relatively frequent in melanoma, occurring in approximately 50-60% and 15% of tumors, respectively.[102]

Curtin et al have shown that mutations in the *KIT* gene are more frequent in patients with melanomas arising from mucosal, acral and sun-damaged skin primary sites. NRAS and BRAF mutated melanomas are more commonly derived from non sun-damaged skin.[103,104] Several clinical trials have been published that tested the concept of inhibiting melanomas overexpressing the KIT protein, generally identified by immunoperoxidase stains for CD117. These trials have uniformly yielded negative results demonstrating that CD117 overexpression alone is not a valid selection criterion for treatment with KIT-targeting drugs. Recent reports describing major responses in KIT-mutated melanomas treated with imatinib mesylate and other drugs that inhibit KIT tyrosine kinase have led to larger trials of imatinib mesylate in mutation enriched populations, in an attempt to confirm that mutated KIT is a clinically important target in this small subpopulation of patients with melanoma. Another randomized phase 3 trial will evaluate nilotinib, a multitargeted kinase inhibitor, compared with dacarbazine as first-line therapy in patients with advanced melanoma harboring centrally confirmed KIT receptor mutations; the primary end point of this study is PFS.[105-108]

The most common BRAF mutation in melanoma (in 90% of BRAF-mutated melanomas) is the V600E mutation, which activates BRAF 500-fold. Sorafenib inhibits the BRAF serine/threonine kinase as well as various receptor tyrosine kinases, with significant activity in the VEGFR. As discussed earlier, two randomized clinical trials testing sorafenib in combination with chemotherapy in melanoma produced negative results. The most likely explanation is that sorafenib is not very active against V600E mutated BRAF kinase. Better, more spe-

cific BRAF-targeting drugs have been developed are under investigation. Very encouraging data have been reported with the drug PLX4032, an oral, selective inhibitor of oncogenic V600E BRAF kinase. In a phase 1 trial recently published, PLX4032 induced complete or partial tumor regression in 81% of patients who had melanoma with the V600E BRAF mutation, with responses being observed in all sites of disease. Cutaneous side effects, fatigue, and arthralgia were the most common. Squamous-cell carcinoma, keratoacanthoma type, developed in 31% of the patients.[109,110] Seven of 9 patients treated with the greater doses of a formulation with high bioavailability demonstrated tumor regression with acceptable toxicity.[110,111] The results of a completed phase 2 trial have not yet been reported. In the BRIM3 (BRAF inhibitor in Melanoma) open-label randomized phase 3 trial investigators are evaluating PLX4032 compared with dacarbazine in previously untreated patients with advanced melanoma. Eligible patients must have the BRAF V600E point mutation.[112]

Angiogenesis and signaling through the ref/mitogen-activated protein/extracellular signal-regulated kinase kinase/extracellular signal-regulated kinase cascade have been reported to play important roles in melanoma.[113,114] The combination of the ref/mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor AZD6244 plus dacarbazine compared with dacarbazine alone as first-line therapy in patients with BRAF mutation-positive advanced melanoma is being evaluated in a randomized phase 2 trial. The primary endpoint of this study is OS. Another ongoing randomized phase 2 study is comparing single agent AZD6244 to temozolomide in patients with advanced melanoma. Interim results from this trial reported no difference between in PFS, the primary endpoint, but mature OS data from this trial have not been reported.[115,116]

Other important molecular pathways have been found to be altered in melanoma, opening new avenues for therapeutic intervention. These include the phosphatidylinositol-3-kinase, microphtalmia-associated transcription factor, cyclin-dependent kinases, notch-1, and iNOS pathways.[117,118] Early clinical trials with drugs that are active in these pathways are being conducted.

A very recent report identified the presence of activating human epidermal growth factor 4 mutations in 19% of melanoma samples tested; the same report noted that treatment of cultured cells with lapatinib, a human epidermal growth factor tyrosine kinase inhibitor currently approved for use in breast cancer, blunted the growth of mutated melanoma cells but not of wild-type cells.[119]

The sonic hedgehog pathway appears to play a pivotal role in several human cancers and inhibition of this pathway has been shown to have antitumor effects.[120] Hedgehog signaling is active in melanocytes and melanomas, particularly in RAS-induced tumors, and crosstalk with the RAS/AKT pathway has been reported.[121] These findings suggest a potential new therapeutic approach in melanoma.

The future has never before looked more promising for the treatment of advanced melanoma, a disease that has been quoted as giving cancer a bad name. Further understanding of the molecular and immunologic mechanisms that promote survival of melanoma tumor cells will undoubtedly lead to the development of better, more specific and perhaps less toxic agents. Approval of some of these new agents for clinical use in melanoma soon appears likely.

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