Time for a New Paradigm in the Treatment of Metastatic Melanoma

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Abstract

Metastatic melanoma is a very common disease with an increasing incidence worldwide and is notoriously difficult to treat. The long-established treatments including dacarbazine and interleukin-2 have shown limited response rates and are associated with significant toxicities. More recently, treatments have been developed that decrease inhibition of T-cell action against melanomas. Among these, ipilimumab was recently approved for use in metastatic melanoma and has shown improved overall survival (OS) and progression-free survival rates (PFS). Another such treatment currently in development is the monoclonal antibody, anti-PD-1. This blocks PD-1 inhibition of T-cells and has shown promising response rates in early clinical trials. Another treatment approach is to use targeted therapies in patients with mutations in BRAF or CKIT signaling pathways and it is vital that the mutational status of these genes be determined in patients with metastatic melanoma to best determine effective therapeutic options. Vemurafenib was recently approved for metastatic melanoma and targets the *BRAF* V600E mutation which occurrs in about 50 % of cutaneous melanomas. Recent results from the ongoing Phase III BRIM-3 study comparing vemurafenib with dacarbazine showed that median 12-month OS rates and the risk of death were reduced with vemurafenib. Other BRAF inhibitors such as dabrafenib and MEK inhibitors such as trametinib are also in development. New treatments in ongoing clinical trials coupled with an improved biologic understanding are likely to improve responses and outcomes for patients with metastatic melanoma.

Keywords

Metastatic melanoma, targeted treatments, BRAF-, MEK-, CKIT-inhibitors, PD-1, PD-1ligand, anti-PD-1

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The incidence of melanoma is high and is the sixth most common cancer in US men and eighth most common cancer type in US women.[1,2] Moreover, the incidence of metastatic melanoma has been increasing worldwide at a rate faster than any other solid malignancy.[3] There were an estimated 76,250 new cases of melanoma and 9,180 deaths from the disease in the US alone this year.[4] Melanoma has been shown to affect a large number of younger patients and thus it is one of the leading cancers in terms of patient years-of-life lost.[5]

The prognosis for patients with metastatic disease has traditionally been poor with a median survival of approximately 6–9 months due to lack of effective therapeutic options.[6,7] Indeed, no therapy had ever shown a survival advantage for patients with advanced melanoma until 2011. Survival for patients with stage III disease is quite varied as patients with low tumor burden (stage IIIa) do much better than those with multiple lymph node metastases or in-transit metastases (stage IIIb/IIIc disease).[8]

While melanoma has been resistant to chemotherapy, it does express tumor-specific antigens that have made immunotherapy a viable treatment option. Key research in determining gene mutations that drive melanoma growth have been instrumental in helping to develop targeted therapies that show great promise in treating patients with advanced disease. Two new agents, ipilimumab and vemurafenib, have recently received approval based on clinical evidence that they impart a statistically significant survival advantage over control patients receiving vaccine or chemotherapy. Appropriate combination and sequencing of old and new agents holds the promise of increasing the number of complete durable responses.

The paradigm shift for melanoma will be to consider long-term durable responses and a potential cure of the disease as the goal of future therapeutic trials, rather than simply palliation. This article provides an overview of traditional and emerging management approaches as well as reviews strategies for combining and sequencing available treatments to optimize outcomes.

Challenges in Treating Metastatic Melanoma

Melanoma is a particularly difficult disease to manage for several reasons. Firstly, it has a high metastatic potential with a tendency to disseminate to distant sites, often including the brain, via hematogenous

and lymphatic channels leading to poor prognosis.[9] It is the only cancer where millimeters (not centimeters) of tumor are used in the staging system, with a 4 mm melanoma imparting as much risk as a 10 cm lung tumor. Furthermore, melanomas can downregulate patients' own intrinsic immune system pathways creating both a local and systemic immune-depleted state.[10]

Current Standard of Care

Three drugs have long been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic melanoma: hydroxyurea, dacarbazine and IL-2; hydroxyurea was approved in 1967 and is now rarely used as a treatment for melanoma. Dacarbazine gained approval for treating metastatic melanoma in the 1970s, but it has consistently failed to show a significant impact on survival in the last 40 years of use.[11] More recent studies place response rates of dacarbazine at the 5–10 % range with very few long-term survivors and with significant associated toxicities including nausea, vomiting and myelosuppression.[12–14]

High-dose interleukin-2 (HD IL-2) was approved based on an analysis of pooled Phase II data showing an overall response rate of approximately 16 %. However, 6 % of treated patients are complete responders, most of which are durable with some patients surviving many years after receiving therapy.[15,16] However, HD IL-2 must be administered in hospital by trained, experienced personnel owing to its toxicity profile and requires referral of patients into these centers. At present, use of IL-2 in the US is limited to specialist centers with the resources and expertise in managing administration of this drug regimen. Dacarbazine and its analog temozolomide[6] are likely the most frequently administered drugs in this country for metastatic melanoma despite no evidence of improved survival. Temozolomide is currently only approved for primary brain tumors.[17,18] Other agents which have been employed include platinum, taxanes, vinblastine, interferon, and fotemustine, which is approved in Europe.[19]

Combinations of these various agents has been disappointing to date in demonstrating either additive or synergistic effects. However, biochemotherapy is an aggressive treatment using three chemotherapeutic agents (cisplatin, vinblastine, dacarbazine) in conjunction with intermediate dose IL-2 and interferon-α and has demonstrated positive efficacy in single institutions for patients with advanced disease.[20] Unfortunately, when explored in multicenter trials, outcomes have shown little to no advantage versus chemotherapy alone or HD IL-2.[21] Interestingly, a three-month course of biochemotherapy administered adjuvantly for patients with completely resected stage IIIa-IIIc disease showed a doubling of progression-free survival (PFS) versus the approved one year of interferon¬-α in a recent study (SWOG 0008). Thus, while biochemotherapy does have activity in the metastatic setting, administration of this therapy is limited to treatment centers with experience in administering this highly toxic regimen.

In 2011, two new drugs were approved by the FDA for treatment in metastatic melanoma patients: ipilimumab and vemurafenib. Ipilimumab was approved in March 2011 after being fast-tracked for priority approval[21,22] and vemurafenib followed soon after in August 2011.[23] Both of these products have shown improvements in overall survival (OS) and PFS rates in unresectable stage IIIc or stage IV melanoma in large, randomized multicenter trials.

New Agents

Checkpoint Inhibitors

Ipilimumab

Ipilimumab is a first-in-class checkpoint-inhibiting immunotherapy; it is a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), a regulatory molecule upregulated on T-cells in the setting of immune activation. Upregulated CTLA-4 competes for binding onto antigen presenting cells and leads to immunosuppression, thereby acting as an immune system "brake". By blocking this molecule, existing tumor antigen-reactive T-lymphocytes may avoid normal immune downregulation and mediate tumor regression.[24,25] Similar to HD IL-2, ipilimumab has low overall response rates, but response appear to be durable in a subset of patients.[26]

A Phase III study showed a significant survival advantage with ipilimumab at a dose of 3 mg/kg compared with a control vaccine against the melanoma antigen glycoprotein100 (gp100).[27] Subjects were randomized 3:1:1 to receive ipilimumab plus gp100 (n=403), ipilimumab alone (n=137) or gp100 alone (n=136). One-year survival rates were 44 % for ipilimumab plus vaccine, 46 % for ipilimumab plus placebo and 25 % for vaccine only. Two-year survival rates were 22, 24 and 14 %, respectively. Median OS was significantly longer in the ipilimumab groups than the gp100 only group (hazard ratios for death 0.68, p<0.001 and 0.66, p=0.003 for the combination and ipilimumab alone versus gp100 alone, respectively). However, Grade 3 or 4 immune-related adverse events were observed in 10–15 % of subjects given ipilimumab versus only 3 % of subjects treated with vaccine only.[27] In general, immune-mediated adverse events can range from being minimal to life-threatening in the case of serious diarrhea, colitis or hypophysitis, and close monitoring of patients on ipilimumab is therefore necessary. It is thought that experiencing any immune-mediated adverse effect is predictive of responsiveness to ipilimumab although the severity of immune related event does not correlate with treatment effectiveness.

A second Phase III trial was performed evaluating ipilimumab together with dacarbazine.[13] A total of 502 patients with previously untreated metastatic melanoma were randomized in a 1:1 fashion to receive either the combination or dacarbazine alone. Here, a dose of 10 mg/kg of ipilimumab was administered with or without dacarbazine (850 mg/m^2) at weeks one, four, seve, and 10, followed by dacarbazine alone every three weeks until week 22. This study used a 10 mg/kg dose during the induction and maintenance phases because this level had been previously shown to provide significantly improved response rates over the 3 or 0.3 mg/kg dose levels (p=0.002).[28] It was found that ipilimumab plus dacarbazine improved OS in patients compared with dacarbazine alone and there were higher survival rates at years one, two, and three (HR for death: 0.72, p<0.001) but grade 3 or 4 adverse events were higher with the combined therapy.[13]

PD1 and PD1 Ligand

An anti-PD-1 monoclonal antibody treatment (BMS-936558, MDX-1106) that blocks the inhibitory action of PD-1 on T-cells is in clinical development for metastatic melanoma. This is a novel treatment that has raised much interest among oncologists and has much potential in the treatment of advanced melanoma. A diagrammatic scheme

indicating the action of PD1/PD1-Ligand and CTLA-4 blockers on T-cell function is given in *Figure 1*. A recent Phase I study investigated the use of BMS-936558 given at 1, 3, or 10 mg/kg doses combined with a multipeptide vaccine (MART-1/gp100/NY-ESO-1) in patients with stage IV melanoma who had previously received treatment.[29] The results show that the 1 and 3 mg/kg dose levels were well tolerated; the 10 mg/kg dose part of the study is ongoing. Responses were seen at all dose levels and PD-1 levels on T-cells decreased but CTLA-4 levels increased in CD4 T-cells in all dose groups. There was a dose-related decrease in CD8 T-cells and in viral-specific T-cells. It was concluded that further work was needed to determine the optimal dose. Interim results were recently published from an ongoing larger clinical trial of BMS-936558.[30] These showed that 95 patients with advanced melanoma had been treated and there was an objective response in 20 patients. To date in this study, BMS-936558 has produced a durable clinical benefit in patients with advanced melanoma, including those who had received previous immunotherapy. Further results from this trial on a larger group of patients are awaited.

Targeted Agents

Mitogen-activated protein kinase (MAPK) pathways are a set of signaling mechanisms that regulate a diverse range of cellular functions including differentiation, proliferation and apoptosis. In melanomas and other tumor tissues, the discovery of a series of mutations in genes encoding kinases involved in these pathways led to various new anti-cancer treatments that exploit these as targets for treatment.

Faulty activation of the MAPK pathway has been reported over 80 % of cutaneous melanomas due to abnormalities at various points in the RAS-RAF-MEK-ERK pathway.[31] Among the mutations in the MAPK pathways, those of a serine/threonine protein kinase (BRAF) are the most extensively studied. These mutations are found in 35–59 % of primary melanomas and 42–66 % of metastatic melanomas and have been found in human skin sites after exposure to the sun.[32–34] Other genetic changes associated with melanoma include high cyclin (CCND1) and cyclin-dependent kinase (CKD4) copy numbers.[35] Increased copy numbers of some scaffold protein GAB2 and mutation in the *CKIT* and *NRAS* are also strongly correlated with melanoma.[36,37]

Vemurafenib

Vemurafenib is a highly specific BRAF inhibitor that targets the *BRAF* V600E mutation which is found in approximately 50 % of patients with melanoma.[38] In *BRAF*-mutated tumors, signaling through the MAPK pathway is constitutively activated which leads to increased growth of melanoma cells, greater ability of malignant cells to spread throughout the body, and increased blood vessel formation around the tumor. A pivotal Phase I trial showed that 81 % of patients with detectable *BRAF* V600E mutations in their tumor have treatment response to vemurafenib. While most patients will have a dramatic reduction in their tumors within weeks of initiating therapy, patients will likely progress after approximately seven months of treatment.[39] These results were confirmed in a Phase II trial[40] in which the overall response rate was 53 %, median OS and PFS were 15.9 and 6.8 months, respectively. Re-analysis of the response rate in the Phase 1 study according to the response criteria used in the Phase 2 study yielded a similar overall response rate of 56 %.

The Phase III trial (BRAF Inhibitor in Melanoma; BRIM-3) of vemurafenib versus dacarbazine accrued 675 patients very quickly and was found to demonstrate a statistically significant benefit at the first interim analysis leading the Data Safety Monitoring Board to recommend that patients randomized to dacarbazine be allowed to crossover to vemurafenib.[12] The data generated by this trial eventually led to the approval of vemurafenib. At six months, OS was 84 % in the vemurafenib group and 64 % in the dacarbazine group with response rates of 48 and 5 %, respectively. Common side effects associated with vemurafenib included arthralgia, rash, fatigue, alopecia, photosensitivity, nausea, and diarrhea.[12] Updated results from the BRIM-3 study after median lengths of follow-up on vemurafenib and dacarbazine of 10.5 months and 8.4 months, showed that median OS times with vemurafenib and dacarbazine were 13.2 months and 9.6 months and 12-month OS rates were 55 and 43 %, respectively.[41] The HR for death was 0.62 in favor of vemurafenib. In total, 81 dacarbazine patients crossed over to vemurafenib. Post-progression ipilimumab was given to 13 % of vemurafenib-treated patients and 19 % of dacarbazine-treated patients. Therefore, after a longer period of follow-up, vemurafenib treatment continued to be associated with improved OS in this study.

Development of cutaneous squamous-cell carcinomas is seen in approximately 20–25 % of patients treated with single-agent vemurafenib. This is the result of paradoxical activation of MAPK signaling in squamous epithelial cells with pre-existing *RAS* mutations. Molecular studies have shown that patients developing a cutaneous squamous cancer tend to harbor co-existing *RAS* (particularly *HRAS*) mutations; this is considered to be an on-target effect.[42]

Acquired resistance to BRAF inhibition is unfortunately very common; studies investigating resistance to vemurafenib will be important and multiple mechanisms of resistance have been determined.[43] At present, these include: reactivation of the MAPK pathway, upregulation of *NRAS/c-Raf* to bypass *BRAF*, upregulation of Cot, and activation of alternative signaling pathways including the phosphoinositide-3-kinase (PI-3K) pathway.

Recently *BRAF(V600E)* splicing variants that lack the RAS-binding domain have been detected in tumor tissues from six out of nineteen patients with acquired resistance to vemurafenib. This observation suggests that inhibition of ERK signaling by RAF inhibitors requires the levels of RAS-GTP to be sufficiently low that RAF dimerization does not occur. The expression of splicing isoforms of *BRAF(V600E)* that dimerize in a RAS-independent manner was also detected and is possibly a novel mechanism of acquired resistance in melanoma patients.[44]

Dabrafenib

A recent Phase I dose-escalation trial in the US on the BRAF inhibitor dabrafenib (GSK2118436) included 184 patients with various advanced solid tumors including melanoma.[45] There was also a small cohort of patients with melanoma brain metastases, and in nine out of 10 patients with brain metastases, the treatment produced a reduction in lesion size. Patients with other BRAF-mutant solid tumors, including gastrointestinal stromal tumor, papillary thyroid cancers, non-small-cell lung cancer, ovarian cancer, and colorectal cancer in addition to melanoma, also showed apparent anti-tumor activity. The most

common treatment-related adverse events of grade 2 or worse were cutaneous squamous-cell carcinoma (20 patients, 11 %), fatigue (14, 8 %), and pyrexia (11, 6 %). These toxicities are slightly different to those associated with vemurafenib but in terms of activity against brain metastases, both drugs have shown similar results and may improve prognosis as well as quality of life.

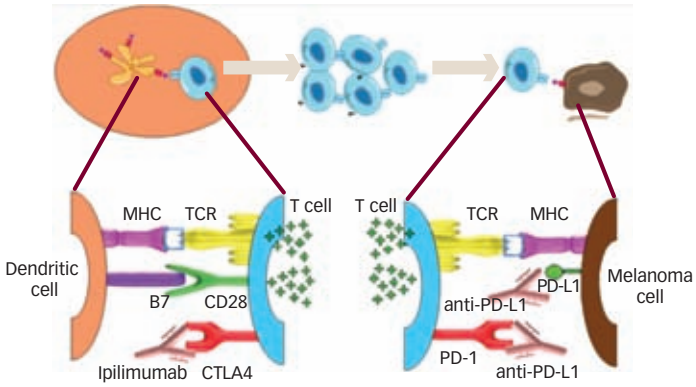
MEK inhibitors

A series of MEK inhibitors are currently in development, several of them for the treatment of melanoma. The furthest in development is trametinib (GSK 1120212). In the ongoing METRIC Phase III study, patients with metastatic melanoma who were *BRAF V600E/K* were randomized to trametinib (n=210) or a comparator treatment (dacarbazine or paclitaxel) over an 8-month period.[46] The PFS times for trametinib and comparator treatments were 4.8 months versus 1.4 months and the HR for this criterion was 0.44 (p<0.0001) which showed an advantage for trametinib; the overall response rates were 24 and 7 %, respectively. The interim OS HR was 0.53 (p=0.0181) which also showed an advantage for trametinib. The most frequent adverse events with trametinib were skin rash, diarrhea, edema, hypertension, fatigue. Grade 3 adverse events with trametinib arm were hypertension (12 %) and rash (7 %). Trametinib therefore, is the first of the MEK inhibitors to show significant improvements in PFS and OS compared with current treatments in patients with *BRAFV600E/K*-mutant metastatic melanoma.

Combinations of BRAF and MEK inhibitors have also shown promise in the treatment of metastatic melanoma. A prominent example is the combination of dabrafenib and trametinib which is being investigated in an ongoing Phase I/II study on 77 patients with melanoma in the US and Australia.[47] In this trial, a single group is treated with four escalating dose levels of dabrafenib/trametinib (mg twice daily [BID]/mg daily [QD]) combination: 75/1, 150/1, 150/1.5, and 150/2. The latest results show the response rates for each dose level were 67 % (n=6), 64 % (n=22), 48 % (n=25), and 54 % (n=24), respectively, and the overall PFS was 7.4 months. There were two deaths caused by pneumonia and hyponatraemia. The most common grade 3/4 adverse events were pyrexia (n=6, 5 %), fatigue (n=6, 5 %) and dehydration (n=6, 5 %). These results show the combination of dabrafenib/trametinib has an acceptable safety profile and promising efficacy and is to be further investigated in a Phase III trial.

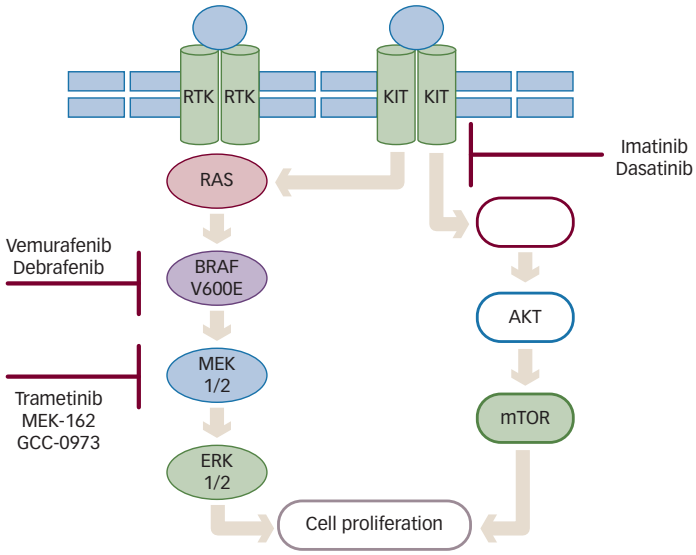
In recent years, evidence has emerged that mutations in type III transmembrane receptor tyrosine kinase (RTK) family of proteins (*KIT* mutations) that have been used as therapeutic targets in various cancers such as lung and gastrointestinal tumors also have potential as therapeutic targets in melanoma.[48] Investigation of KIT inhibitors in melanoma is at an early stage but some initial small studies have shown promising results. An example is a Phase II, open-label, single-arm trial in China in which 43 patients with metastatic melanoma with *CKIT* mutations were treated with imatinib 400 mg/day.[49] The median PFS was 3.5 months, the six-month PFS rate was 36.6 % and the rate of total disease control was 53.5 %. In the study, the overall response rate was 23.3 %, 30.2 % achieved stable disease (SD) and 41.9 % showed regression of the tumor. The one-year OS rate was 51.0 %. Escalation of the imatinib dose to 800 mg/day, however, could not restore disease

Figure 1: Differences between Blocking of T-cells by CTLA4/B7 and PD-1/PD-L1



+ = stimulation of T-cell function; B7 = type of peripheral membrane protein; CD28 = Cluster of Differentiation 28; CTLA4 = Cytotoxic T-Lymphocyte Antigen 4 (also known as CD152); MHC = major histocompatibility complex; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death protein 1 ligand; TCR = T-cell receptor. Source: Adapted from Ribas et al. 2012.[42]

Figure 2: Overview of Mammalian MAPK Pathways



control. It was of interest that nine of 10 partial responses (PRs) were recorded in patients who showed mutations in exons 11 or 13. Overall, imatinib 400 mg/day was well tolerated. In another study in the US on 295 patients with CKIT mutations, the response rate was greater in patients who had mutations that affected recurrent hotspots or with a mutant to wild-type allelic ratio of more than one (40 versus 0 %, p=0.05). This result indicated positive selection for the mutated allele.[51] Further work is required to evaluate the *CKIT* mutations as targets in melanoma but early results show promise.

Strategies for Improving Outcomes in the Treatment of Metastatic Melanoma

While there is currently little consensus regarding optimal therapy for metastatic melanoma, several general recommendations can be made; in particular, *BRAF* mutational status should be determined on all patients at diagnosis in order to determine potential options. Likewise, *CKIT* mutations should be analyzed especially in acral lentiginous

Table 1: Common Mutations Known to be Present in Metastatic Melanoma

Gene Mutated	Prevalence	Reference
BRAF (V600E; V600K)	48 %	Colombino et al., 2012[63]
NRAS	15 %	Colombino et al., 2012[63]
p16CDKN2A	14 %	Colombino et al., 2012[63]
MAP3K5 or MAP3K9	24 % in cell lines	Stark et al., 2011[64]
KIT	3 %	Tran et al 2012[65]

melanoma or melanoma arising in chronically sun-damaged skin. *BRAF* mutations in melanoma can be atypical and heterogeneous, even in different tumors from the same patient. Reliably detecting and monitoring these mutations can be challenging. The optimal method to detect *BRAF* mutations remains unclear due to differences is sensitivity and specificity.[51] In one study that analyzed melanoma tissues taken from patients, different methodologies were compared. Mutations were detected in 32 % of melanomas using direct sequencing but they were detected in 76 % of melanomas using mutant-specific PCR.[52] In a subgroup that was further analyzed, six of nine tumors, showed differing proportions of *BRAFV600E* and *BRAF* wild-type cells in separate microdissected tumor regions. Repeated analyses of tumor samples from a group of individual patients using a highly sensitive mutant-specific PCR technique showed that 26 % patients had metastases that were discordant for the *BRAFV600* mutation. In light of these results, the authors urged that further studies should be initiated to determine what effect *BRAF* mutational heterogeneity within and between tumors has on eventual clinical outcomes.

Predictors of Response

Clinical measures such as pretreatment lactate dehydrogenase, performance status and the presence of visceral versus non-visceral metastases may be useful in distinguishing likely responders. Much research has attempted to further define the patients most likely to benefit from immunotherapy.[53] Indeed, a clinical trial testing the utility of proposed predictors is ongoing.[54] Certain mutations may play a role in disease susceptibility to immunotherapy as *NRAS*-mutated patients appear to have increased response rates to HD IL-2.[53] Success in the prediction of outcomes has come with understanding the mutations that drive the malignant behavior of melanoma. Testing for *BRAF* and *KIT* mutations is essential when choosing a therapy because only patients with identified mutations will respond to certain treatments. In fact, patients must have a *BRAF* mutation detected by the FDA-approved Cobas® assay according to the vemurafenib label in the US, although this is not the case in Europe. While this assay is efficient for the detection of most V600E mutations, it detects a smaller proportion of non-V600 mutations and a trial is ongoing to test the effectiveness of vemurafenib in *BRAFV600* variants. Small subsets of melanoma patients have an activating KIT mutation and may therefore benefit from *KIT* inhibitors; these populations include 11 % of acral lentiginous melanomas 21 % of mucosal melanoma, and 16.7 % of melanoma patients with chronically sun-damaged skin.[9]

It is our practice to obtain *BRAF* mutational status on all patients with advanced melanoma. *CKIT* mutation status can also be considered in patients with acral lentininous or mucosal melanomas or in patients with chronic sun damaged skin. *NRAS* mutational testing should also be considered as research is ongoing in finding agents effective in *NRAS*-mutated disease. *Table 1* lists the approximate prevalence of the more common mutations observed in metastatic melanoma.

Design and Findings of Ongoing Studies

In patients whose melanomas are symptomatic and harbor a *BRAF* mutation, a *BRAF*-directed therapy should be used preferentially as symptom management is most rapid from this treatment approach. Vemurafenib can be used alone, however the use of a combination of this agent with another targeted agent or immunotherapy on clinical trial is preferable if possible, as virtually all patients eventually become resistant to single agent vemurafenib. For patients with asymptomatic unresectable or metastatic melanoma, first-line immunotherapy is recommended because a small percentage of patients will show a sustained clinical response without further therapy.

Combination and Sequential Therapies

Novel combination approaches have been investigated in recent years. The National Cancer Institute combined HD IL-2 with ipilimumab in a Phase I/II trial of 32 patients which showed no added toxicity and a 22 % overall response rate, with 8 % experiencing a CR.[55] The dose combination employed in the Phase II portion used 3 mg/kg ipilimumab at three-week intervals with a standard cycle of HD IL-2 during the second and third doses of ipilimumab. A follow-up report showed 17 % of patients alive and disease-free with a median follow-up of >6 years. Two additional patients in this group were put into a sustained CR by tumor-infiltrating lymphocyte therapy[56] Ipilimumab plus bevacizumab has been evaluated in a Phase I trial for metastatic melanoma; response rates appeared to be superior to that of ipilimumab alone with negligible toxicity.[57]

Both ipilimumab and HD IL-2 have been assessed in conjunction with the peptide vaccine gp100 in controlled trials. Interestingly, the gp100 vaccine arm did better when it was combined with HD IL-2[59] and fared worse when it was combined with ipilimumab[28]—compared with the respective drugs as single agents. In contrast, both drugs have been associated with improved objective systemic response when given in conjunction with radiation therapy.[59,60] Seven melanoma patients were treated with one to three 20 Gy single dose fractions of stereotactic body irradiation administered to one of multiple metastatic lesions and immediately started on HD IL-2. Five (74 %) of these patients achieved a negative positron emission tomography scan after two to six cycles of HD IL-2. With a median of 480 days of follow-up, only one responder relapsed with a brain metastasis, which was retrospectively determined to have existed prior to therapy. In a second report, a patient slowly progressing for 15 months on ipilimumab was treated with three 950 cGy fractions of radiation to a symptomatic paraspinous mass. The disease outside the radiation port began to shrink in follow-up and after another dose of ipilimumab a stable partial response was achieved. This so-called `abscopal effect' highlights the potential synergy of radiation and immuno-therapeutics. They also are reminders of the importance of sequencing and timing of administration of the various agents.

Other clinical trials on melanoma treatments are ongoing, or are about to commence. These will investigate combinations of vemurafenib

plus IL-2, vemurafenib plus ipilimumab, ipilimumab plus IL-2, and *BRAF* inhibitors plus *MEK* inhibitors. Preliminary results using a combination of *BRAF* plus *MEK* inhibitors have been promising and may help avoid drug resistance in melanomas with the *BRAF* mutations.[61]

The side effects of the different agents used in melanoma are fairly well known and it is anticipated that they can largely be managed in combinations.

Summary and Conclusions

Metastatic melanoma remains a challenge for oncologists. However, with the advent of multiple new agents, there is now the potential for much improved outcomes. The current advances in this field hold the promise of more patients in the future experiencing long-term complete responses.

Better understanding of the disease biology and drug mechanisms will allow for optimal benefits from combinations and sequences of agents with the ultimate goal of curing this disease. ■

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