A therapeutic renaissance: emergence of novel targeted agents for metastatic melanoma


The therapeutic landscape of metastatic melanoma has recently moved from the dark ages to a period of renewed hope. Until recently, treatment options for patients with this devastating disease have had limited activity with no therapy resulting in an improvement in survival. The year 2011 triggered a new dawn for melanoma therapeutics with two novel agents receiving regulatory approval. With the approval of vemurafenib, a first-in-class inhibitor of BRAF V600E mutant melanoma, and ipilimumab, a first-in-class CTLA-4 inhibitor, we now have two agents that improve survival for patients with this devastating disease. Additionally, several agents are currently in development and hold promise to further advance clinical outcomes for patients.

Keywords: BRAF inhibitor • CTLA-4 inhibitor • dabrafenib • ipilimumab • MEK inhibitor • melanoma • PD-1 inhibitor • trametinib • vemurafenib

Malignant melanoma has long had a reputation of being simply a devastating disease that is innately resistant to common oncologic therapeutic approaches. In addition, melanoma is unfortunately not a rare diagnosis with approximately 76,250 new cases expected in 2012, resulting in 9180 deaths [101]. It is a cancer that affects a younger population than many other cancers with an average age of diagnosis of 55. Metastatic melanoma is typically a rapidly fatal process with an expected median survival of around 6–9 months [1]. Previously, the disease had a dearth of therapeutic options with the only US FDA-approved agents being high-dose IL-2 and dacarbazine (DTIC), both of which have very limited efficacy for the average patient with response rates (RRs) between 5 and 15% [2,3]. Although responses are infrequent for high dose-IL2, it should be noted that patients who do respond can have durable remissions. Cytotoxic chemotherapies have been extensively studied in melanoma, but none of these agents alone or in combination with immune therapies have been shown to improve survival outcomes in Phase II and III trials [4]. All of these facts, taken together, created a dire scenario in the field of melanoma oncology, which has been in desperate need of new hope and drug discovery for decades.

Fortunately, over the last decade there have been major advances in our understanding of the specific genetic aberrations that occur in melanoma cells. Previously, melanomas were classified by their histologic subtype, for example superficial spreading, nodular, mucosal and acral lentiginous subtypes. The novel discovery of higher frequencies of mutations in certain subsets of melanoma has led to a restructuring of the clinical classification system based on mutational status, for example BRAF mutants (seen in ~50% of melanomas) cKIT mutant (seen more commonly in mucosal and acral lentiginous histologies) and NRAS mutants. Over the last 5–10 years there has been a push to develop treatment paradigms that focus on identifying a genetic defect within an individual patient’s melanoma tumor and deploying a
drug that is specific to that target. Not surprisingly, melanoma is quickly becoming a model for individualized medicine in medical oncology, just like chronic myelogenous leukemia (CML) and non-small-cell lung cancer (NSCLC) before it. Adding to these exciting advances include improvements in immunotherapies that are able to target the immune system in a more specific and effective manner. These advances are showing promise in enhancing durable RRs with more acceptable toxicity profiles. In this review, I will discuss the exciting progress that has been made in the development of targeted agents for melanoma.

**Inhibition of protein kinases with activating mutations**

Over the last decade there have been dramatic advances in several cancer treatments due to the discovery of a common driver mutation and development of a targeted agent to inhibit the mutated protein. Key examples of mutated proteins in oncology for which targeted drugs have made a major impact include the BCR-ABL mutation in CML (imatinib) [13], ALK and EGFR mutations in NSCLC (gefitinib) [14], and KIT mutation in gastrointestinal stromal tumors (imatinib/ sunitinib) [15]. A similar advance for metastatic melanoma began in 2002 when a landmark report by Davies et al. showed that up to 66% of melanomas may harbor a mutation in the BRAF serine/threonine kinase [16]. This finding sparked a critical series of preclinical and clinical investigations to develop targeted agents for this disease. In addition to BRAF mutations, other activating mutations such as NRAS and KIT have also been identified with agents targeting these pathways being evaluated (Figure 1).

**BRAF inhibition**

One of the most common growth signaling pathways affected by activating mutations is the mitogen-activated kinase pathway (RAS-RAF-MEK-ERK) [17]. Within this pathway, mutation of the BRAF gene occurs in approximately 50% of melanoma cases. Approximately 90% of the mutations seen in the BRAF gene result in a V600E (valine to glutamine substitution) alteration in the kinase domain, which results in a constitutively activated protein kinase. Other less common BRAF mutations are also seen, including V600K, V600Q, and V600R mutations. While the BRAF gene appears to be most commonly mutated in melanomas, BRAF may play an important role in BRAF inhibitor resistance. NRAS mutations are also often seen in melanoma with a frequency of around 20% [18]. While these BRAF and NRAS mutations appear to be mutually exclusive, together they account for the majority of the activating mutations seen in melanomas, making the MAPK pathway a key target for drug development.

**Sorafenib**

Sorafenib was the first RAF inhibitor extensively explored in clinical studies for metastatic melanoma patients. While sorafenib was originally developed for its ability to inhibit RAF, it was later discovered to be a potent inhibitor of the VEGF receptor and PDGF [19]. Following the important discovery of the high frequency of BRAF and NRAS mutations in the disease, several clinical trials with sorafenib in melanoma have been conducted. Based on promising results of a Phase I trial [20] of the combination of carboplatin, paclitaxel and sorafenib (n = 105 metastatic melanoma patients with RR of 26% and progression-free survival [PFS] of 8.8 months) two large Phase III trials have been performed. In the Phase III cooperative group trial E2603, 823 patients with chemotherapy-naive metastatic melanoma were randomized to receive carboplatin and paclitaxel with or without sorafenib [21]. The median overall survival (OS) was 11.1 months for the sorafenib-containing group versus 11.3 months for the chemotherapy alone arm (HR: 1.0; p = 0.878). There also was no statistical difference for PFS and RR. Additionally, a separate Phase III trial has been reported in which 270 patients who had failed prior DTIC or temozolomide were randomized to receive carboplatin and paclitaxel with or without sorafenib [22]. This trial’s primary end point of PFS was not met, with a median PFS of 17.9 weeks for the chemotherapy alone arm compared with 17.4 weeks sorafenib-containing arm. Additionally, secondary end points of RR and OS were also not met. The failure of sorafenib to improve outcomes in these trials is likely multifactorial. For instance, sorafenib appears to be a greater inhibitor of CRAF compared with BRAF. Also, given sorafenib potently inhibits numerous other kinases, it is likely that drug levels are not allowed to reach high enough levels for adequate BRAF inhibition prior to dose-limiting side-effects from other kinase inhibition. Additionally, patients were not prescreened and selected for BRAF mutations and, therefore, the effect of a BRAF inhibitor on an unscreened population would likely have dulled its potential efficacy. Despite these negative results, much was learned from these studies and they paved the way for more successful approaches.

**Vemurafenib**

Unlike sorafenib, vemurafenib is a selective and potent inhibitor of the mutant BRAF V600E kinase. This drug (previously known as PLX4032) was initially tested in a unique Phase I trial, which involved solid tumor patients during a dose-finding phase, followed by an expansion cohort that was specific to metastatic melanoma patients that harbored the V600E BRAF mutation [23]. In this landmark trial by Flaherty et al., 55 patients were included in a dose-finding phase with an additional 32 patients with BRAF V600E mutant melanoma included in an expansion phase. The dose-escalation part of this study identified the appropriate dose as 960 mg twice-daily and dose-limiting toxicities as rash, arthralgia and fatigue. As proof-of-concept, in the dose-escalation group of patients that harbored a V600E BRAF mutation (n = 16) and received >240 mg twice-daily of the drug, 11 of them had responses (69% RR). Five patients in the dose-escalation group had BRAF wild-type melanoma and no responses were seen (four with progressive disease within 7 months of treatment). In the BRAF V600E melanoma expansion cohort, this proof-of-concept was further underscored with an overall RR of 81% and a PFS of greater than 7 months. Despite the exciting results, two subsequent trials were rapidly launched, a Phase II second-line, single-arm trial and a randomized Phase III...
trial, both including only V600E mutant melanoma patients.

The Phase II and III trials, single-arm trial of vemurafenib included patients with metastatic or locally advanced, unresectable melanoma that harbored the V600E mutation and had at least one prior systemic therapy. The median OS for vemurafenib was 13.2 months, which was statistically significant (p < 0.001). Updated data from the vemurafenib and DTIC arm was found to be 0.37, for metastatic melanoma patients. The HR comparing the vemurafenib and DTIC with a primary end point of PFS. The median PFS was 5.1 compared with 2.7 months for the control arm (HR: 0.30; p < 0.0001). Confirmed overall RR for dabrafenib was 53% (3 complete responses) compared with 6% for DTIC. Common adverse events for dabrafenib included fever, fatigue, arthralgia, headache and SCC/KAs. Interestingly, photosensitivity was uncommon and the frequency of SCC/KAs was <10%, which is notably different from what is observed with vemurafenib. The results from this study should pave the way for FDA approval of dabrafenib. Targeting downstream MEK

Trametinib

Activation of the MAP kinase pathway by BRAF or NRAS leads to signaling through the downstream MEK serine/threonine kinase. As activating mutations in the MAP kinase pathway occur in the majority of metastatic melanomas (~50% BRAF mutations, ~20% NRAS mutations), targeting of this pathway by blocking downstream MEK activity is scientifically appealing. Trametinib (GSK1120212) is a MEK 1/2 inhibitor that has been explored in Phase I and II trials [34]. In a recently reported Phase II study of trametinib, 97 patients with BRAF V600 mutant melanoma were treated with 2 mg daily [35]. Patients were enrolled into two cohorts including prior BRAF inhibitor or previous systemic therapy but BRAF inhibitor naive. In the cohort that had received a prior BRAF inhibitor (n = 40), the ORR was 3% with a median PFS of 1.8 months. These preliminary results imply that single-agent use of a MEK inhibitor in BRAF refractory patients is not likely to be a reasonable approach. However, in the cohort that was BRAF inhibitor naive (n = 57), the ORR was 33% with a median PFS of 4 months. Common adverse events included fatigue, rash, nausea, diarrhea and edema. Evaluation of single-agent trametinib in a randomized Phase II trial for patients who obtained durable complete responses. Interestingly, the patients who had responses all had mutations in exon 11 and 13. In a similar Phase II trial, 322 patients with BRAF V600 mutant melanoma were randomized 2:1 to receive trametinib or chemotherapy (single-agent dacarbazine or paclitaxel). Patients were allowed to receive one prior systemic therapy, but not a BRAF inhibitor or ipilimumab. The primary end point of the study was PFS with secondary end points of OS and ORR. The overall RR, OS and median PFS for the trametinib cohort was 4.8 compared with 1.5 months for the chemotherapy control arm (HR: 0.45; p < 0.001). Overall RR was 22% for those treated withtrametinib compared with 12% (p = 0.03). 6.4 months for OS of the trametinib group was 81% compared with 67% for the chemotherapy group (HR: 0.54; p = 0.01). It is important to note that patients who were allowed to cross over from the chemotherapy arm to the trametinib arm upon progression and these survival data are despite this crossover. Final OS results are anticipated. Common side effects from trametinib included rash, diarrhea, fatigue, dermatitis acroainflect and peripheral edema. Less common side effects included decreased ejaculation fraction or left ventricular dysfunction (7%) and ocular toxicity (blurry vision and choroidal neovascularisation). Interestingly, no SCC or KAs were noted as seen with the BRAF inhibitors. Based on the results of this study, trametinib is currently being evaluated for FDA approval. 

CKIT inhibition

Acral lentiginous melanoma, mucosal melanoma and melanomas that arise in the setting of chronic sun damage have been found to harbor higher frequencies of mutations in the CKIT receptor tyrosine kinase (frequency of 19–25%); however, these mutations represent only a small subset of the general melanoma population (~3–5%). Imatinib is an orally bioavailable, potent small-molecule inhibitor of the CKIT receptor that has been FDA approved for treatment in CML and gastrointestinal stromal tumors [36]. Imatinib, to date, has been the most extensively explored CKIT inhibitor in melanoma. In unselected melanoma populations, Phase II trials exploring CKIT inhibitors have resulted in a striking lack of efficacy [37–39]. Responses have been largely limited to a handful of patients who were subsequently found to have a CKIT mutation (in exon 11 and 13). In subsequent trials, patients have been selected for enrollment who were either known to have tumors that harbor an activating mutation in the CKIT gene or have gene amplification. In a study reported by Carvajal et al., 25 patients with known CKIT mutation or activation were treated with imatinib with a 24% RR [40]. This included two patients who obtained durable complete responses. Interestingly, the patients who had responses all had mutations in exon 11 and 13. In a similar Phase II trial,
Guo et al. reported findings on 43 patients with CKIT mutations or amplifications who were also treated with imatinib (35). In this trial, there was a RR of 23% in patients treated with another eight patients having a minor response. Based on knowledge gained from these early trials, it is apparent that selection of patients with mutations that are known to have a heretofore responsive, CKIT mutation would yield the highest RR and potential for durable responses. Other agents that target CKIT, such as dasatinib (NCT01982278), nilotinib (NCT01082622) and masatinib (NCT01280565), are currently being explored in clinical studies. While the dasatinib trial is looking to enrich their population with CKIT mutations, the nilotinib and masatinib trials require CKIT mutations for enrollment. These studies should help to advance our understanding of the use of CKIT inhibitors in this uncommon melanoma population and, if possible, hopefully add to our approved therapeutic arsenal.

Targeted immunotherapeutics

- Immune checkpoint inhibitors
  - Compared to other cancers, melanoma has an uncommon sensitivity to immunotherapies. Interferon and IL-2 have both been FDA-approved for the treatment of malignant melanoma based on their ability to induce responses in some patients. However, these responses are infrequent and have not improved average survival for patients with metastatic melanoma, either as single agents or in combination regimens. T-cell lymphocyte activation is a principle component of the immune-directed anticancer effect for melanoma. Recently, the identification and clinical use of checkpoint receptors and their respective ligands are represented (PD-1, CD137), in addition to T-cell activation resulting in T-cell potentiation. Other immune checkpoints include PD-1, OX-40 and CD137. T-cell modulation for which drugs are being explored include PD-1, OX-40 and CD137.

- Ipilimumab
  - The clinical activity of ipilimumab, a first-in-class, fully humanized monoclonal antibody that binds to CTLA-4, is expressed in increased T-cell activation and proliferation (36). These surface proteins bind to ligands on the antigen-presenting cell to inhibit intracellular signaling. For instance, CTLA-4 is transported to the cell surface where it binds to the B7 ligand, which is present on the antigen-presenting cell surface resulting in an inhibition of T-cell activity. Ipilimumab represents a first-in-class, fully humanized immune checkpoint inhibitor, binds to CTLA-4 blocking its ability to impair T-cell activation, resulting in inhibition of T-lymphocyte activation. Ipilimumab, a first-in-class immune checkpoint inhibitor, binds to CTLA-4 blocking its ability to impair T-cell activation, had a bireated new effect for the field of immunology in metastatic melanoma. There are several important differences between the combination of molecules that work in concert on the T-cell surface to either upregulate or downregulate T-cell activity, respectively (Figure 2). These surface proteins bind to ligands and antigen presentation was statistically different to both the combination arm, p = 0.84, and the vaccine-alone arm, p = 0.001. Immune-related adverse events (e.g., diarrhea, colitis, rash, pruritus and endocrinopathy) were commonly reported with 60% of patients receiving ipilimumab experiencing at least one event. Grade 3 or higher adverse events were seen in 10–15% of patients receiving ipilimumab. Diarrhea was the most common immune-related adverse event occurring in 27–31% of the ipilimumab-containing groups, with Grade 3 or higher diarrhea reported in <10% of patients. Of note, 14 patients (2.1%) died from treatment-related events, with half of these events being immune-related adverse events. Based on the results of this trial, the FDA approved ipilimumab for the treatment of metastatic melanoma on 25 March 2011. The four PD-1/PD-L1 antibodies, pembrolizumab, nivolumab, atezolizumab, and avelumab, are currently in clinical trials with ipilimumab in treatment-naïve metastatic melanoma patients has been reported (37). In this placebo-controlled trial, ipilimumab (at a dose of 10 mg/kg) was combined with DTIC and compared with DTIC alone. The dose selected in this trial was based on earlier work showing that ipilimumab therapy had a dose–response relationship and the 10 mg/kg dosing might result in a greater RR than smaller doses (20). The key entry criteria for the study required systemic therapy naïve for metastatic melanoma, absence of CNS metastases, absence of ocular primary melanoma and absence of autoimmune disease or requirement of immunosuppressives. The primary end point was OS with secondary end points of DFS, PFS, or RR, duration of response, time to response and safety. There were 502 patients randomized, with 250 patients receiving ipilimumab/DTIC combination and 252 receiving DTIC/placebo. The median OS for the ipilimumab/DTIC combination arm compared with the vaccine arm alone. The secondary end points included survival difference between the ipilimumab-alone arm and the GP100 vaccine arm, survival difference between the two ipilimumab arms, ORR, duration of response, and PFS. Important entry criteria included HLA-A*0201 positivity (required for GP100 vaccine activity), no history of antecedent radiation therapy, no concomitant use of immunosuppressive agents. The trial completed accrual in August of 2008, and was reported in 2011. The primary end point of OS was met with a significant difference in the ipilimumab plus ipilimumab plus gp100 vaccine arm (10.0 vs 6.4 months, HR: 0.68; p < 0.0010). There was also a significant difference between the ipilimumab alone arm and GP100 arm (10.1 vs 6.4 months, HR: 0.66; p < 0.001). There was no significant difference between the ipilimumab arm and ipilimumab alone arm (HR: 1.04; p = 0.76). The best ORR for the combination, ipilimumab alone and GP100 vaccine alone arms were 5.7, 10.9 and 1.5%, respectively. No differences in adverse events were observed between the two combination arms, p = 0.04, and the vaccine-alone arm, p = 0.001. Immune-related adverse events (e.g., diarrhea, colitis, rash, pruritus and endocrinopathy) were commonly reported with 60% of patients receiving ipilimumab experiencing at least one event. Grade 3 or higher adverse events were seen in 10–15% of patients receiving ipilimumab. Diarrhea was the most common immune-related adverse event occurring in 27–31% of the ipilimumab-containing groups, with Grade 3 or higher diarrhea reported in <10% of patients. 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Also, with the advent of other checkpoint inhibitors, the question is currently under investigation. With other treatments is appealing. There are a variety of ongoing clinical trials that hope to answer these questions.

- Other immune checkpoint inhibitors in development
  - Tremelimumab, another antibody inhibitor of CTLA-4, has also been evaluated in a randomized Phase III study (42). This trial randomized 655 metastatic melanoma patients 1:1 to receive either tremelimumab (15 mg/kg q 90 days) or chemotherapy (DTIC or temozolomide). The primary end point was OS. The trial was ended prior to completion due to an interim analysis showing futility. The final efficacy analysis showed a 12.6 month median OS for tremelimumab compared with 10.7 months for chemotherapy (HR: 0.72; p = 0.012). Due to this negative trial, the continued development of tremelimumab has been hindered. A variety of other agents that block activity of correlative molecular agents involved in T-cell regulation are in development. BMS 936558 (MDX1100) is a monoclonal antibody that binds to PD-1 resulting in T-cell activation, which has recently shown high evidence of activity and tolerability in a Phase I clinical study (44,45). In this trial, 296 patients with melanoma, NSCLC, castrate-resistant prostate cancer, renal cell carcinoma or colorectal cancer were enrolled. Dosing ranged from 0.1 to 10 mg/kg intravenously every 2 weeks for up to 12 8-week cycles. No maximally tolerated dose was found and expansion of the melanoma cohort was performed. At the time of report 94 patients with melanoma were treated with 26 of those having a partial response. Of those with a partial response, 16% experienced grade 3 or higher adverse events were seen in 14% of patients with common adverse events, including fatigue, decreased appetite, diarrhea, nausea and rash. 42 patients’ tumors were evaluated for the expression of PD-1L and its presence as a potential biomarker. Of these patients whose tumor did not express PD-1L, no patients had a response. Of the 25 patients whose tumor did express PD-1L, there were two responses (36%RR; p = 0.004). Based on signs of early activity for melanoma, a Phase I combination trial with BMS 936558 and ipilimumab...
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has been initiated (NCT01242231). Additionally, single-agent Phase II/III trials are planned with this agent, which should shed further light on its clinical activity for melanoma.

One final agent in this class that has recently had Phase I results reported is BMS-936559, which is a IOD-11 monoclonal antibody [46]. This agent was evaluated in a Phase I trial of 207 patients with either NSCLC, ovarian carcinoma, renal cell carcinoma, pancreatic cancer, gastric cancer or breast cancer. In this cohort, patients were treated in dose-escalation cohorts (ranging from 0.3–10 mg/kg). No maximum tolerated dose was reached in this study. Grade 3 or 4 toxicity was seen in 9% of patients. Common adverse events included fatigue, infusion reactions, diarrhea, arthralgias, rash, nausea, pruritus and headache. Of the 52 patients with melanoma that received treatment in the study, there were nine responses. The RRs per dosing cohort for melanoma were 6, 29 and 19% (for 1, 3 and 10 mg, respectively). Based on the results of this trial, further exploration of BMS-936559 is expected for metastatic melanoma.

Combination approaches
Combining targeted therapeutics provides multiple theoretical advantages to the use of sequential single agents. Some of these potential advantages include inducing higher RR, particularly complete RR, providing more durable responses, and overcoming resistance mechanisms with hopes of longer survival. Early investigation into the mechanism of BRAF inhibitor resistance has shown that most tumors have a reactivation of the MAP kinase pathway [47]. Furthermore, separate analyses have shown that BRAF inhibitor-induced reactivation of the MAP kinase pathway can occur through a variety of different mechanisms including NRAS [48], CRAF [49], COT [50], PI3K [51], PDGFR [48], IGER [52], MEK [52] and BRAF splice variants [48]. Currently, the frequencies of various resistance mechanisms have been shown and further evaluation of larger numbers of patients who develop resistance to BRAF inhibitors is needed to quantify these events. Given the large number of potential resistance mechanisms present, overcoming all resistance mechanisms may be challenging without targeting farther downstream in the MAP kinase pathway (i.e., targeting MEK or ERK); and selecting patients based on these putative mechanisms of resistance (e.g., selecting those patients with PI3K driver reactivation for PI3K inhibitor combinations). Also complicating the development of combination therapies is the large hurdle of potential additive toxicities that may make preclinically exciting combinations intolerable in the real world.

Currently, combinations of several emerging therapies are being explored (Table 2). Furthest among these combination approaches is that of the dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor). A Phase I/II trial of this combination was presented at ASCO 2011 by Infante et al. [52]. At the time of the report, 16 patients with BRAF mutant melanoma had been treated in the dose-escalation and expansion cohort with a RR of 81% of patients. Of the ten patients who received the optimal dose, the combined agents, nine patients had responses. Adverse events included pyrexia, vomiting and fatigue, with an interesting paucity of KAs and rash. Interestingly, the rates of skin toxicity (e.g. KA and hyperkeratosis) appear to be decreased suggesting some nullifying effects of certain toxicities with the combination. In a separate update from this study, Flaherty et al. described a cohort of 24 patients that had failed prior single-agent BRAF inhibitor who received the combination dabrafenib/trametinib therapy. In this preliminary report, ten of 18 evaluable patients had tumor shrinkage (three partial responses) with an additional two patients having stable disease (clinical benefit rate of 67%). Further updates on this Phase I/II study are eagerly anticipated, particularly the Phase II trial of 50 patients will be difficult to randomize to the combination therapy versus single-agent dabrafenib. Based on the emerging data from this study, two randomized Phase III trials are being launched which will compare the combination of dabrafenib and trametinib to dabrafenib alone (primary end point: PFS, NCT01597908); and the other will compare the combination of dabrafenib and trametinib to vemurafenib (primary end point: NCT01597908). In a separate trial, the combination of vemurafenib and a different MEK inhibitor (GDC-0973) is also in Phase I development (NCT01271803).

Besides BRAF/MEK combinations, there are also many other interesting early-phase combination trials in progress. For example, a trial of the PI3 kinase inhibitor BKM120 and vemurafenib is in Phase I development (NCT01512251), which should give some insight into simultaneous horizontal blockade of the MAPK and PI3K pathways. Other targeted combination approaches being examined include: vemurafenib and PKI inhibitors (NCT01596440); vemurafenib and bevacizumab (VEGF inhibitor, NCT01495988); and vemurafenib and sorafenib (NCT01531361). Additionally, evaluations exploring the combination of molecularly targeted agents with immunotherapies are being conducted. This includes the combination of ipilimumab and vemurafenib in a Phase I trial (NCT01400451), which will shed light on the tolerability and efficacy of combined targeted immunotherapy and BRAF inhibitor, with the hope being to maximally ‘debulk’ tumor burden followed by extension of the duration of response with ipilimumab. Combinations of ipilimumab and H-L2 (NCT01489589), and ipilimumab and bevacizumab (NCT00799010) are also being explored.

Table 1. Ongoing combination trials for metastatic melanoma and stage of development.

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<th>Combination</th>
<th>Molecular targets</th>
<th>Stage of development</th>
<th>Clinical trial.gov identification number</th>
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Table 2. Future perspectives

Future perspective
After years of clinical trial failures, therapeutic options for metastatic melanoma are now rapidly expanding. There have been two drugs with different mechanisms of action that have been FDA-approved based on their ability to extend survival for the average patient, a feat that had not been seen previously for this disease. A host of other similar agents (kinase inhibitors and immune checkpoint inhibitors) are in clinical development, with potential to continue to improve on this progress as both single agents and combination treatments. As new agents become available, there has been great interest in studying them in the adjuvant setting where their benefit may be the greatest. The severe toxicity of these agents and the potential for metastatic setting may bring about more cues in the adjuvant setting. Currently, adjuvant therapy consists of interferon, which has many shortcomings including severe toxicity (e.g., fatigue, hypothyroidism). This agent was withdrawn in the US due to debatable capability of improving survival for high-risk patients. At present there are several studies ongoing or soon to be initiated exploring the benefit of various agents in the adjuvant setting. These adjuvant trials include an ipilimumab versus placebo trial (completed accrual, NCT00636468), an ipilimumab versus interferon trial (NCT01274338), and a vemurafenib versus placebo trial. Results from these studies are highly anticipated.

Although vemurafenib and ipilimumab have improved treatment options, there is still a host of unmet needs for patients with metastatic melanoma. In the area of BRAF-mutant melanoma patients who develop BRAF inhibition resistance, a better understanding of resistance mechanisms is needed. It appears that there are a variety of escape mechanisms and, thus, multiple drugs may be needed to deal with this population of patients and postprogression biopsies will likely become necessary to identify patients suitable for treatment. Studies that are launching based on their unique mechanism of action that have been FDA-approved based on their ability to extend survival for the average patient (e.g., ipilimumab versus interferon trial (NCT01274338), and an ipilimumab and bevacizumab trial (NCT01279873) is also in Phase I development (NCT01271803). For BRAF wild-type patients, exploration of targeted therapies for other activating mutations, such as CKIT and NRAS, are ongoing. Certainly there is a large subset of patients who are BRAF, CKIT and NRAS wild-type (i.e., ‘triple negative’, ~40%). Further exploration of this melanoma subset is required with a focus on identifying druggable molecular defects that can be exploited. This will require an extensive sequencing approach followed by validated pharmacologically driven drug X for identified molecular defect X. Until other targeted therapies can be found for these triple negative metastatic melanoma patients, use of immune therapies is most reasonable. An additional area of need is the discovery of effective treatment options for the patient.
use a combination of three or more agents for melanoma will likely require that we 
serve a first step in this particular melanoma subtype has already been found to have frequent mutations in the G proteins GNAQ and GNA11, identification of a way to exploit this pathway is in desperate need. The patients have very poor survivals ranging from 3 to 6 months.

Currently, final immune therapies (ipilimumab, HD-IL-2) can be very effective for a minority of selected patients. Identification of biomarkers that help to select these immune therapies from potentially serious complications. Additionally, this would be a first step in discovering what might be driving immunotherapy resistance in the immunonegative-sensitve tumors with the possibility of manipulation of these tumors to make them more sensitive. As with other metastatic cancers that are commonly cured, such as testicular cancer and lymphoma, curative treatment for melanoma will likely require that we use a combination of three or more agents (probably both protein kinase inhibitors and immune-based therapies) to result in commonly seen cures for metastatic melanoma patients, which is our ultimate goal.

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Executive summary

The identification of commonly occurring molecular defects, such as BRAF V600E mutations, as well as the discovery of immune checkpoint inhibitors, has led to a revolution in the development of drugs for metastatic melanoma. 

Vemurafenib, which is a selective and potent inhibitor of BRAF V600E mutant melanoma, has gained US FDA approval based on its ability to extend progression-free survival, improve response rates and extend survival for metastatic melanoma patients compared with dacarbazine.

Iplilimumab, a monoclonal antibody that binds to CTLA-4 resulting in T-cell activation, has gained FDA approval for patients with unresectable melanoma based on its ability to extend survival.

Many other agents, both molecularly targeted kinase inhibitors and other T-cell checkpoint inhibitors, are in development for the treatment of metastatic melanoma.

With the advent of novel therapeutic approaches for melanoma, combination approaches are in early clinical development and will hopefully further advance outcomes for patients with this devastating disease.