Advances in the Treatment of Metastatic Melanoma

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UT Southwestern Medical Grand Rounds

October 12th, 2012

UT SOUTHWESTERN MEDICAL CENTER

This is to acknowledge that Amy Harker-Murray M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Amy Harker-Murray M.D. will be discussing off-label uses in her presentation.

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Dr. Amy Harker-Murray's clinical interests are breast cancer and melanoma.

Purpose:

The purpose of today's presentation is to review the latest advances in the treatment of metastatic melanoma. The past 18 months have seen the first major developments in the treatment of metastatic cutaneous melanoma in almost twenty years and the results of the clinical trials which led to FDA approval made the national news. This prompted great interest on the part of patients and physicians. It is important for primary care physicians, and subspecialists, to be aware of these treatments, and in particular, aware of some of their more problematic and unique side effects.

Overview:

1. Epidemiology of Cutaneous Melanoma
2. Historic Treatment of Metastatic Melanoma
3. Recent Advances
    a) Ipilimumab (Yervoy ™)
    b) Vemurafenib (Zelboraf ™)
    c) Dabrafenib
    d) Trametinib
4. Unanswered questions
5. Ongoing trials.

Educational Objectives:

1. To review common treatment options for metastatic melanoma as of 2010.
2. To review the latest immunotherapy for metastatic melanoma including mechanism of action, efficacy, side effects and limitations.
3. To review the latest targeted therapies for metastatic melanoma including mechanisms of action, efficacy, side effects and limitations.
4. To review new agents pending FDA approval for the treatment of metastatic melanoma

Epidemiology of Cutaneous Melanoma

It is estimated that 76,250 new cases of melanoma will be diagnosed in the U.S. in 2012, with 9,180 deaths [1]. Melanoma is the fifth most common cancer in men and the seventh most common cancer in women in the United States [2] and affects white patients more frequently than Hispanic or black with a lifetime risk of 1/50 vs. 1/200 vs. 1/1,000 respectively [1].

The incidence of cutaneous melanoma is rising rapidly with a 15% increase in the age-adjusted SEER incidence rate per 100,000 people from 1975 to 2009 [3]. It is uncertain how much of this is due to detection bias from increased screening [2],[4],[5],[6], the use of tanning beds [7], or increased ultraviolet exposure [8],[9].

Fortunately, most cases of melanoma are diagnosed in an early, curable stage (Fig. 1) [3]. But the prognosis for metastatic melanoma is dismal with a median overall survival of 8 -18 months depending on the presence or absence of visceral metastases and elevation in lactate dehydrogenase [10].

Stage Distribution and 5-year Relative Survival by Stage at Diagnosis for 2002-2008, All Races, Both Sexes

Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
Localized (confined to primary site)	84	98.2
Regional (spread to regional lymphnodes)	9	62.4
Distant (cancer has metastasized)	4	15.1
Unknown (unstaged)	4	75.8

Figure 1. [3]

Historic Treatment of Metastatic Melanoma

Dacarbazine

Dacarbazine is an intravenous alkylator which is hepatically metabolized to the active metabolite MTIC. It has been the gold standard treatment for metastatic melanoma since it

was approved by the FDA in 1975 [11] despite the lack of any phase III clinical trials demonstrating a survival benefit against observation [12]. Among recent clinical trials with dacarbazine as the control arm, response rates range from 7–32%, with a median overall survival of 5.6–11 months and one year overall survival of 20–30% [13].

Temozolomide

Temozolomide is an oral alkylator which is metabolized to the same active metabolite as dacarbazine. A direct comparison between dacarbazine and temozolomide revealed no difference in response rates or overall survival [14]**.** Temozolomide can cross the blood brain barrier and has some effectiveness in brain metastases [15]. Despite these findings, temozolomide has not been FDA approved for the treatment of melanoma and its use is off label.

High dose interleukin 2 (IL-2)

In 1992, the FDA approved a second drug for the treatment of metastatic melanoma, interleukin 2 [11]. IL-2 is a T-cell growth factor, induces natural killer cell activity, and increases interferon-ɣ production [16]. Multiple phase II trials have demonstrated a complete response rate of 0-15% and these complete responses can be very durable, 1.5–148 months, with a median duration of response of 70 months [17]**,** [18]. Treatment is very toxic, requiring intensive care level monitoring, and strict adherence to toxicity management [19]**.** Only carefully selected patients with a good performance status and excellent cardiopulmonary function are appropriate candidates for this potentially curable therapy.

Recent Advances

Ipilimumab (Yervoy ™)

Ipilimumab, or 'Ipi' as patients have taken to calling the drug, is a fully humanized monoclonal antibody to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) whose mechanism of action was described by Robert et al (Fig. 2)[20]. In order for a T cell to be fully activated, two steps must occur. First, an antigen presenting cell (APC) offers an antigen bound to major histocompatibility complex (MHC) to bind with the T cell receptor (TCR) of a naïve T cell. Second, CD 80 (alternatively named B7) on the APC must bind with CD 28 on the T cell.

When this occurs, the T cell is activated. In order to control the subsequent cellular immune response, there is a negative feedback loop within the T cell. CTLA-4 is mobilized from intracellular stores and presented on the surface of activated T cells to competitively bind with the APC CD 80 receptor acting as an inhibitory signal. Ipilimumab blocks the CTLA-4 and CD80 interaction, preventing the negative feedback loop and allowing the cellular immune response to persist with an increased antitumor response.

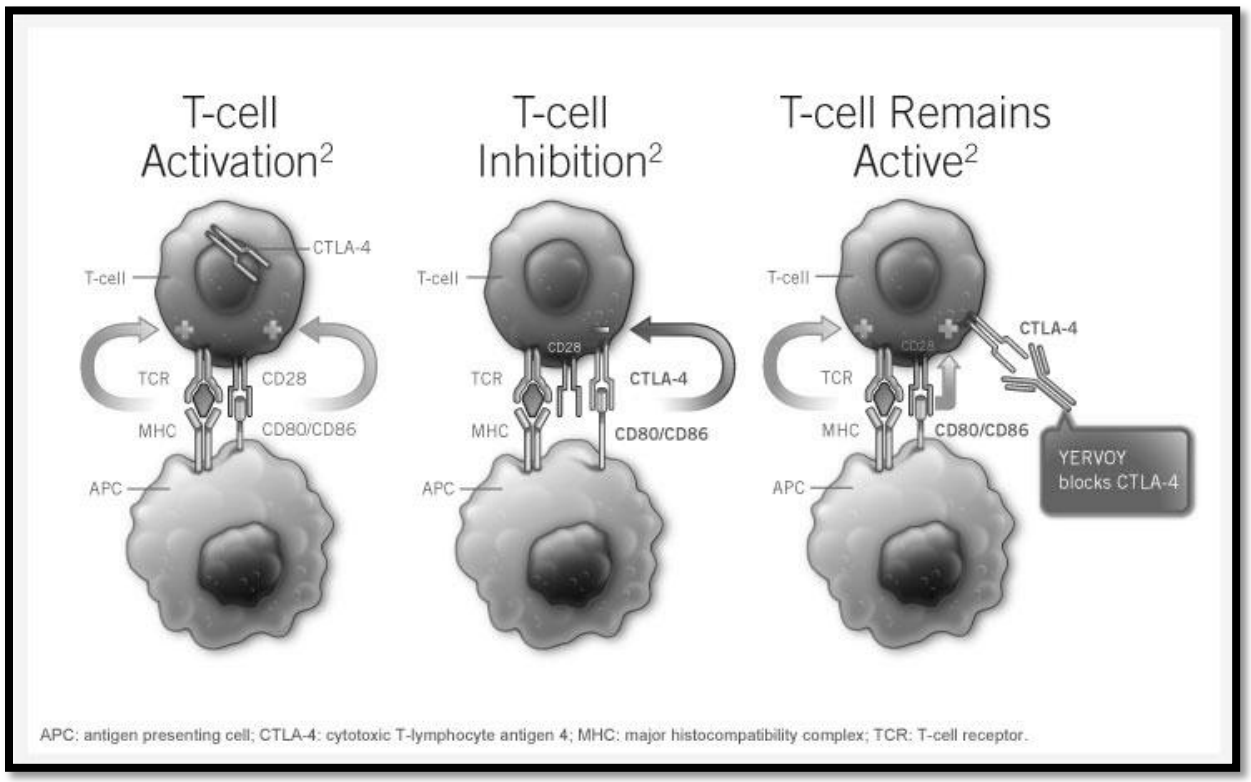

Figure 2: Steps in T cell activation and mechanism of action of ipilimumab. Bristol-Myers Squibb, [21].

Ipilimumab was approved by the FDA in March of 2011 for the treatment of metastatic melanoma based on the results of a multicenter, phase III, double blind, randomized clinical trial, conducted by Hodi et al, and involving 676 patients with unresectable stage III or IV cutaneous melanoma whose disease had progressed on prior immunotherapy or chemotherapy [22]. Patients were randomized in a 3:1:1 fashion to Arm A: ipilimumab plus glycoprotein 100 peptide vaccine (gp100), Arm B: ipilimumab alone, or Arm C: gp100 alone. Patients with primary ocular melanomas, untreated brain metastases, or autoimmune disease were excluded. The dose of ipilimumab was 3 mg/kg intravenously every three weeks for four doses. The primary endpoint of overall survival (Fig. 3) was met, median follow-up of approximately

two years, with a statistically significant improvement in median overall survival of almost 4 months comparing either ipilimumab containing arm to gp 100.

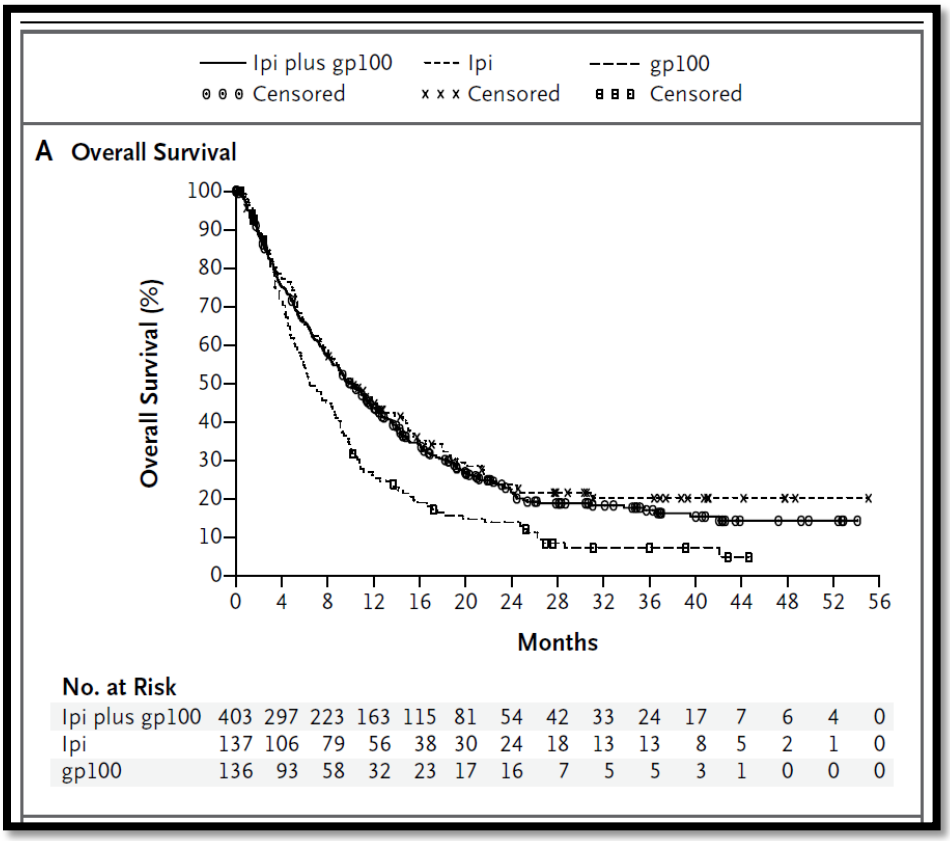

Figure 3: Kaplan-Meier curves for overall survival. 10 months ipilimumab plus gp100 vs. 6.4 months gp100 (HR 0.68, P<0.001). 10.1 months ipilimumab vs. 6.4 months gp100 (HR 0.66, P=0.003). [22]

These results made ipilimumab the first drug to show an improvement in overall survival in metastatic melanoma. Even more impressive when one considers the participants were a group of pre-treated, high risk patients with >70% having visceral metastases or elevated LDH [22].

Interestingly, the overall response rates were quite low. Complete and partial responses were seen in only 5.7% of the ipilimumab plus gp100 group, 11% of the ipilimumab group, and 1.5% of the gp100 (both of which were partial responses). But those few responses were durable with 60% of responders in the ipilimumab alone arm and 17% in the combination arm maintaining responses for at least two years and a handful of patients in each arm maintaining response out to almost four years[22].

Robert el al. was the first to confirm the overall survival benefit of ipilimumab in a treatment naïve population (Fig. 4) [23]. Over 500 patients with previously untreated, unresectable stage III or IV metastatic melanoma were randomized in a 1:1 ratio to arm A: ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m2) or arm B: dacarbazine alone (850 mg/m2) given intravenously every four weeks for twelve doses and then arm B patients received dacarbazine every three weeks for another four doses. Patients were ineligible if they had brain metastasis, primary ocular or mucosal melanoma, or autoimmune disease.

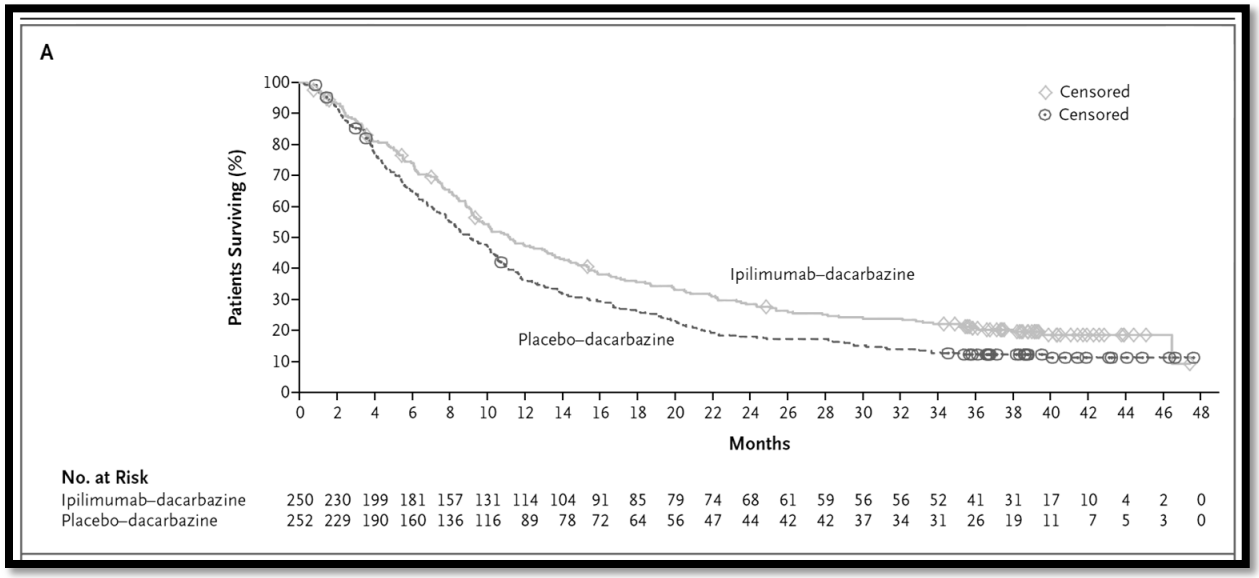

Figure 4: Kaplan-Meier curves for overall survival. 11.2 months combination arm vs. 9.1 months dacarbazine arm (HR 0.72, P<0.001) [23].

As noted in the prior phase III trial, overall response rates were low. Only 15.2% complete and partial responses in the ipilimumab-dacarbazine arm vs. 10.3% with dacarbazine alone (P=0.09) but the duration of those limited responses was significantly longer, 19.3 months v. 8.1 months (P=0.03) [23].

Because of ipilimumab's mechanism of action, responses are typically slow and patients are not assessed for disease response until week 12. Responses are confirmed at weeks 16, 20 and 24. Robert et al. noted a further improvement in response after week 24 in a subset of patients [23]. In the combination arm, 3 patients with initial disease progression improved to stable disease, 3 patients with stable disease improved to partial response, and 1 patient with a partial response improved to a complete response [23]. Similar results were seen in the ipilimumab alone arm in the phase III first line trial [22]. In fact, four different responses have been described: initial response, stable disease with a slow decrease in tumor burden, an initial increase in tumor burden followed by a subsequent decrease, and the appearance of new

lesions followed by a response in the index and new lesions[24]. The initial increase in tumor burden, followed by a subsequent decrease in a small subset of patients, can not only be very disconcerting for both the patient and physician, but also make it difficult to decide when the treatment is failing and alternatives should be pursued.

Side effects of ipilimumab are very different from classic cytotoxic chemotherapy and are predominantly immune mediated. Hodi et al noted 58-61% immune-related events of which 10-15% were grade 3 or 4 and when ipilimumab was combined with dacarbazine, immune-related events jumped to 78%, with 42% grade 3-4 [22] [23]**.** The biggest difference between the two trials was the incidence of immune-mediated increase in alanine aminotransferase and aspartate aminotransferase with 3-4% of any grade in the first trial vs. 46% in the second [22] [23]**.** Almost every organ system can be involved with the most commons sites including skin (rash, pruritus, vitiligo), gastrointestinal (diarrhea, ileus, perforation), liver (hepatitis, elevated ALT/AST), endocrine (hypopituitarism, adrenal insufficiency, hypo- and hyperthyroidism, Cushing's syndrome) and neurologic (sensory or motor neuropathy, myasthenia gravis, Guillain-Barré). There are case reports of panenteritis [25], neutropenia [26], enteric neuropathy with severe constipation [27], Graves disease [28], posterior reversible encephalopathy syndrome [29]**,** hemophilia A [30] [31]**,** lupus nephritis [32], and red cell aplasia [33]. Symptoms can be severe enough to lead to cessation of ipilimumab, treatment with corticosteroids, use of infliximab to treat colitis [22, 34], and mycophenolate mofetil to reverse hepatitis [23]. More sobering are the 14 deaths (2%), of which 7 were immune mediated [22]. As a result, the FDA has instituted a risk evaluation and mitigation strategy (REMS) to help educate health care professionals and patients about these significant sobering side effects.

Ipilimumab is clearly a great addition to the armamentarium against metastatic melanoma. Its ground breaking improvement in overall survival of 2-3 months, in both the first and second line settings, and the reported long term duration of response are major leaps forward. This treatment cannot be universally applied to all patients with unresectable stage III and IV disease though, as those with autoimmune disorders must be excluded for their safety, and those with rapidly progressive visceral disease do not have the luxury of 12 weeks for a decrease in their disease burden. Finally, our enthusiasm must be tempered by the significant immune mediated side effects.

Vemurafenib (Zelboraf ™)

While ipilimumab represents a leap forward in immune therapy for metastatic melanoma, vemurafenib is an equally important development in genome-specific anticancer therapy. In 50% of melanomas, there is an activating mutation in the serine/threonine protein kinase B-RAF (BRAF) resulting in an constitutively activated BRAF which leads to increased downstream signaling through the MAPK pathway, promoting cell proliferation and decreasing apoptosis [35] [36] [37] (Fig. 5). Approximately 90% of BRAF mutations are V600E (substitution of glutamic acid for valine) [38], and 16% are V600K (substitution of lysine for valine) [39]. Vemurafenib is potent inhibitor of both the V600E and V600K mutations [40].

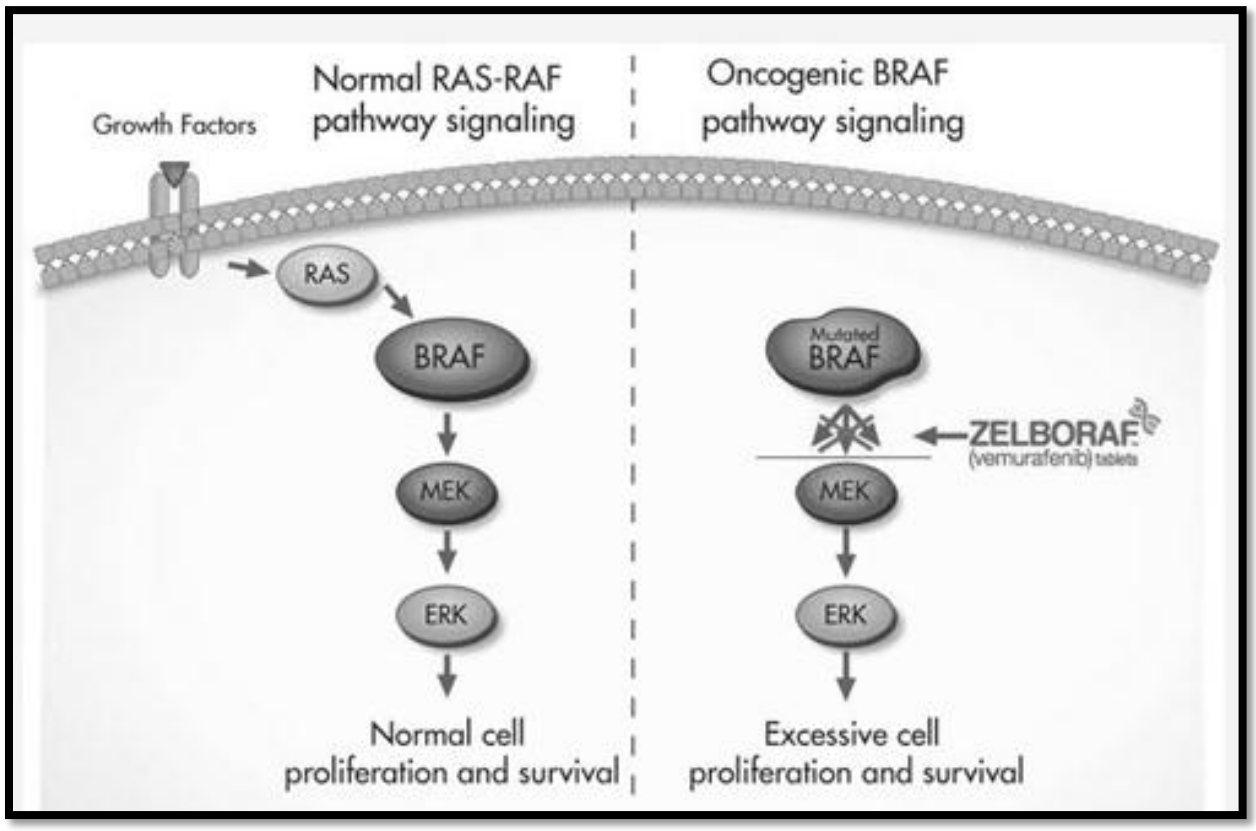

Figure 5: BRAF signaling and site of action of vemurafenib. Genentech, [41].

Vemurafenib was approved by the FDA in August, 2011 for the treatment of unresectable or metastatic melanoma harboring a V600E mutation. The basis of approval was a phase III, open label, randomized clinical trial involving 675 patients with untreated, unresectable stage IIIC or IV melanoma, who were randomized on a 1:1 ratio to vemurafenib 960 mg twice daily orally or dacarbazine 1000 mg/m2 intravenously every three weeks until disease progression[42]. All but 20 patients' melanomas harbored a V600E mutation, 19 of

which were V600K [42]. With a very brief median follow-up less than 4 months, there was a statistically significant improvement in overall survival (Fig. 6) [42]. One and two year survival rates were not reported because of the short follow-up period.

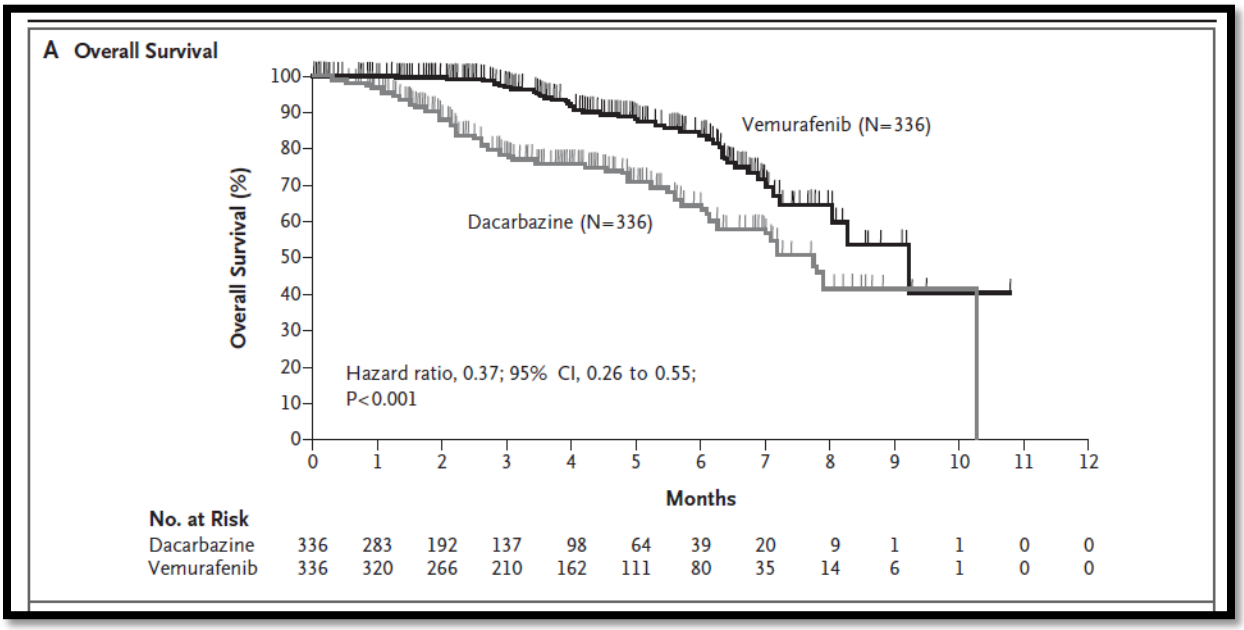

Figure 6: Kaplan-Meier curves for overall survival. Six month overall survival vemurafenib 84% (95% CI, 78 to 89) vs. dacarbazine 64% (95% CI, 56 to 73) [42].

The objective response rate to vemurafenib was an impressive 48%, majority partial responses, versus 5% objective response rate to dacarbazine (P<0.001). Interestingly, the authors also reported a 40% response rate for patients whose melanomas harbored a V600K mutation [42]. The responses can also be very rapid with a decrease in FDG avidity on PET scans by day 15 of treatment [38].

A phase II clinical trial of 132 previously treated patients with stage IV BRAF V600 mutated (122 V600E, 10 V600K) melanoma confirmed Chapman et al.'s findings [37]. With a longer median follow-up of 13 months, the response rate for V600E mutations was 53% and 40% for V600K mutations and the median duration of response 6.7 months (95% CI, 5.6 to 8.6). The median overall survival was 15.9 months (95% CI, 11.6 to 18.3) [37].

The most common grade 2 – 3 side effects were cutaneous 39% (rash, alopecia, pruritus, hyperkeratosis, photosensitivity), arthralgia 21%, and fatigue 13% with the only grade 4 side effect being neutropenia <1% [42]. Elevated liver function tests have also been reported [37]. A unique side effect of vemurafenib is the development of cutaneous squamous-cell carcinoma 12%, keratoacanthoma 8%, and basal-cell carcinomas 6% which require excision and regular

dermatologic evaluations [42]. The pharmaceutical company also reports 8 cases of new melanomas arising in the phase III trial, but the authors did not comment on this finding [41] . Up to 60% of cutaneous squamous cell carcinomas and keratoacanthomas which developed during vemurafenib therapy contained *RAS* mutations with a resultant paradoxical activation of the MAPK signaling pathway [43].

Vemurafenib is now considered the standard of care for patients with unresectable metastatic melanoma harboring a BRAF V600E mutation (V600K off label). Its rapid and high response rates make it an attractive treatment option for patients with symptomatic, rapidly progressive disease. Results of long term follow-up from the original phase III trial are needed to clarify duration of response and median overall survival.

Dabrafenib

Dabrafenib is an orally available inhibitor of BRAF V600E. A recent phase III trial of 250 patients with untreated, unresectable, stage III–IV metastatic melanoma randomized patients in a 3:1 ratio to treatment with dabrafenib or dacarbazine and patients who progressed on dacarbazine were allowed to cross over [44]. Patients without a BRAF V600E mutation were excluded, including those with V600K mutations. The response rate was 50% (42.4-57.1%) for dabrafenib vs. 6% (1.8-15.5%) for dacarbazine and there was a statistically significant increase in progression free survival from 2.7 months to 5.1 months ($P<0.0001$) but there was not a significant improvement in overall survival (HR 0.61, 95% CI 0.25-1.48). Similar to the phase III trial with vemurafenib, median follow-up was short, 5 months, so more mature data is awaited. The toxicity profile was better than vemurafenib with only 6% development of cutaneous squamous cell carcinomas and keratoacanthomas with dabrafenib vs. 20% with vemurafenib. Other cutaneous events, arthralgia, and fatigue were also decreased.

Trametinib

Trametinib inhibits MEK1 and MEK2 and blocks the downstream signaling in the MAPK pathway which occurs in constitutively activated, mutated BRAF V600E and V600K melanomas [45]. Trametinib was compared to single agent dacarbazine and single agent paclitaxel in a phase III trial of 322 patients with stage IIIC or IV, previously treated, unresectable metastatic melanoma harboring either a BRAF V600E or V600K mutation. Prior treatment with ipilimumab or other BRAF and MEK inhibitors were not allowed. Comparisons between trametinib and chemotherapy (collective data for dacarbazine and paclitaxel) revealed a response rate of 22%

vs. 8% (P=0.01), progression free survival of 4.8 months vs. 1.5 months (P<0.001) and overall survival is not reported, but HR for death was 0.54 (95% CI, 0.32-0.92; P=0.01). Duration of response for trametinib was similar to the BRAF inhibitors at 5.5 months. There were no reports of cutaneous squamous cell carcinomas but there were 14 cases (7%) of decreased ejection fraction, and 9% incidence of ocular events mostly grade 1-2. Overall, trametinib appears to have a lower response rate but better side effect profile than the BRAF inhibitors, vemurafenib in particular.

Unanswered questions

Despite the excitement generated by the two new FDA approved agents, many questions still remain unanswered.

Ipilimumab:

What is the ideal dose of ipilimumab?

What are the predictors of response? Given its toxicity and low response rates, subsets of patients need to be better defined so only those patients with the greatest possibility of achieving durable responses are treated. Predictors may include single nucleotide polymorphisms or SNPs in the *CTLA4* gene [46].

Does ipilimumab have activity in non-cutaneous melanoma? There are case reports of responses in uveal, mucosal, and acral melanomas, rare subsets of melanoma for which randomized clinical trial data are scant [24] [47].

Is ipilimumab active in brain metastases? Case reports do support responses in brain metastases including some complete responses [48], [49].

Vemurafenib:

What is the consistency of BRAF mutation status between the primary cutaneous melanoma, the local lymph node metastases, and the distant visceral metastases? And mutation status at which site best predicts response to BRAF inhibitor therapy?

Ongoing trials

There are several phase III clinical trials in the pipeline to address some of these unanswered questions. One is a direct comparison of adjuvant ipilimumab (3mg/kg or 10 mg/kg) vs. high dose interferon α2B for resected stage IIIB-IV disease. This will hopefully answer the question of the best dose of single agent ipilimumab and provide the oncology community with an effective adjuvant therapy other than interferon α2B.

There are two phase III trials in the BRAF/MEK inhibition area. The first compares the combination of trametinib and dabrafenib to single agent dabrafenib to confirm the increased response rates and progression free survival reported in the phase II trial. And the second compares the same combination therapy to vemurafenib.

Summary

With the array of options for the treatment of metastatic melanoma, the decision of which agent to offer a patient has become more difficult. As high dose IL-2 is the only treatment with long term follow-up confirming a small number of durable complete responses, maybe even cures, it remains a first line option for carefully selected, excellent performance status patients. For patients who are not candidates for high dose IL-2, have small volume or asymptomatic disease, and no autoimmune disease, ipilimumab is a viable option regardless of BRAF mutation status. Treatment with vemurafenib is reserved for patients with a V600E or V600K mutation (latter off label) who have symptomatic or rapidly progressive disease which cannot wait for the slow response to ipilimumab, patients who have failed ipilimumab and/or IL-2, or patients who are not candidates for either drug. Finally, dacarbazine and temozolomide can provide symptom improvement, rare durable response, and should not be automatically discarded as treatment options.

After thirty years of having only two FDA approved agents for the treatment of metastatic melanoma, there has been a recent explosion of exciting new possibilities. Ipilimumab and vemurafenib were approved within five months of each other and both trametinib and dabrafenib have been submitted for FDA approval. There is finally hope that one day metastatic melanoma may not be the dreaded disease it is today.

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