

## Metastatic Melanoma: Perspectives on Current Treatment and Insights Into Emerging Approaches

**An Interview With Paul Chapman, MD  
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*The incidence of melanoma has been increasing steadily since 1930. Melanoma is particularly devastating because it affects a broad range of age groups. Although the average age of patients at diagnosis of melanoma is 55 years, patients can be in their 20s or 30s, or younger. Unfortunately, in metastatic disease, combination chemotherapy or biochemotherapy has not improved median survival over single-agent dacarbazine, which confers a response rate of about 15% and a median survival of approximately 6 months.<sup>1,2</sup> High-dose interleukin 2 (IL-2) produces a response rate of approximately 16%; however, a subset of these responses is durable.<sup>3</sup>*

*Our increased understanding of the biology of melanoma and the immune system has generated new approaches to its treatment. It is important for the practicing oncologist to know and understand the therapies that are clinically available and those on the horizon. Only with this information can we fully counsel and educate patients on their options. New agents will likely find their way into use in the community setting.*

*This issue of CMEConnection highlights important data that are impacting the care of patients with metastatic melanoma today and may influence care in the future.*

### Faculty

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### Target Audience

Oncologists

### Activity Goal

To provide participants with information regarding current treatment and insights into emerging treatment approaches for metastatic melanoma.

### Learning Objectives

After completing this activity, participants should be better able to:

1. List the new agents for melanoma in late clinical development and describe the mechanism of action, efficacy, and toxicity profiles.
2. Describe the most up-to-date studies on the treatment for metastatic melanoma.
3. Discuss recent data and apply the findings to the treatment of advanced melanoma.
4. Educate patients on the approach to the treatment of metastatic melanoma, including available clinical trials.

### Faculty Disclosure

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**Dr Chapman:** *honoraria:* Bristol-Myers Squibb Company; *grant/research support:* AstraZeneca Pharmaceuticals LP, Schering-Plough Corporation.

The Planning Committee for this activity included Kathy Johnston-Kavanagh and Margaret Astrologo of New York Medical College, and Ruth Cohen of Continuing Education Alliance. The members of the Planning Committee have no significant relationships to disclose. We gratefully acknowledge Pfizer Inc for its generous support of this educational activity.

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Physicians wishing to receive credit must:

- Read the newsletter.
- Relate the activity content to the Learning Objectives.
- Complete the Self-Assessment Questions and Evaluation Form (pages 6 and 7) and submit as indicated.

The estimated time to complete this activity is 1 hour.

**Release date:** April 15, 2008.

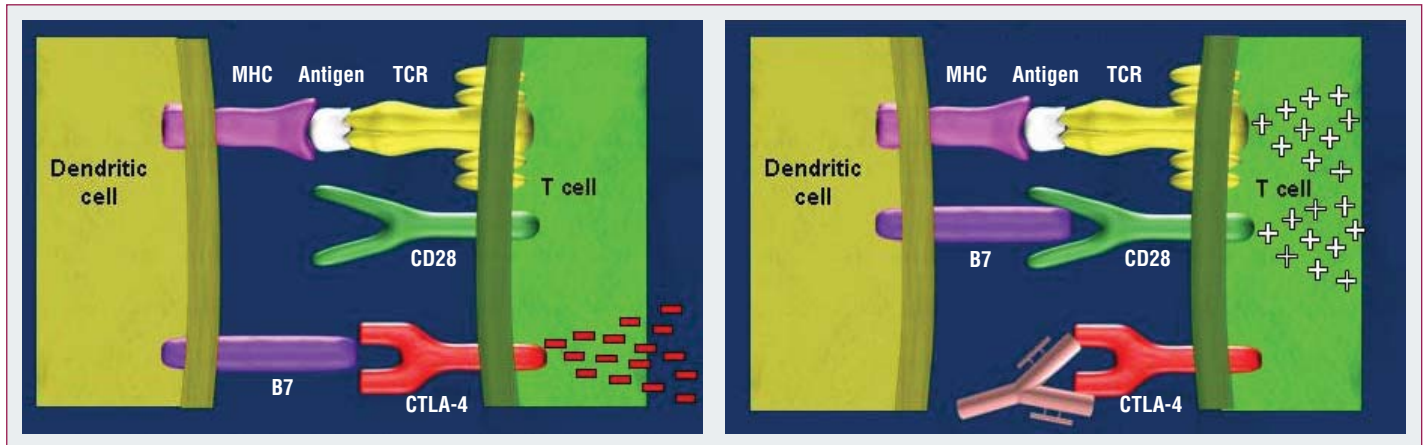
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### Disclaimer

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**Figure 1. Anti-CTLA-4 mechanism of action.** Left: CTLA-4 negatively modulates T-cell activation. Right: Blocking antibodies to CTLA-4 allow positive signaling from costimulatory molecules to T cells. MHC = major histocompatibility complex; TCR = T-cell receptor. Ribas A et al.<sup>4</sup>

### ***What are your general thoughts on the current treatment options for metastatic melanoma?***

**Dr Chapman:** The general feeling is that nothing works for treating metastatic melanoma, but this isn't entirely true. Granted, most tumors do not melt away, but some do. There is certainly just as much activity with current treatments for melanoma as there is for many other routinely treated solid tumors, such as gastrointestinal tumors. It is definitely worth treating metastatic melanoma. I hope this newsletter will be of value in conveying that point and helping to highlight potential therapeutic options.

### ***Despite extensive research, immune approaches have as yet not provided tumor control in the clinical setting. Why is there continued research?***

**Dr Chapman:** Melanoma is thought to be immunogenic; this idea was first based on the observations that primary melanomas can regress spontaneously and that tumors are often infiltrated with T lymphocytes. Research into immunotherapy for melanoma has been ongoing for a long time, but for the most part it has produced only anecdotal clinical responses. Currently, there is little immunotherapy—other than IL-2—available for use in the metastatic setting by a community oncologist off protocol. Because of its side effects, the number of institutions set up to administer IL-2 is limited. In any event, only a select group of patients can tolerate it. However, it has produced a few

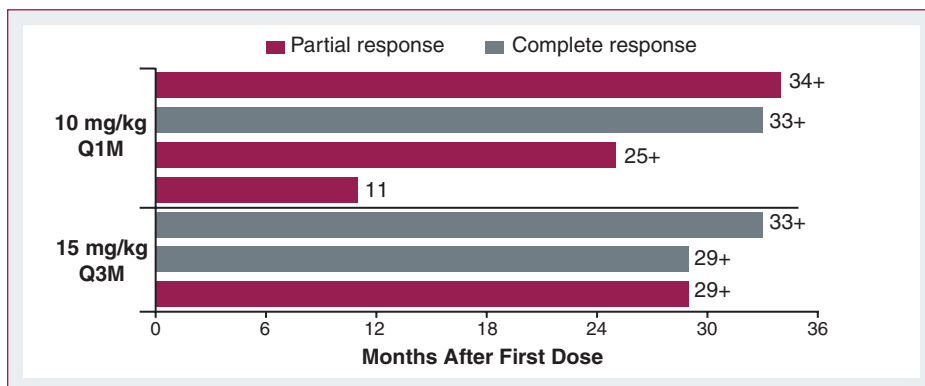
long-term responses, making it valuable to some patients and worth consideration. Based on our increased understanding of the immune system, there are new approaches. Immune responses can be generated by vaccines; we just have to be able to take the research to the next level and produce tumor responses.

### ***What new approaches to melanoma immunotherapy are important for the community oncologist to know?***

**Dr Chapman:** The anti-CTLA-4 monoclonal antibodies in development are a hot topic in melanoma immunotherapy. Because of their relative ease of administration (at least compared with IL-2), they are likely to be used in the community if they get US Food and Drug Administration (FDA) approval. The anti-CTLA-4 antibodies have a unique mechanism of action. Basically, they are immunomodulators that increase the immune response by removing a negative signal on the T cell. CTLA-4 is a homolog to the costimulatory molecule CD28. When CD28 is bound to antigen on an antigen-presenting cell, it helps to generate an immune response. When CTLA-4 is bound, it sends a negative signal to turn off the T cell. It is essentially a brake on the immune system. The anti-CTLA-4 monoclonal antibodies block the binding of CTLA-4 and stop it from giving a negative signal, thus removing the brake (Figure 1).<sup>4</sup>

Tremelimumab and ipilimumab are the 2 fully human anti-CTLA-4

monoclonal antibodies in development. As of now, it is hard to say whether there are clinical differences between them, although the dosing schedules are different. There have been reports of durable responses to both antibodies and stable disease.<sup>5</sup> In a phase 2 trial presented at the American Society of Clinical Oncology (ASCO) in 2007, patients with advanced melanoma received tremelimumab.<sup>4</sup> Complete or partial responses were seen in 7 of 84 evaluable patients, and stable disease was seen in 26. One of the responses lasted 11 months and the rest were ongoing at the time of reporting, with a range of 25 to 34 months (Figure 2).<sup>4</sup> A phase 2 trial of ipilimumab in patients with advanced melanoma was also reported at that meeting.<sup>6</sup> Four of 88 patients had complete or partial responses, and durable stable disease was achieved in another 10 patients. The responses lasted 29 to 39 weeks at the time of reporting, with 3 of them ongoing. Also, the durable stable disease ranged from 21 to 79 weeks, with 4 ongoing at the time of reporting. Both antibodies are in phase 3 trials, although recently, the phase III trial with tremelimumab was stopped for lack of efficacy. One potential difference between the 2 antibodies is that tremelimumab was given every 3 months whereas ipilimumab was given every 3 weeks. It is possible that this schedule difference resulted in less activity seen with tremelimumab. This is a very interesting



**Figure 2.** Survival of patients who responded to treatment with tremelimumab. In the study by Ribas and colleagues, 7 of 84 patients had complete or partial responses. At the time of reporting these responses were durable, lasting from 11 months to at least 34 months. Ribas A et al.<sup>4</sup>

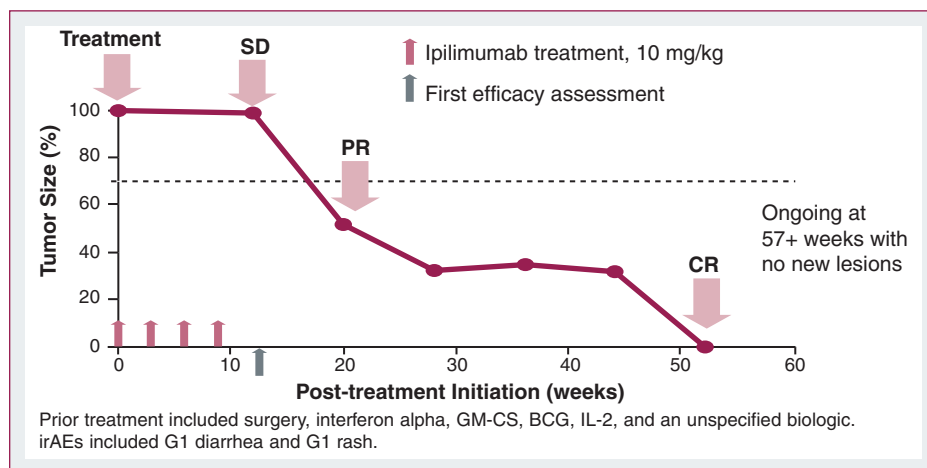
time for these antibodies and I expect an avalanche of data on the anti-CTLA-4 antibodies to be presented at the upcoming ASCO annual meeting.

***In addition to their mechanism of action, are there any other aspects of anti-CTLA-4 agents that we should be aware of?***

**Dr Chapman:** These agents present 2 new challenges for oncologists. First, the primary adverse effects are autoimmune toxicities, which are quite manageable but require vigilance to avoid becoming life-threatening. They can also occur at any time during therapy. The most important autoimmune toxicity is colitis. If colitis occurs, action must be taken immediately. If a patient has just 2 loose bowel movements, we need to know. They require close

attention and may need to be admitted to the hospital. By doing this, we avoid disasters. With other autoimmune adverse effects, such as thyroiditis with hypothyroidism, the hypothyroidism can be treated and patients can continue to receive the anti-CTLA-4 agent. However, colitis is the toxicity to be most cognizant of. You have to follow patients closely and educate them on when to call the office.

The second interesting challenge is that anti-CTLA-4 agents are the first immunotherapeutic agents that actually seem to work by activating the patient's immune system. Although the immune system becomes activated fairly soon after treatment begins, it can take 10 to 12 weeks before antitumor effects are evident (Figure 3).<sup>6</sup> Patients can often get worse before they get better. This is



**Figure 3.** Evolution of response. A study by Weber and colleagues showed that response to treatment with an anti-CTLA-4 antibody may first become evident several weeks after therapy. BCG = bacille Calmette-Guerin; CR = complete response; GM-CSF = granulocyte monocyte colony stimulating factor; irAEs = immune-related adverse events; PR = partial response; SD = stable disease. Courtesy of Steven J. O'Day, MD, The Angeles Clinic and Research Institute. Weber JS et al.<sup>6</sup>

very important and a paradigm shift for oncologists who are used to chemotherapy. In fact, we think that when these later responses are taken into account, the overall response rate to anti-CTLA-4 antibodies may be significantly higher than believed at first.

In patients receiving chemotherapy, once we observe tumor progression, we virtually never see subsequent tumor shrinkage and so we are quick to stop therapy. With the anti-CTLA-4 therapies, on the other hand, it is relatively common to see “progression” up to 10 weeks but then see subsequent tumor shrinkage 4 or 8 weeks later. This makes the discussion with the patient a bit complicated because we don't want to give up on the treatment too soon. I don't even check a computed tomography (CT) scan until week 12, and that is often the hard part for patients—not knowing how treatment is going for so long. Also, we usually don't decide a patient's disease has progressed unless we see progression at 2 time points separated by at least a month. This is another change from what oncologists are used to with chemotherapy.

There are other immunomodulating antibodies to look out for as well, although they are in earlier testing than the anti-CTLA-4 antibodies. These include anti-PD-1, anti-4-1BB (also called CD137), and anti-CD40.

Toll-like receptor (TLR) agonists may also prove to be an interesting immunotherapeutic approach. There are 10 TLRs recognized to date. Stimulation of these receptors induces immune responses. In a phase 2 trial using a TLR9-activating oligonucleotide, 2 of 20 patients (10%) had a partial response, 1 of which lasted more than 140 weeks at the time of reporting.<sup>7</sup> Much further study is needed to see how this approach will help patients.

***Are there any other new immunotherapeutic approaches to watch for?***

**Dr Chapman:** T-cell adoptive transfer therapy is an approach that practicing oncologists should know about. Right now, this treatment regimen is only available at the National Cancer Institute (NCI), but a few other centers are beginning to set up for this

treatment. It is a process that involves removing tumor antigen-specific lymphocytes from a patient, performing an in vitro expansion of these cells, and then reinfusing them into the patient. The NCI has developed improved methods of generating tumor-infiltrating lymphocytes in vitro. One regimen they studied consisted of administering lymphodepleting chemotherapy with fludarabine and cyclophosphamide followed by infusion of the expanded lymphocytes along with high-dose IL-2. Recent NCI data showed that 18 of 35 patients (51%) had an objective response to this therapy, including 3 complete remissions.<sup>8</sup> The mean duration of the partial responses was 11.5 months.<sup>9</sup> Specific eligibility criteria for current protocols are in place but may change; oncologists interested in NCI studies for a particular patient should call the NCI for up-to-date information.

To be eligible for this treatment, patients typically have to have an excellent performance status despite having had disease progression through prior therapy. Further, it typically takes 6 weeks to generate the cells in the laboratory. Afterward, patients must have a good performance status and no brain metastases to receive the reinfusion. Because this was a select group of patients, it makes it difficult to apply results to the general melanoma population. Nonetheless, the research is exciting and it is worth considering referring appropriate patients.

***Vaccines have been under investigation for a long time. Despite much research, none are FDA-approved. It can be hard for a busy clinician to know whether it's really worth spending the time to evaluate the data. Is there anything new to report?***

**Dr Chapman:** Vaccine data do remain pretty negative. There are many ongoing trials, but there still have not been any real clinical breakthroughs. It is hoped that rational combinations, such as an anti-CTLA-4 antibody to increase the immune response with a vaccine, will improve outcomes. It makes sense that this would work. But a study done a couple of years ago by

Jeffrey Weber, MD, and colleagues reported that the combination of a peptide vaccine with ipilimumab did not result in increased immunogenicity.<sup>10</sup> Immune responses were generated but were not greater than what would be expected with the peptides combined with other adjuvants like granulocyte-macrophage colony-stimulating factor (GM-CSF). On the upside, toxicity was not increased and was consistent with ipilimumab alone. This first experience was disappointing, but studies are ongoing. Other immunomodulating agents, such as anti-PD-1, anti-CD40, and anti-4-1BB, may also be useful as adjuvants to increase the immune response with vaccines.

**To check on available clinical trials and refer patients for adoptive transfer protocols, call the Immunotherapy Service at the National Cancer Institute: 866.820.4505 or go to [www.cancer.gov/cancertopics/factsheet/NCI/clinical-center](http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-center)**

DNA vaccines represent a new generation of vaccines that we think are interesting. The cDNA encoding the tumor antigen gene of interest is cloned into a plasmid, which is then administered to the patient. The gene then produces protein that can result in patient immunization. In a recent report, 7 of 18 patients vaccinated with a tyrosinase DNA vaccine developed T-cell responses.<sup>11</sup> Further study is required to determine whether this translates into clinical benefit.

Of interest, the only vaccine available for use outside a protocol is licensed for the treatment of dogs. It is a tyrosinase DNA vaccine developed by Jedd D. Wolchok, MD, and colleagues for treating canine metastatic melanoma. This vaccine is now being studied in the adjuvant setting in humans. We are hoping to start a trial for metastatic disease in humans. In dogs, there was an improvement in survival, but the hurdle for licensing for use in animals is lower than the FDA's requirements for approval for humans. It does

signal that this is an avenue that should be pursued. We are several generations beyond the initial vaccines of chopped up tumor cells, but the results are still slow in coming.

***What other aspects of the biology and treatment of melanoma should practitioners be aware of?***

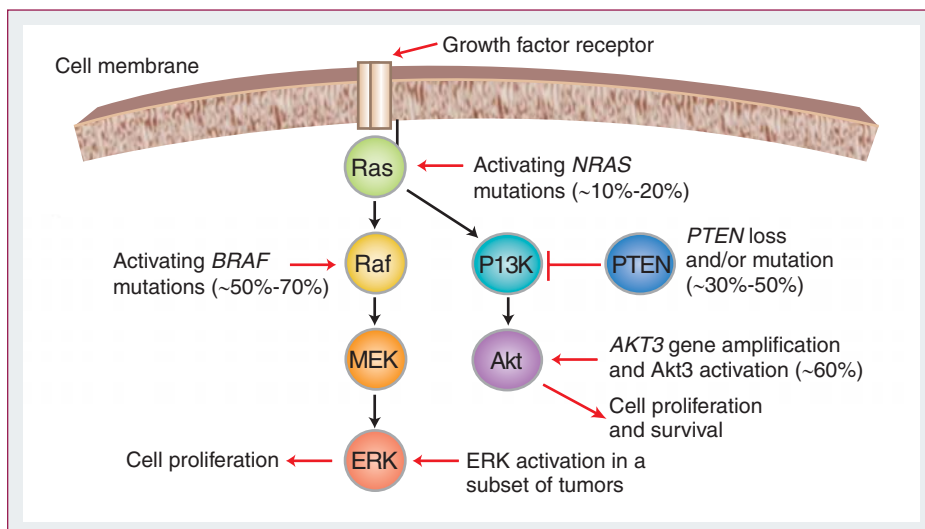
**Dr Chapman:** Oncologists should be aware of the B-Raf mutation story, which is driving the development of new drugs (Figure 4).<sup>12</sup> The Ras/Raf/MEK/ERK cellular pathway is a key regulator of cell proliferation and survival. Mutations in this pathway have been identified in melanoma. When activating mutations are present, greater cellular proliferation and resistance to apoptosis can occur. The most common mutation in this pathway occurs in B-Raf, which is 1 of 3 Raf genes.

Sorafenib has some B-Raf inhibitory activity, but as a single agent it has not shown activity in melanoma.<sup>13</sup> In a second-line trial with carboplatin and paclitaxel, sorafenib did not improve outcomes over chemotherapy alone<sup>14</sup>; however, there is an ongoing trial of this regimen in first-line treatment of metastatic melanoma. Sorafenib has been used with dacarbazine and with temozolomide, as well. Of interest, patients with brain metastasis were included in the temozolomide study and the regimen did show activity.

New B-Raf and MEK inhibitors are in development. Phase 1 and 2 data will likely be a hot topic at ASCO's annual meeting this year. There are several molecules being developed.

***Are there any other targeted agents in late clinical testing?***

**Dr Chapman:** First, I have to say that I don't much like the term "targeted therapy" since it is now used to include a wide variety of agents, many of which show fairly broad specificity. What systemic therapy does one consider not targeted? What is more targeted than methotrexate? I'm not sure what term would be better, but "targeted" seems misleading.



**Figure 4. Schematic of the canonical Ras effector pathways Raf/MEK/ERK and PI3K/Akt.** Mutations that most often activate these pathways in patients with melanoma are shown. Adapted from Chudnovsky Y et al.<sup>11</sup>

Having said this, bevacizumab, oblimersen, and elesclomol are all in randomized studies for the treatment of metastatic melanoma. Elesclomol (formerly STA-4783) is thought to induce oxidative stress in tumors making them more sensitive to chemotherapy. It shows no single-agent activity, but a small study did show benefit when it was added to paclitaxel.<sup>15</sup> That study enrolled 53 patients in the combination arm and 28 in the paclitaxel monotherapy arm. Cross-over was allowed from the paclitaxel arm to the combination arm. The study met its primary end point by showing that 6-month progression-free survival was statistically better with the combination treatment than with the control treatment (35% vs 15%;  $P = .035$ ). However, these results were not considered entirely convincing because the treatment arms were not balanced for prognostic variates. There is an ongoing phase 3 trial that should help resolve this issue.

Bevacizumab is being tested in phase 2 combination trials in melanoma. Currently, an ongoing randomized phase 2 study is comparing carboplatin and paclitaxel with or without bevacizumab. This research is based on a prior study showing a 15% response rate and 60% stable disease (lasting at least 8 weeks) seen in a single-arm phase 2 study of the same drugs.<sup>16</sup>

Results of a recent phase 3 trial of dacarbazine with or without oblimersen, a Bcl-2 antisense oligonucleotide, were negative<sup>17</sup>; however, a subset analysis suggested benefit in the group with a normal lactate dehydrogenase (LDH) value. This led to the current trial of dacarbazine with or without oblimersen only in patients with a normal LDH level.

### **What do you recommend as first-line treatment for advanced melanoma?**

**Dr Chapman:** For patients with stage IV melanoma, I think it would always be proper to consider a phase 2 or phase 3 trial (Table). This is especially true in patients with previously untreated melanoma because receiving off-protocol treatment often decreases protocol treatment options. In patients who are not going to be enrolled in a trial, it would be reasonable to start with dacarbazine or temozolomide. Off protocol, I use a combination chemotherapy regimen of cisplatin, vinblastine, and temozolomide. This is not a protocol, but we are hoping to start a trial with this combination, as we have had fairly high response rates, including in bone and in patients who had previously progressed through temozolomide. We want to study the tumors and figure out who responds and who does not.

As a second-line treatment off protocol, sometimes high-dose IL-2 is appropriate if the patient is in good shape. The overall response rate is relatively low (16%), but complete responses can be seen, especially in patients with M1a or M1b disease.

For patients with brain metastasis, I prefer surgery or stereotactic radiosurgery if there are fewer than 4 metastases. If these modalities are not feasible and there are metastases outside the brain, I prefer using systemic chemotherapy and steroids to treat cerebral edema. The response rate to whole-brain radiation in melanoma is relatively low, so I don't use it unless the number of symptomatic brain metastases leaves no other choice.

### **What are your concluding thoughts?**

**Dr Chapman:** Although systemic therapy for melanoma is not as effective as we would like, some patients definitely benefit. One of our immediate goals is to understand why some patients respond and others do not. I am hopeful about new agents currently being tested, and I look forward to encouraging data at the upcoming ASCO annual meeting.

#### **Table**

#### **Select Ongoing Randomized Clinical Trials in Advanced Melanoma**

##### **Phase 3**

- Carboplatin and paclitaxel ± sorafeniba
- Tremelimumab vs either dacarbazine or temozolomide<sup>a</sup>
- Dacarbazine ± ipilimumaba
- Ipilimumab, MDX-1379 melanoma vaccine, or ipilimumab + MDX-1379
- Paclitaxel ± STA-4783<sup>b</sup>
- Dacarbazine ± oblimersen<sup>b</sup>
- High-dose IL-2 ± gp100 antigen

##### **Randomized Phase 2**

- Carboplatin and paclitaxel ± bevacizumab<sup>a</sup>
- Bevacizumab ± low- or high-dose IFN- $\alpha$

<sup>a</sup>No prior treatment for metastatic melanoma.

<sup>b</sup>No prior treatment with cytotoxic chemotherapy for metastatic melanoma.

More information available at:

<http://www.cancer.gov/clinicaltrials>

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## Self-Assessment Questions

Select the 1 best answer to each question and circle that letter on the Answer Grid on the Evaluation Form (page 7).

1. Single-agent dacarbazine confers a response rate of approximately:
  - a. 5%.
  - b. 15%.
  - c. 20%.
  - d. 25%.
2. Tremelimumab and ipilimumab target:
  - a. B-Raf.
  - b. CD137.
  - c. CD40.
  - d. CTLA-4.
3. The primary adverse effect associated with anti-CTLA-4 antibodies is:
  - a. Colitis.
  - b. Embolism.
  - c. Hypertension.
  - d. Pruritus.
4. A phase 2 study of a TRL-activating agonist showed a response rate of:
  - a. 10%.
  - b. 15%.
  - c. 20%.
  - d. 25%.
5. In a recent NCI study employing T-cell adoptive transfer therapy, the reported objective response rate was approximately:
  - a. 10%.
  - b. 25%.
  - c. 50%.
  - d. 75%.
6. In melanoma, the most common mutation in the Ras/Raf/MEK/ERK cellular pathway occurs in:
  - a. B-Raf.
  - b. ERK.
  - c. MEK.
  - d. Ras.
7. Sorafenib as a single-agent has shown:
  - a. No activity.
  - b. Limited activity.
  - c. Moderate activity.
  - d. Substantial activity.
8. Elesclomol (formerly STA-4783) is thought to:
  - a. Have significant single-agent activity.
  - b. Induce oxidative stress.
  - c. Inhibit angiogenesis.
  - d. Inhibit cell growth.
9. A single-arm, phase 2 study of bevacizumab by Perez et al in combination therapy resulted in a:
  - a. 15% response rate and 50% stable disease.
  - b. 15% response rate and 60% stable disease.
  - c. 10% response rate and 50% stable disease.
  - d. 10% response rate and 60% stable disease.
10. A subset analysis of a recent phase 3 trial of dacarbazine found the addition of oblimersen was of benefit to:
  - a. All patients.
  - b. No patients.
  - c. Patients with elevated LDH values.
  - d. Patients with normal LDH values.



# CMEConnection

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CMEConnection

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