Clinical Challenges in the Management of Melanoma

Dates of Certification:
January 19, 2015- January 19, 2016

Medium: *Print with online posttest, evaluation, and request for credit*

Medical Writer

Jennifer Klem

Disclosure: *No relevant financial relationships with commercial interests to disclose.*

The American Journal of Hematology/Oncology Editorial Board

Debu Tripathy, MD
Professor of Medicine and Chair
Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, TX
Disclosure: Grant/Research Support: *Genentech/ Roche, Pfizer, Puma, Inc. (clinical trial support contracted to University of Southern California);* Consultant: *Eisai, Novartis*

Faculty

Adil I. Daud, MD
Clinical Professor of Medicine and Dermatology
Division of Hematology/ Oncology
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, CA
Disclosure: *Grant/Research Support: Merck, Pfizer, GlaxoSmithKline, OncoSec, Novartis Pharmaceuticals, MedImmune, Genentech, Roche, and Bristol-Myers Squibb; Consultant: Genentech, Bristol-Myers Squibb, Amgen, and Celgene Corporation.*

Ragini Kudchadkar, MD
Assistant Professor
Department of Hematology and Medical Oncology
Emory University Winship Cancer Institute
Atlanta, GA
Disclosure: *Consultant: Bristol-Myers Squibb, and Genentech; Speaker's Bureau: Bristol-Myers Squibb, and Genentech.*

Mario Sznol, MD
Professor of Medicine (Medical Oncology)
Yale School of Medicine
Clinical Research Program Leader, Melanoma Program
Co-Director of Yale SPORE in Skin Cancer
Yale Cancer Center
New Haven, CT
Disclosure: *Consultant: Bristol-Myers Squibb, Genentech, Roche, MedImmune, Amgen, Nektar, Symphogen, Merus, NeoStem, Anaeropharma, BeiGene, Kyowa-Kirin, Immune Design, Lion Biotechnologies, Seattle Genetics, and Pfizer; Stock/ Shareholder: Amphivena.*

Jeffrey S. Weber, MD, PhD
Senior Member and Director
Donald A. Adam Comprehensive Melanoma Research Center
Moffitt Cancer Center
Tampa, FL
Disclosure: *Grant/Research Support: Bristol-Myers Squibb, GlaxoSmithKline, Merck, Genentech, Novartis Pharmaceuticals, and Macrogenetics; Consultant: Bristol-Myers Squibb, GlaxoSmithKline, Merck, Genentech, Novartis Pharmaceuticals, AstraZeneca, cCAM Biotherapeutics, Celldex Therapeutics, Altor Bioscience, and Lion Biotechnologies.*

Staff/Planner Disclosures and Conflict of Interest Resolution

The staff of PER® (Debbie Augustus, Ann C. Lichti, CCMEP, and Megan O'Connell) as well as the editorial staff of The American Journal of Hematology/Oncology *(Devera Pine) have no relevant financial relationships with commercial interests to disclose.*

In accordance with ACCME's Standards for Commercial Support℠, *PER® resolved all conflicts of interest (COI) prior to the release of this CME activity using a multistep process.*

Overview

The panel is structured using the Medical Crossfire platform, which is based on an engaging discussion among faculty that address treatment choices, provocative questions, and challenges in the clinic. This activity is designed to aid physicians in assessing the wealth of new data, choosing treatment based upon patient and tumor characteristics, and applying those findings to their practices.

Target Audience

This activity is directed toward medical oncologists and hematologists who treat patients with solid tumors and hematologic malignancies. Fellows, nurses, physician assistants, nurse practitioners, and other healthcare providers may also participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

1. Choose treatment based on patient characteristics, such as presence of brain metastases
2. Manage toxicities of targeted and immune therapies
3. Evaluate emerging clinical data regarding new agents and evolving strategies

Accreditation/Credit Designation

Physicians' Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Physicians' Education Resource®, LLC, designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

No commercial support was received for this CME-certified activity. This activity was funded entirely by PER®.

Instructions for Participation/How to Receive *AMA PRA Category 1 Credit*™

1. Read the article in its entirety.

2. Use the QR Code or type http://www.gotoper.com/LINK/131 into your Web browser to access the posttest.

3. Complete and pass the posttest with a score of 70% or higher.

4. Complete the evaluation and request for credit. Participants may immediately download a CME certificate upon successful completion of these steps.

Off-Label Disclosure and Disclaimer

This CME activity may or may not discuss investigational, unapproved, or off-label use of drugs. Participants are advised to consult prescribing information for any products discussed. The information provided in this CME activity is for continuing medical education purposes only, and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options for a specific patient's medical condition.

Disclaimer

The opinions expressed in the content are solely those of the individual faculty members and do not reflect those of PER®.

Contact information for questions about the activity:

Physicians' Education Resource®, LLC
666 Plainsboro Road, Suite 356
Plainsboro, NJ 08536
Phone: (888) 949-0045
E-mail: info@gotoper.com

Recently, several melanoma experts convened in Dallas to discuss clinical issues important to community oncologists when treating patients with melanoma. They were Jeffrey Weber, MD, PhD, senior member and director of the Donald A. Adam Comprehensive Melanoma Research Center at Moffitt Cancer Center in Tampa, Florida; Adil Daud, MD, professor in the Department of Medicine at the University of California, San Francisco Medical Center, and also at the Helen Diller Comprehensive Cancer Center in San Francisco; Ragini Kudchadkar, MD, assistant professor at Winship Cancer Institute of Emory University School of Medicine in Atlanta, Georgia; and Mario Sznol, MD, professor of Medicine at Yale School of Medicine and co-director of SPORE in Skin Cancer at Yale Cancer Center in New Haven, Connecticut.

During their discussion, these experts focused on some of the most common clinical challenges associated with treating patients with metastatic melanoma. Patients with metastatic melanoma used to have few treatment options, but in the past several years, 5 new agents have been introduced into the care of these patients, including new immunotherapies, BRAF inhibitors, and a MEK inhibitor. Although these therapies have provided much-needed treatment options, their existence has also created a number of practical challenges that directly impact patient management, including who should receive these agents, how to sequence them, if they should be provided in combination with one another, and how to manage their associated toxicities. The following is a discussion of these and other relevant melanoma topics by Drs Weber, Daud, Kudchadkar, and Sznol.

Treatment of Patients With Brain Metastases

Dr Weber: We'll begin our time today by discussing the treatment of brain metastases in patients with melanoma. These patients represent one of the most challenging populations of melanoma patients, due to the inability of most conventional agents to cross the blood-brain barrier. Ragi, which of the new agents are being utilized in this difficult-to-treat population?

Dr Kudchadkar: When we see patients with brain metastases, it creates new challenges for us, both in how to utilize standard therapies, like surgery and radiation, and systemic therapies. It's very clear that the BRAF inhibitors, both vemurafenib and dabrafenib as well as dabrafenib/trametinib combination therapy, have activity in the brain. Ipilimumab has also established responses in the brain. There are fewer data on the response rates in the central nervous system of the PD-1 antibodies nivolumab and pembrolizumab.

The response rates in general for systemic therapies in the brain are approximately 20% to 30%, depending on how you measure response. Patients with brain metastases are always challenging because they are often receiving steroid therapy, which contraindicates the use of immunotherapies like ipilimumab and nivolumab. However, I think other systemic therapies are great options for patients with brain metastases who have high systemic disease burden outside the brain. This is especially true when the brain metastases are so small—in the millimeter range—as is becoming common with surveillance MRIs.

Dr Weber: Are there circumstances in which you would dispense with radiation and simply treat a patient with brain metastases by using systemic therapy alone?

Dr Kudchadkar: I think the role of whole-brain radiation is rapidly diminishing because its toxicities have become more evident as our patients live longer. I think patients with a high burden of systemic disease and a very low burden in the brain can be considered for systemic therapy alone. Also, utilizing stereotactic radiation and surgery for solitary or symptomatic brain metastases rather than whole-brain radiation allows us to use more systemic therapy earlier in the course of these patients.

Dr Weber: Adil, are there scenarios in which you've had success using ipilimumab in patients with brain metastases?

Dr Daud: We've had some patients with amazing responses to ipilimumab. I have 1 patient with multiple brain metastases who was treated with ipilimumab 3 years ago. She subsequently developed hypophysitis and has been on chronic steroid replacement therapy, but she's still free of disease both systemically and in the brain. However, I wouldn't say response rates are higher in the brain. I think responses to systemic agents are in the 10% to 30% range, and these rates tend to be lower in the brain.

Dr Weber: Mario, have you treated patients who have brain metastases with BRAF or BRAF/MEK inhibitors and achieved long-term survival?

Dr Sznol: No, but that's not because it can't occur. We're very aggressive treating metastatic disease in the brain upfront with Gamma Knife radiation. We have not yet tried to treat these patients with targeted agents or immunotherapy alone. However, one exception is an ongoing clinical trial of pembrolizumab in patients with active brain metastases.

Dr Daud: I also can't say that with targeted agents alone I've seen long-term responses in patients with multiple brain metastases—not without using stereotactic radiation as well.

Dr Kudchadkar: I've had patients on trials who have had responses in the brain, but they haven't been long term. We use systemic agents primarily to reduce disease burden and get patients off steroid therapy, which opens more options for systemic therapy.

Dr Weber: I've had the best experience with patients who receive either ipilimumab or PD-1 antibodies, but I always radiate the disease first and then administer the immunotherapy because I believe that destroying the local tumor might produce immunologic priming. There is evidence of this in the pivotal ipilimumab 020 trial. In that trial, the 11% of patients who had previously radiated brain metastases had outcomes as good as those without brain metastases, suggesting that simply by radiating the brain metastases, the immune system is somehow primed to more successfully control the disease in the brain.

Dr Sznol: In the absence of a clinical trial, I do things differently, starting with ipilimumab, and then later giving the stereotactic radiation. When giving stereotactic radiation first, I worry about a couple of things: patients receiving Gamma Knife radiation can develop late radiation necrosis, which is very difficult to differentiate from metastatic disease. In addition, some patients can develop substantial neurologic complications from the vasogenic edema related to radiation necrosis. We have surgically removed very large lesions that have turned out to be purely ra-

diation necrosis. We have also started seeing MRI reports of new metastatic lesions in the brains of patients treated 2 years earlier with Gamma Knife radiation. These lesions are often just areas of recurrent enhancement and radiation necrosis in the previously treated area. When following them over time, sometimes that enhancement disappears without any additional treatment.

The other phenomenon we've seen is in patients previously treated with immunotherapy who develop new brain metastases. If they don't have significant edema and the lesions are small, we sometimes simply follow the disease, particularly if they had responded systemically to the immunotherapy. In these patients, just like with pseudo-progression in the body, we sometimes see those lesions disappear.

Dr Kudchadkar: We have had a very similar experience at Emory with development of radiation necrosis 6 months or a year after systemic therapy. We recently had a patient who we thought had developed tumor progression more than 1 year after radiation therapy, but after surgically removing the tumor, we found it was only radiation necrosis.

Dr Sznol: I think it is very important to emphasize that radiation necrosis may not develop all at the same time. Lesions can start to show more vasogenic edema or appear to progress months apart from one another.

Using Combination Therapy for Patients With *BRAF*-Mutated Metastatic Melanoma

Dr Weber: Let's move on to our next topic, which is combination therapy for patients with *BRAF*-mutated disease. This topic is of great interest, thanks to the recent ESMO meeting in which 3 pivotal trials testing 2 different combination regimens were presented (**Table 1**). Results from one of these trials, COMBI-d, has already been published in *The New England Journal of Medicine*.[1] In the COMBI-d study, patients were randomly allocated to receive either dabrafenib plus trametinib, the BRAF/MEK inhibition combination, or dabrafenib alone, which is now approved as monotherapy for metastatic disease. Results of this large phase 3 study showed that progression-free survival (PFS), the primary end point, was clearly greater for the combination than for the single-agent dabrafenib. The difference in median PFS was pretty modest (9.3 months vs 8.8 months), but the PFS hazard ratio was 0.75, and response rate was also superior for the combination therapy (67% vs 51%). Because this was a crossover study, the overall survival (OS) data were modest but significant, with a hazard ratio of 0.63 (P =.02). Not surprisingly, the squamous cell cancer incidence was reduced from 9% with dabrafenib alone to 2% with the combination. In contrast, the incidence of severe fevers was increased, from 2% with monotherapy to 6% with the combination therapy. Overall, the investigators concluded that the toxicity of both arms was a wash, and I think we all agree that COMBI-d was a successful study.

Another study presented at ESMO 2014 was the COMBI-v study. In this large randomized study, 704 patients were randomly allocated to either dabrafenib/trametinib or the then-standard single-agent vemurafenib. The primary end point was OS, with a planned interim analysis after half of the death events occurred. This study was stopped at the time of interim analysis because of its clearly positive results. Response rate was significantly better for the combination regimen (64% vs 51%; P <.001), and the OS hazard ratio of 0.69 favored the combination arm (P =.005), stopping the study because the P value crossed the predetermined boundary.[2] Median survival for the vemurafenib arm was a pretty favorable 17.2 months; median survival of the combination arm has not yet been reached, but back-of-the-napkin calculations suggest that it will be approximately 2 years, which is consistent with survival for dabrafenib/trametinib in phase 2 studies. Median PFS for the combination was 11.4 months compared with 7.3 months for vemurafenib alone, with a hazard ratio of 0.56 (P <.001).

Finally, the last ESMO 2014 trial was coBRIM, another large, definitive, randomized melanoma study. This time, vemurafenib was combined with a novel MEK inhibitor, cobimetinib, and compared with vemurafenib alone. The primary end point was PFS, and the investigators projected that the addition of cobimetinib would improve median PFS from 6 months to 11 months.

TABLE 1. Primary Outcomes of Three Phase 3 Combination Trials in Metastatic Melanoma[1-3]

Study Name/ Trial Number	Study Design	Primary Outcome	HR	*P* Value
COMBI-d/ NCT01584648	Dabrafenib/trametinib vs dabrafenib	PFS: median, 9.3 vs 8.8 months	0.75	.03
COMBI-v/ NCT01597908	Dabrafenib/trametinib vs vemurafenib	OS: median, NR vs 17.2 months	0.69	.005
coBRIM/ NCT01689519	Vemurafenib + cobimetinib vs vemurafenib	PFS: median, 6.0 vs 11.3 months	0.60	.0003

HR indicates hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

In this trial, as with the other combination trials, combination therapy reduced the skin toxicity seen with vemurafenib alone but other toxicities showed an increase, primarily cardiac issues and serous retinopathy.[3] The difference in response rate was striking, with 68% for the combination regimen versus 45% for vemurafenib. Just as investigators predicted, median PFS improved from exactly 6 months with single-agent vemurafenib to 11.3 months for vemurafenib/cobimetinib. The hazard ratio was 0.60 (P =.0003). Despite the crossover design of this study and its relatively short follow-up, there was a significant difference in OS, with a hazard ratio of 0.65 (P =.046).

Adil, do you think the data from these 3 combination trials will have a major impact on clinical practice in the community?

Dr Daud: Yes, I do. I personally have difficulty coming up with a patient to whom I wouldn't give combination therapy. Perhaps someone who has congestive heart failure or a history of glaucoma, but I don't think I've treated anyone with a BRAF inhibitor alone in the last couple of years.

Dr Weber: So, Ragi, how are you going to choose between dabrafenib/trametinib and vemurafenib/cobimetinib when the seemingly inevitable approval for that latter combination comes through?

Dr Kudchadkar: That's going to be a difficult choice, but I think it will be decided on toxicity profile. Dabrafenib/trametinib produces more fevers, which can be difficult for patients because they get shaking chills and feel terrible. However, vemurafenib/cobimetinib appears to cause more photosensitivity reactions, so it's a trade-off.

Another reason to choose one combination over the other is reimbursement, but any such differences between the combinations will not be apparent for some time.

Another issue that came up in one of my patients was the importance of pill size. Vemurafenib is given as 4 large pills, which are challenging to swallow. One of my patients had a Zenker's diverticulum, making it difficult to swallow pills, so dabrafenib/trametinib was a better choice for him because he could swallow the smaller pills.

Managing Toxicities of Targeted and Immune Therapies

Dr Weber: Let's turn our attention to our last topic, managing the toxicities associated with these novel agents. Mario, what are some of the most common toxicities associated with the new immunotherapies, like ipilimumab and pembrolizumab, and how do you manage them?

Dr Sznol: Clinicians have extensive experience with ipilimumab, whose primary toxicities are autoimmune-related, specifically rash, colitis or enteritis, elevations of liver function tests, and endocrinopathies that include hypophysitis, thyroiditis, or adrenalitis (**Table 2**). The most dangerous of these is colitis because if it is not controlled, patients can get very sick, develop a bowel perforation, lose their bowel, or even die as a result. The hypophysitis is probably the next most difficult toxicity to manage. Patients present feeling tired, a little confused, possibly with a frontal headache. Often, you can make the diagnosis over the phone because the symptoms are so characteristic. To manage this, you need to draw the right hormone blood studies and start them on low-dose prednisone, and possibly also on thyroid hormones. For colitis, hepatitis, and sometimes rash, steroids are the primary mode of treatment, but for patients resistant to steroids, second-line immune-suppressive agents like infliximab can be used. With all of these toxicities, there are standard algorithms in place for their management, and once you become accustomed to them, they're fairly straightforward to manage.

Dr Weber: Mario, you have a lot of experience at your institution with combination checkpoint protein inhibition, particularly nivolumab and ipilimumab. Do you find that these toxicities are more difficult to manage? Is it a different spectrum?

Dr Sznol: It's not a different spectrum, but the toxicities are definitely more frequent and some are more resistant to steroids, forcing the use of either higher doses of steroids or second-line immune-suppressive agents. Clinicians really need to keep on top of toxicities when you use this combination. For instance, patients who initially respond to steroids may become refractory very quickly. Also, some patients will develop multiple autoimmune toxicities, sometimes across multiple organ systems. However, again, with close monitoring of these patients and good communication between the patient and your staff, these toxicities can be managed very easily in the vast majority of patients. One other point about this combination is that many of the grade 3/4 adverse events are laboratory abnormalities, such as lipase, amylase, and hepatic function elevations. The significance of lipase and amylase elevations is unclear. Obviously, liver function test abnormalities have to be managed with steroids or, in some cases, mycophenolate.

Dr Weber: What kinds of toxicities do you see with targeted agents like the BRAF or MEK inhibitors? Which toxicities are most common, and how do you manage them?

Dr Sznol: Well, the one that we most frequently deal with are the fevers related to dabrafenib and trametinib. It's important not to underestimate the potential severity of these fevers. Some

TABLE 2. Immune-Related Adverse Events Reported in the Ipilimumab-Alone Arm of the Phase 3 MDX-010-020 Trial[4]

Immune-Related AEs	Study Design	
	Total AEs n (%)	Grade 3/4 AEs n (%)
Any immune-related event	80 (61.1%)	19 (14.5%)
Dermatologic	57 (43.5%)	2 (1.5%)
Pruritus	32 (24.4%)	0
Rash	25 (19.1%)	1 (0.8%)
Vitiligo	3 (2.3%)	0
Gastrointestinal	38 (29.0%)	10 (7.6%)
Diarrhea	36 (27.5%)	6 (4.6%)
Colitis	10 (7.6%)	7 (5.3%)
Endocrine	10 (7.6%)	5 (3.8%)
Hypothyroidism	2 (1.5%)	0
Hypopituitarism	3 (2.3%)	2 (1.5%)
Hypophysitis	2 (1.5%)	2 (1.5%)
Adrenal insufficiency	2 (1.5%)	0
Increase in serum thyrotropin level	1 (0.8%)	0
Decrease in serum corticotropin level	2 (1.5%)	1 (0.8%)
Hepatic	5 (3.8%)	0
Increase in alanine aminotransferase	2 (1.5%)	0
Increase in aspartate aminotransferase	1 (0.8%)	0
Hepatitis	1 (0.8%)	0
Other	6 (4.6%)	3 (2.3%)

AE indicates adverse event.

patients feel very sick, and occasionally a patient will get admitted to the hospital with hypotension. We always try to rule out infection. Sometimes fevers "burn out" when treatment is repeatedly stopped and restarted. The other toxicities seem to be easy to manage in these patients.

Dr Daud: Fevers are incredibly common, with over 60% of patients on combination therapy developing some type of fever. However, stopping and restarting dabrafenib/trametinib is an effective way to manage fevers in our hands. Patients should hold both drugs the first time they get a fever and not restart until 24 hours after the fever has subsided. The most common mistake is that patients don't stop treatment and instead add agents like acetaminophen or ibuprofen. In that case, patients can develop very resistant fevers that persist for days or even weeks. However, if they stop and restart treatment, most patients won't have more than a couple of episodes of fevers, and very few will have 4 or more episodes.

Dr Weber: Ragi, do you usually use methylprednisolone to manage fever, or do you just hold the drugs?

Dr Kudchadkar: We usually hold the drugs. The first time someone has a fever, we always do a basic infectious workup, including chest x-ray, urinalysis, and other basic tests, just to make sure we're not missing anything. It's important to note that dose reductions are not effective at managing fevers. Both drugs should be held 3 to 5 days, and then restarted at full doses once fever resolves. Some patients will periodically get fevers every few weeks. I have patients who can feel a fever coming on, and they will simply hold the drugs and have a treatment holiday. For the small group of patients with refractory, persistent fevers, very-low-dose steroids, such as prednisone 10 mg/day or even 10 mg every other day, can provide effective management.

Dr Weber: Mario, what are the side effects you worry most about, aside from the fevers?

Dr Sznol: Aside from fevers, we haven't seen terrible adverse events. There are arthralgias. The squamous cell carcinomas with single-agent therapy are not major problems; we simply surgically remove them. Single-agent dabrafenib, trametinib, or vemurafenib can result in an increase in secondary cancers because of the paradoxical activation of CRAF kinase. However, with combination therapy, I'm not certain there is a corresponding increase.

Dr Weber: In all of the combination studies presented at ESMO 2014, the noncutaneous secondary malignancy rates were equal between arms. However, the head-and-neck cancers, colon cancers—although rare—still scare me because they can be devastating. Mario, what worries you most about managing immunotherapeutic toxicities?

Dr Sznol: Severe colitis and enteritis are probably the most difficult to manage. If you use these agents frequently enough, you will see a whole spectrum of autoimmune toxicities that go beyond rash, colitis, endocrinopathies, and hepatitis. We've seen ascending paralysis, which we managed with IVIg [intravenously administered immunoglobulin] and steroids, severe pneumonitis, hematologic toxicities, and even severe arthralgias requiring

steroid therapy. Those toxicities are rare, but you need to be cautious because adverse events can occur in almost any organ.

Dr Weber: I'd absolutely agree with you. The colitis scares me the most, followed by the neurologic toxicities. The pneumonitis, thankfully, is rare, as are the neurologic and kidney toxicities. The main message, however, is that the vast majority of patients on drugs like pembrolizumab or nivolumab go through treatment with a pretty modest if not minimal level of side effects.

In closing, I'd like to thank each of the panel members for sharing your expertise with us today. Perhaps we can get a clinical pearl from each of you, something that the community oncologist can use right away in caring for their patients with melanoma.

Dr Daud: I would suggest that community oncologists familiarize themselves with either the dabrafenib/trametinib or vemurafenib/cobimetinib combination. That can then be used as a go-to regimen because the data look so similar for each of these combinations.

Dr Kudchadkar: I'd like to emphasize the importance of having specialists lined up who are interested in and familiar with these drugs. These include a dermatologist for skin-related toxicities and squamous cell carcinoma, an endocrine doctor for pituitary and endocrine disorders, and even a neurologist for some of the rarer toxicities. Having a plan for these patients upfront, especially when you're not in an academic environment with specialists down the hall from you, can be helpful in managing any toxicities that develop.

Dr Sznol: I'd like to remind community oncologists to consider clinical trials for their melanoma patients. Some patients obviously can't be referred for clinical trials because of their comorbidities, performance status, or geographic location. However, clinical trials are still crucial to the future advancement of melanoma therapies. We've made so many improvements, but we haven't hit 100% cure rates yet. Some of the new investigational agents may get us closer to that goal. Therefore, in addition to managing patients with the currently available drugs, I would strongly recommend considering a clinical study for those patients who are eligible.

REFERENCES

1. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med.* 2014;371(20):1877-1888.

2. Robert C, Karaszewska B, Schachter J, et al. COMBI-v: a randomized, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (V) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. Presented at: the European Society for Medical Oncology 2014 Congress; September 26-30, 2014; Madrid, Spain. Abstract LBA4_PR.

3. McArthur GA, Ascierto P, Larkin J, et al. Phase 3, double-blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma. Presented at: the European Society for Medical Oncology 2014 Congress; September 26-30, 2014; Madrid, Spain. 2014; Abstract LBA5_PR.

4. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-723.