Combination Therapy for Metastatic Melanoma

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Overview
This activity is designed to inform physicians about the latest treatment advances in metastatic melanoma, including approved and investigational management strategies.

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat patients with melanoma. Dermatologists, surgical oncologists, radiation oncologists, pathologists, fellows, physician assistants, and other healthcare providers interested in the management of melanoma are also invited to participate.

Learning Objectives
After participating in this CME activity, learners should be better prepared to:
- Review FDA approvals for melanoma since 2011
- Explain the mechanism by which combining a BRAF inhibitor with a MEK inhibitor increases responses/survival and decreases toxicities
- Describe the differences in toxicities between vemurafenib and dabrafenib
- Summarize pivotal data coming out of the CheckMate trials
- Discuss the factors involved in the choice between monotherapy and combination therapy for first-line treatment of metastatic melanoma

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Although skin cancer is the most common type of cancer, melanoma accounts for less than 2% of skin cancers. Nonetheless, the majority of skin cancer-associated deaths can be attributed to melanoma. Almost 74,000 new cases were estimated to be diagnosed in the United States in 2015, with almost 10,000 estimated related deaths.[1] Interest in this type of cancer is evidenced by the fact that about 200 abstracts on melanoma were presented at the 2015 annual meeting of the American Society of Clinical Oncology.[2]

Whereas survival rates are favorable for patients with early-stage melanoma (approximately 95% 10-year survival for Stage 1A), these rates decline with advancing disease.[1] Thus, significant research effort has been focused on the treatment of advanced-stage/metastatic melanoma in the past 5 years, with major changes in standard-of-care therapy introduced. The ClinicalTrials.gov website currently lists 193 trials in metastatic melanoma that are active or not yet recruiting.[3]

Before 2011, cytotoxic chemotherapy, and, for fit patients, interleukin-2, were the only available standard systemic therapies for melanoma. A great deal of progress has been made in the past 5 years, however, largely because of a growing understanding of the biology of melanoma and, hence, of potential therapeutic targets.[4] These advances have been in the areas of molecularly targeted therapy and immunotherapy,[5] with eight new agents approved by the US Food and Drug Administration (FDA) since 2011— the immune checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab; the targeted therapies vemurafenib, dabrafenib, trametinib, and cobimetinib; and the oncolytic virotherapy talimogene laherparepvec (T-VEC).[4,6-9]

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors, such as ipilimumab and tremelimumab, have demonstrated similar efficacy to, but greater tolerability than less-specific agents, such as high-dose interleukin-2 (IL-2, aldesleukin). Programmed cell death protein 1 (PD-1) inhibitors, such as pembrolizumab and nivolumab, yield high response rates with fewer toxicities. The concept that the complementary effects of these newer agents may confer greater survival than either agent alone for patients with advanced melanoma has led to trials of combination therapy.[10,11]

The PD-1 inhibitor pembrolizumab has been tested as monotherapy, with response rates in the same range as those with single-agent nivolumab and similar toxicities.[12,13] In the KEYNOTE-006 study, response rates and 6-month progression-free survival (PFS) rates were greater with pembrolizumab, and rates of treatment-related adverse events (AEs) lower, than with ipilimumab.[14] Pembrolizumab is being studied in various combinations, including with other immune modulators, such as T-VEC,[15] and the indoleamine 2,3-dioxigenase (IDO) inhibitor epacadostat.[16] The safety and efficacy of a combination of pembrolizumab and low-dose ipilimumab are currently being evaluated.[17]

The phase 2 CheckMate 069 study randomized 142 treatment-naive patients with unresectable or metastatic melanoma to receive ipilimumab alone or in combination with nivolumab. Among 109 patients with *BRAF* wild-type melanoma, objective response rates (ORRs) were 60% with the combination and 11% with ipilimumab alone ($P = .0001$), and median PFS was 8.9 versus 4.7 months, respectively ($P = .0012$). As in CheckMate 067, more Grade 3-4 drug-related AEs occurred in the combination group than in the monotherapy group.[18,19] Results of CheckMate 069 led to accelerated FDA approval of the combination treatment for patients with wild-type *BRAF* V600 unresectable/metastatic melanoma.[18]

CheckMate 067 was a phase III study in which 945 treatment-naïve patients with stage III or IV melanoma were randomized to receive nivolumab alone, ipilimumab alone, or the two drugs in combination. The ORRs for the three groups were 43.7%, 19.0%, and 57.6%, respectively, and the median PFS was 6.9 months, 2.9 months, and 11.5 months, respectively. Treatment-related Grade 3-4 AEs occurred in 16.3%, 27.3%, and 55.0% of the groups, respectively. Patients are still being followed for overall survival (OS).[20,21] The toxicities of combination treatment were manageable, and two-thirds of the 36% of patients in the combination group, who discontinued treatment because of AEs, actually responded. This suggests that shorter courses or lower doses of combination therapy should be investigated.[11]

Approximately 50% of melanomas have mutations in the *BRAF* gene that activate the mitogen-activated protein kinase (MAPK) pathway.[7] For patients with melanoma who have *BRAF* V600 mutations, treatment with BRAF inhibitors results in prolonged OS and PFS.[22] Treatment with MEK inhibitors also leads to increased OS and PFS.[4] Acquired resistance to BRAF inhibitors, due to reactivation of the MAPK pathway and other genetic and nongenetic mechanisms,[23] develops frequently with BRAF inhibitor monotherapy, limiting its efficacy; however, concomitant use of BRAF and MEK inhibitors significantly delays the emergence of resistance and reduces the incidence of BRAF inhibitor-induced skin tumors, yielding prolonged median PFS and OS.[22]

The success of two-drug combinations, at both increasing survival and reducing toxicities, led to exploration of the potential of triple combinations for advanced melanoma. Several trials are under way evaluating various combinations of BRAF, MEK, and immune checkpoint inhibitors.[10,24,25] Although the optimal sequences and combinations of agents need to be elucidated further, it is clear that the increasing number of options available for treating advanced melanoma brings the ultimate goal of individualized therapy closer.[10]

Data on current and emerging treatment options for metastatic melanoma were presented at the 2015 ASCO Annual Meeting. Antoni Ribas, MD, PhD, of the University of California Los Angeles, shares his insights on the significance of recent discoveries, the issues surrounding application of emerging data to the planning and implementation of treatment strategies for patients with melanoma, and potential future research and therapeutic directions.

Moderator: Please address the rationale for combining therapies in metastatic melanoma.

Dr. Ribas: In the last 5 years, we have made a lot of progress in melanoma treatment. We have, I think, eight new agents approved in a short period, new indications.

We started with single agents—CTLA-4 blockers, BRAF inhibitors, MEK inhibitors, and then with PD-1 blockers. Those agents have dramatically changed how we treat patients with melanoma, but also, have changed our view of what can be achieved with treatment. Some years ago, having something that worked for more than 10% of patients seemed to be a major step forward. Now we have raised our expectations. We want to have more patients with longer lives and get rid of this metastatic cancer.

Moderator: Have we raised our expectations because we see that it's possible or for some other reason?

Dr. Ribas: Because we see that it's possible, yes. Single-agent therapy showed us that we can get dramatic regressions of melanoma in a high proportion of patients with the BRAF inhibitors. So the next question is, can we maintain these responses? Can we understand how the melanoma becomes resistant to therapy, and then what should we do about it? That was what led to the exploration of combination BRAF and MEK inhibitors.

With immunotherapy, we had anecdotal responses years ago with some forms of immunotherapies such as vaccines or IL-2; then they became reproducible with ipilimumab and tremelimumab, anti-CTLA-4, but still at a low frequency, and now we have them at a much higher frequency with the anti-PD-1 antibodies.

But, if a third of the patients are having objective and durable responses with anti-PD-1, the next question is, what happens with the other two-thirds? And that is why we're designing a lot of these combinations that are aimed at addressing what is missing in patients who do not respond to single-agent PD-1 blockade therapy.

Moderator: What about combinations that have been evaluated for patients who harbor *BRAF* V600E or V600K mutations?

Dr. Ribas: For patients who have *BRAF* V600E or V600K mutations, blocking the driver oncogene with a BRAF inhibitor—vemurafenib, dabrafenib, or encorafenib—leads to objective responses in around 50% of patients, but in time—not in all cases, but the majority—the melanoma will regrow.

We have been studying the genetic difference between the baseline biopsy and response in the progressive biopsy, and we know that there is a series of events that allow the cell to re-signal through the MAP kinase pathway, which is where BRAF is located. In two-thirds of cases there is clear evidence that MEK, which is immediately downstream of BRAF, is reactivated. That brought us to the combination of BRAF and MEK inhibitors. The first one approved was dabrafenib plus trametinib, and now we have the approval of vemurafenib plus cobimetinib.

With the combination, we get higher response rates, around 75% to 80%, so it's a better initial treatment. It increases the duration of response, because the combination is addressing some of the mechanisms by which melanoma can become resistant to single-agent BRAF inhibitors. Also, it decreases the toxicities of the BRAF inhibitors. That was a surprise at the beginning and needed to be understood, and I think now we know it at the mechanistic level.

If you give a BRAF inhibitor to a cell that has a *BRAF* mutation, it blocks the oncogenic signaling through the MAP kinase pathway, and that decreases cell growth. But, if you give the same drug to a cell that does not have a *BRAF* mutation, but has an upstream mutation, like in RAS, or an activation of receptor tyrosine kinases that doesn't need to be oncogenic, instead of blocking that cell, it paradoxically activates it in a phenomenon called paradoxical MAP kinase activation that works by the BRAF inhibitor binding to wild-type *BRAF* and blocking wild-type *BRAF*, but transactivating its heterodimer partner, which is usually *CRAF*, and the activation of *CRAF* leads to increased proliferation of that cell.

That is the pathogenic basis of the secondary skin proliferative conditions that happen with BRAF inhibitors when given as single agents, which can range from hyperkeratosis to squamous cell carcinomas. If you give an MEK inhibitor, that will disappear, and that's why the combination has less toxicity.

These two drugs are what we call vertical inhibition; they inhibit two places on the same pathway; the pathway that is important for the cell, the MAP kinase pathway. That's what is driving its growth. The new research on resistance to BRAF inhibitors is moving away from just looking at what happens when acquired resistance is established and the cancer regrows, and looking earlier at how some cells that have a *BRAF* mutation can persist, despite having the *BRAF* mutation turned off by the BRAF inhibitor.

We know that whenever we give BRAF inhibitors to cells that have *BRAF* mutations, the majority of cells will die, but a minority find a way to adapt to that drug, and they change the series of signaling pathways and upregulate a whole bunch of receptor tyrosine kinases that provide a survival signal. That cell will not grow for a period. In vitro, it will take a month or 2 to regrow. In patients, it takes 6 to 9 months to regrow. With time, that persisting cell can acquire a gain of function that allows it to grow and go from a drug-persisting cell to an acquired resistance and then progressive growth.

Moderator: Do you see any difference between the two combinations of BRAF and MEK inhibitors that we have? Is either superior to the other, or do they have similar effects?

Dr. Ribas: Both of these combinations are really good at what they do. They seem to have mostly equivalent benefits in terms of response rates and duration of response. I think that clinical trials that have been done do not support saying that one combination is superior to the other. We do not have direct testing, and probably, we do not need direct testing.

There are some differences. They are minor, but they may be important. The toxicities are roughly overlapping, but vemurafenib and dabrafenib have specific toxicities that are different. Vemurafenib induces photosensitivity, and patients on vemurafenib can have

sunburns very easily within 5 or 10 minutes of direct sun exposure. On the other hand, dabrafenib does not have this toxicity but has another peculiar toxicity, which is high fevers or pyrexia. That increases, when it is given with trametinib, by a mechanism we do not understand. In some patients it becomes problematic enough that treatment needs to be stopped either temporarily or permanently. So managing these toxicities may lead to prescribing one or the other, or some patients who may be more sensitive to one or the other may prefer one of the combinations.

Moderator: What about immuno-oncology and combinations in that field?

Dr. Ribas: I think it is safe to say that anti-PD-1 therapy with pembrolizumab or nivolumab will be the front-line and mainstream treatment for patients with metastatic melanoma, and that is regardless of *BRAF* mutation status, because these therapies can give a significant rate of durable response with very few adverse effects. The majority of patients who receive nivolumab or pembrolizumab have no adverse effects, or maybe they have mild fatigue and skin rash as the main adverse effects.

Obviously, that's great for the patients who respond and not good for the patients who do not respond, so we want to look for treatments that yield more frequent responses, and that comes with the combination of ipilimumab and nivolumab. This combination releases two checkpoints or two brakes to the immune system. By releasing two brakes, we are starting to push the limits of what the body tolerates, because those brakes are there to protect us from our own immune systems. If we keep releasing them, we are going to run into toxicities that are related to autoimmunity and turning on the immune system in a nonspecific way against internal organs in addition to turning it against the cancer.

Moderator: Can you review the pivotal data presented from CheckMate-067 and CheckMate-069 that evaluated this combination?

Dr. Ribas: The combination of nivolumab and ipilimumab was shown to be superior to either agent alone in the CheckMate trials, with a response rate around 55%, which is significantly higher than the 35% response rate that nivolumab or pembrolizumab would give by itself. The adverse effects also increase in a greater way, however. With a single agent anti-PD-1, the rate of adverse effects would range from 10% to 15%; the rate goes to more than 50% with the combination, and I'm talking about grade 3 to 4 toxicities with these therapies. That tells us that we are achieving the goal of higher responses but at the expense of higher toxicities. Some of these toxicities can be serious, and some patients need to be treated with corticosteroids, and that would dampen the immune response that we were trying to turn on. So it defeats the purpose to turn on the immune system so much and then have to dial it down.

Some data indicate that corticosteroids, at least if they are given a while after an immune response is established, would not decrease the responses. We do not yet have good statistics or follow-up of patients, however, to determine if corticosteroids are detrimental or not. Overall, it seems that they are not as detrimental as we would think they would be, but they may be doing things that we are not aware of.

The biggest question we have with these therapies, and now with the approval of ipilimumab and nivolumab as a combination therapy for patients with metastatic melanoma, is should we start with the combination or should we start with a single agent? This question is important, because if we start with the combination, we are choosing the therapy that has the higher response rates but also has more toxicities.

If some of those patients would respond to single-agent anti-PD-1 therapy with a lot less toxicity, then why use the combination?

Moderator: But if they're not going to respond to single-agent, are you losing some time for response to the combination if you don't start with that?

Dr. Ribas: We haven't tested that question. So we do not know if patients who start on anti-PD-1 alone, if they don't respond and we add ipilimumab and continue with the combination, does that rescue some patients and give them a response? That is a question that we hope we will be able to test. There is a trial proposal being advanced through SWOG to test this question.

Going back to the initial question, do we treat with a combination or a single-agent PD-1? Analyses that have been done on patient biopsies at baseline are hinting that we will be able to decide whether we should use one therapy or the other. The patients who respond to anti-PD-1 therapy have preexisting T cells in the tumor that are being turned off by PD-L1 expressed by the tumor. If we detect those T cells, those immune cells, in the tumor that have the PD-1 brake on, then we just need to unleash them and we do not need the combination. That is done with research assays right now, but I think it may become mainstream oncology in the near future.

That would make a case for personalizing immunotherapy, where when we look at the biopsy, we would see what the baseline interaction was between the immune system and the tumor in that patient, and then give the therapy that is more appropriate. Either take away 1 brake, because that's what is limiting that patient's immune system, or take 2 brakes, because the immune system has not made it into the tumor and it needs to be released further upstream—that is what ipilimumab would do—and also release it downstream when it gets into the tumor with PD-1 blockade.

Moderator: It seems as if all therapy in oncology is moving more and more towards individualizing treatment choices.

Dr. Ribas: I think that melanoma is certainly leading the way in this field, and I am pretty sure that the concepts that we're discussing for melanoma and treatment with anti-PD-1 antibodies will be applied to other cancers as well.

Moderator: What about pembrolizumab? Is that being evaluated in

combination trials?

Dr. Ribas: Both nivolumab and pembrolizumab are being tested in several combination trials beyond combining with anti-CTLA-4. Some of the trials that have some results reported are in combinations with T-VEC, an injectable oncolytic virus, with the idea that in tumors that do not have T cells inside, or that have made it to the tumor and they do not have an inflammatory response, you can create that by injecting T-VEC in some lesions, attracting immune system cells, and then that would attack other lesions.

There is a combination with IDO inhibitors. IDO is an immune-suppressive enzyme that is upregulated in T-cell-inflamed tumors. The combination would allow release of both IDO and PD-1 at the same time. Data that have been reported suggest that this combination has a higher response rate.

A series of studies are being conducted to modulate macrophages in the tumors, and pembrolizumab is being tested with ipilimumab, but at a lower dosage than the combination of nivolumab and ipilimumab, with the hope that you can get the same benefit, but with fewer toxicities. Then there's a whole field of combinations of immunotherapies with targeted therapies.

Moderator: Which ones are being tested now?

Dr. Ribas: The first attempt was when vemurafenib, the BRAF inhibitor, and ipilimumab, the CTLA-4- blocking antibody, were approved. We were all interested in seeing whether we could combine these therapies, because the immune system cells do not have a *BRAF* mutation. So it would be possible to block *BRAF* from the cancer and then turn on the immune system with ipilimumab. The phase I trial had to be stopped, however, after patients in the first couple of cohorts developed liver toxicities. That was rather unexpected, but it is probably related to the paradoxical MAP kinase activation that BRAF inhibitors have, where if you give a BRAF inhibitor and then give an immune stimulant, the MAP kinase pathway may be activated in the immune cells, and that may lead to some toxicities.

Then we started to test triple combinations, and now usually we'll have several clinical trials open, where we're giving a BRAF inhibitor and a MEK inhibitor plus either a PD-1 or a PD-L1 antibody. We reported the first results of the combination of dabrafenib, trametinib, and the anti-PDL-1 antibody MED14736. That triple therapy showed a very high response rate. I think every patient had either stable disease or a response. There was nobody with progressive disease.

The next question is, how long are these responses lasting? Are we really achieving the goal of having a high response rate with the BRAF and MEK inhibitors and maintaining the response rate without inducing resistance by giving a PD-1-blocking antibody? One of these programs is now going to move to a phase III randomized trial of BRAF plus MEK versus BRAF plus MEK plus PD-1.

Moderator: Is there anything that you think is important to add here?

Dr. Ribas: I've been treating melanoma for 15 years. Before, we had nonspecific therapies that were not mechanistically based. All of this excitement and progress has been because we have begun to understand the biology of the cancer and what makes it grow. We understand its relationship with the immune system and what prevented the immune system from attacking the cancer. So it is all based on scientific understanding and applying mechanistic-based treatments to patients, which suggests to me that we should continue to do better, we should continue to improve treatment, because we understand enough of it right now that all of these advances should not stop.

Moderator: Is it possible that continued research will find even more specific knowledge about the mechanism of the cancer that could add to our knowledge of what the mechanism of the treatment should be?

Dr. Ribas: Yes, that's the goal.

REFERENCES

1. American Cancer Society. What are the key statistics about melanoma skin cancer? Available at http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-key-statistics. Accessed December 22, 2015.
2. American Society of Clinical Oncology. Melanoma abstracts, 2015. Available at http://meetinglibrary.asco.org/search/site/melanoma?content_type[0]=fctContentType%3AAbstract&title=melanoma&meeting_id[0]=156. Accessed December 24, 2015.
3. ClinicalTrials.gov. Open trials in metastatic melanoma. Available at https://www.clinicaltrials.gov/ct2/results?term=%22metastatic+melanoma%22&recr=Open&no_unk=Y&pg=1. Accessed December 24, 2015.
4. Michielin O, Hoeller C. Gaining momentum: new options and opportunities for the treatment of advanced melanoma. *Cancer Treat Rev*. 2015;41:660-670. doi: 10.1016/j.ctrv.2015.05.012.
5. Bhatia S, Tykodi SS, Lee SM, Thompson JA. Systemic therapy of metastatic melanoma: on the road to cure. *Oncology (Williston Park)*. 2015;29(2):126-135.
6. Karachaliou N, Pilotto S, Teixidó C, et al. Melonoma: oncogenic drivers and the immune system. *Ann Transl Med*. 2015;3(18):265. doi: 10.3978/j.issn.2305-5839.2015.08.06.
7. Niezgoda A, Niezgoda P, Czajkowski R. Novel approaches to treatment of advanced melanoma: a review on targeted therapy and immunotherapy. *Biomed Res Int*. 2015; Article ID 851387.
8. U.S. Food and Drug Administration. FDA approves Cotellic as part of combination treatment for advanced melanoma. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm471934.htm. Accessed January 6, 2016.
9. U.S. Food and Drug Administration. FDA approves first-of-its-kind product for the treatment of melanoma. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm469571.htm. Accessed January 6, 2016.
10. Luke JJ. Have we won the race in the treatment of advanced melanoma—or are we just learning to walk? *Oncology (Williston Park)*. 2015;29(2):138-139.

11. Dronca RS. 2015 top stories in oncology: PD-1 and CTLA-4 combination blockade in advanced melanoma. Available at http://www.practiceupdate.com/content/2015-top-stories-in-oncology-pd-1-and-ctla-4-combination-blockade-in-advanced-melanoma/31823. Accessed December 21, 2015.
12. Diamond M, Gangadhar T, Schuchter LM. Immunotherapy for melanoma. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. Philadelphia, PA: Elsevier; 2015.
13. Ascierto PA, Marincola FM. 2015: the year of anti-PD-1/PD-L1s against melanoma and beyond. *EBioMedicine*. 2015;2:92-93. doi: 10.1016/j.ebiom.2015.01.011.
14. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521-2532. doi: 10.1056/NEJMoa1503093.
15. Ribas A, Puzanov I, Gajewski T, et al. A multicenter, open-label trial of talimogene laherparepvec (T-VEC) plus pembrolizumab vs pembrolizumab monotherapy in previously untreated, unresected, stage IIIB-IV melanoma. *J Clin Oncol*. 2015;33 (suppl; abstr TPS9081).
16. Society for Immunotherapy of Cancer. Preliminary results from phase I/II study of epacadostat in combination with pembrolizumab demonstrates 53% overall response rate across a number of cancer types. Available at https://www.sitcancer.org/about-sitc/newsroom/press-releases/epacadostat-in-combination-with-pembrolizumab-presented-at-sitc-2015. Accessed December 24, 2015.
17. Atkins MB, Choueiri TK, Hodi S, et al. Pembrolizumab (MK-3475) plus low-dose ipilimumab (IPI) in patients (pts) with advanced melanoma (MEL) or renal cell carcinoma (RCC): data from the KEYNOTE-029 phase 1 study. *J Clin Oncol*. 2015;33 (suppl; abstr 3009).
18. Inman S. FDA approves nivolumab/ipilimumab combination for BRAF wild-type melanoma. Available at http://www.onclive.com/web-exclusives/fda-approves-nivolumabipilimumab-combination-for-braf-wild-type-melanoma. Accessed December 22, 2015.
19. Hodi FS, Postow MA, Chesney JA, et al. Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. *J Clin Oncol*. 2015;33 (suppl; abstr 9004).
20. Wolchuk JD, Chiarion-Seleni V, Gonzalez R, et al. Efficacy and safety results from a phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment-naïve patients (pts) with advanced melanoma (MEL) (CheckMate 067). *J Clin Oncol*. 2015;33 (suppl; abstr LBA1).
21. Larkin J, Chiarion-Seleni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *New Engl J Med*. 2015;373(1):23-34. doi: 10.1056/NEJMoa1504030.
22. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372(1):30-39. doi: 10.1056/NEJMoa1412690.
23. Hugo W, Shi H, Sun L, et al. Non-genomic and immune evolution of melanoma acquiring MAPKI resistance. *Cell*. 2015;162(6):1271-1285. doi: 10.1016/j.cell.2015.07.061.
24. NIH Director's Blog. Knocking out melanoma: does this triple combo have what it takes? Available at http://directorsblog.nih.gov/2015/03/31/knocking-out-melanoma-does-this-triple-combo-have-what-it-takes/. Accessed December 24, 2015.
25. Clinical trials.gov. Open trials of triple therapy in melanoma. Available at https://www.clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=k&submit_fld_opt=on&=Update+Display&term=melanoma+AND+braf+AND+mek+AND+%28immune+OR+pd-s+OR+pdl-1+OR+clta%29&show_flds=Y. Accessed December 26, 2015.