Adverse Events with Targeted Therapies and Immunotherapies

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Overview
This activity is designed to inform physicians about the adverse events observed when treating patients with targeted therapies as well as immunotherapies such as checkpoint inhibitors.

Target Audience
This activity is directed toward medical oncologists, dermatologists, pulmonary care specialists, endocrinologists, gastroenterologists, primary care physicians, nurses, and advanced practitioners who treat and/or manage cancer patients who are being treated with targeted therapies or checkpoint inhibitors. Surgical oncologists, radiation oncologists, pathologists, fellows, physician assistants, and other healthcare providers interested in the management of adverse events associated with targeted therapies and checkpoint inhibitors are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Compare and contrast the differences between adverse events from targeted- and immune-related therapies versus those seen with conventional cytotoxic chemotherapy
- Describe the impact of adverse events when targeted therapies or checkpoint inhibitors are combined
- Explain the correlation between immune-related adverse events and the overall survival
- Discuss strategies for managing frequently occurring toxicities from targeted therapies and checkpoint inhibitors

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Enhanced understanding of the immune system in recent years has led to a paradigm shift in the field of oncology; the realization of unique pathways that govern cancer cell growth has led to the development of several therapies targeting those specific pathways. For instance, the discovery, that nearly half of all cutaneous melanomas harbor a mutation in the BRAF gene, has led to the successful development of molecular targeted kinase inhibitors against the mutant kinase. Several kinase inhibitors have been approved since 2011, and for various cancers. Currently, BRAF inhibitors (BRAFi) and MEK (MEKi) have been licensed for the treatment of metastatic BRAF mutant (V600E or V600K) melanoma,[1,2] and targeted drugs attacking the epidermal growth factor receptor (EGFR) protein have been approved for the treatment of lung cancer, among others.[3] Targeted therapy is also being utilized in other solid and hematologic malignancies.

Recent developments in immunotherapies have been based on the knowledge that multiple mechanisms of immune suppression prevent effective antitumor immunity. This realization has led to the development of a new class of immunotherapy, ie, antibody therapies directed against several negative immunologic regulators (checkpoints), commonly referred to as immune checkpoint inhibitors. Based on published data, treatment with checkpoint inhibitors is demonstrating significant improvements in the response and survival from advanced melanoma, lung cancer, and renal cell carcinoma (RCC).[4,5,6]

While approval of these novel immunotherapies and targeted therapies has presented practicing clinicians with opportunities to improve the outcomes of patients who do not respond to conventional therapies, they often present a challenge for practicing physicians as a result of adverse events (AEs); for example, the AEs observed with these therapies are different from those seen with conventional cytotoxic chemotherapies.[1,7]

BRAFi- and MEKi-associated AEs are different from those seen with cytotoxic chemotherapy. While certain toxicities appear to be more specific to individual BRAFi and MEKi drugs, others are common to all agents. Collectively, these agents have been associated with toxicities such as skin reactions, diarrhea, asthenia, and nausea/vomiting.[8] Treatment with EGFR inhibitors is associated with skin toxicities and diarrhea due to the normal presence of EGFR receptors in the skin and GI tract, respectively.[3,9] Similarly, vascular endothelial growth factor (VEGF)/EGFR inhibitors may cause hand and foot syndrome, likely due to peripheral blood vessel contraction in the palms and soles.[3,10] These toxicities are not life-threatening; however, dose interruptions and modifications are often necessary to ensure adherence to therapy and maintenance of quality of life.[1]

Similarly, immune-related adverse events (irAEs), that are distinct from cytotoxic chemotherapies, have been reported with checkpoint blockade, possibly due to unrestrained T-cell activation, which is also the reason for its antitumor response.[11] Similar to targeted agents, some of the irAEs appear to be common to all checkpoint inhibitors, whereas others may vary from one class to another (CTLA4 vs PD-1/PD-L1).[1,12] The kinetics for irAE onset can have varying time, and include dermatologic AEs such as maculopapular rash, GI toxicities such as diarrhea and colitis with/without ulceration, hepatotoxicity, endocrinopathies such as thyroiditis, hypophysitis, adrenal insufficiency, and, rarely, pneumonitis.[11,12] The irAEs can be managed if diagnosed early; for instance, autoimmune colitis, which presents with diarrhea and abdominal pain, will respond to oral corticosteroids.[11,12] Frequent patient-provider communication is, therefore, critical for AE management, and rapid supportive care interventions can go a long way in ensuring optimal management of the AEs associated with these agents.[12]

The use of immune checkpoint blockade has been limited to select malignancies (eg, advanced melanoma, renal cell carcinoma, and non–small-cell lung cancer); however, given that these agents have shown promising results in clinical trials for several other malignancies including head and neck, gastric, bladder, ovarian cancers, and hematologic malignancies, it is likely that these agents may be approved for other cancers.[11] As proactive management is important for mitigation of these AEs, it is important for practicing clinicians, who treat their patients with these therapies, to be able to recognize and intervene early on during their development, in order to maintain quality of life, consistent dosing, and optimal clinical outcome.

Dr. Mario Lacouture, MD, an expert dermatologist from the Memorial Sloan Kettering Cancer Center, New York, NY, offered his insight and practical tips on the management of immune- and targeted therapy-related AEs.

Moderator: How are irAEs different from chemotherapy-associated AEs?

Dr. Lacouture: Immune-related and targeted therapy-related AEs differ from cytotoxic chemotherapy-associated AEs because, with cytotoxic chemotherapy-associated AEs, the toxicities appear to be nonspecific and, in many instances, idiosyncratic. In other words, we don't understand why they are occurring. In addition to that, they almost always are dose-dependent and they are also cycle-dependent, so that the more cycles of chemo a person has received, then, the more severe and the more frequent these toxicities will be. Also, with chemotherapy, when you combine chemotherapy, ie, combine two types of different cytotoxic chemotherapy, it appears that the toxicities will get worse. So the toxicities appear to be additive or synergistic.

Now, if we compare that to irAEs and targeted therapy AEs, the difference appears to be that with these novel agents, the AEs appear to be mechanism-based. In other words, as we understand it, based on the agent's mechanism of action, the AEs are basically a consequence of those drugs working in tissues that are not the cancer tissues. For example, we know that the immune checkpoint inhibitors activate the immune system to attack, not only tumors, but also the other tissues in the body; for example, attacking tissues in the

colon causing colitis and diarrhea. We know that EGFR inhibitors, a type of targeted therapy, block this receptor in colon cancer, as well as lung cancer. But, they will also block EGFR receptor in the skin, which is also of critical importance, therefore leading to the acneiform rash seen with EGFR inhibitors.

The other difference is that the AEs with immune or targeted agents, although usually dose-dependent, do not appear to be cycle-dependent. So, if people receive only one or two cycles of these drugs, they can already develop these toxicities. Therefore, within the first 2 to 4 weeks or the first 2 months of therapy, patients are developing these toxicities that also usually need to be treated in addition to interrupting therapy. With cytotoxic chemotherapy, usually stopping the agent in question will suffice to restore normal health. With these targeted therapies, because of their longer action and their critical action in the way tissues operate, one needs to treat the toxicities in addition to stopping the agent.

And, finally, another thing is that, surprisingly, combining certain types—not all types—of targeted therapies, you have a lower incidence of toxicities. For example, when you combine BRAF inhibitors and MEK inhibitors, you have a lower incidence of dermatologic toxicities, and this is in contrast to cytotoxic chemotherapy or immunotherapies, in which, when you combine these drugs together with similar drugs, you get worse toxicity.

Moderator: Are there any patterns that have been noted for the appearances of these toxicities? For instance, do the skin-related AEs appear in the first few weeks and the systemic AEs appear later?

Dr. Lacouture: Yes, with cytotoxic chemotherapy, it usually will take 2 to 3 cycles for patients to start losing their hair, and with irAE patients to lose their hair and develop other skin or nail toxicities, it will take several months. With targeted therapies such as EGFR inhibitors, the acneiform rash will occur very quickly within the first 2 to 4 weeks, and it appears in a very explosive fashion within those 2 to 4 weeks. The rash due to irAE is a little bit more delayed. It will occur within the first 6 to 8 weeks, and then, around week 8, patients will start to develop the colitis or gastrointestinal toxicities, followed later on by the endocrine-related alterations after the first 2 months or so. With targeted therapies/EGFR inhibitors, toxicities occur usually within the first 2 weeks.

Moderator: How important is multidisciplinary communication and participation in multidisciplinary team meetings to proactively plan and manage targeted- and immunotherapy-related adverse events? Do you see it having an impact in clinical practice?

Dr. Lacouture: Currently, very few institutions have a formal system in which there is multidisciplinary management or discussion about toxicities. Most of the multidisciplinary group meetings' focus is on the therapeutic outcome of therapies, and not supportive care or toxicity management. And this is important because, for example, we know from surveys, that have been conducted in patients receiving EGFR inhibitors, that less than 10% of these patients are ever seen by a dermatologist to manage the skin toxicity. In patients with an oncologist who treats renal cell carcinoma, the majority of them [oncologists] have responded in a survey that we published in the Journal of Clinical Genitourinary Cancer13 that they would like to have more input from other specialists, who perhaps are more knowledgeable about toxicities associated with agents used in renal cell carcinoma, such as cardiologists for cardiac toxicity and hypertension, gastroenterologists from GI toxicity, and dermatologists for skin toxicity. Oncologists understand that there is a need for more multidisciplinary support. Unfortunately, there is a lack of access to these specialists for many oncologists. There are wait times for appointments with these other disciplines, or their patients don't have the luxury of waiting because they need to know and they need to intervene against these toxicities, usually on the same day.

Also, there have been data showing that the grading of toxicities between an oncologist and another specialist will differ, and this could have important implications. A grade 3 toxicity immediately dictates that the drug needs to be held. And, there have been studies showing that oncologists will grade some toxicities grade 3, whereas a specialist will grade it at a lower severity, showing then that you perhaps could continue many patients on these drugs for which they are being interrupted because the grading is not objective.

A proactive approach to intervening or preventing these toxicities may be very helpful. We have developed such systems here at our phase I developmental therapeutics committee, and in other areas where the toxicities are very frequent. But, as a matter of course, and in most institutions, there is no systematic approach to this. It [systemic approach] would be of extreme help, because it would also liberate the oncologist and their nurses to do what is, of course, the most important thing, which is to treat their cancer and minimize these events affecting the dose of the patients, their impact on quality of life, and the need to stop these drugs.

I like the idea of a multidisciplinary [approach]. Most of what they call tumor boards, at the moment in most institutions, as the name implies, they only meet, let's say, for a patient who has a challenging case. But, there is really no toxicity board in which the focus is managing adverse events. There is no such toxicity board in which a group of investigators or clinicians identify better supportive care measures.

Moderator: Our next question was, what impact do targeted therapies have on the patients' emotional well-being, as well as the functioning, based on the data from the Rosen, et al manuscript[14] in which the skindex16 questionnaire was administered to all cancer patients?

Dr. Lacouture: In this study of over 280 patients treated with cytotoxic agents or targeted therapies, a quality of life questionnaire specific for dermatology or skin, hair, and nails was given. And what was found was that patients receiving targeted therapies had a significantly higher negative impact on their quality of life when compared with those treated with cytotoxic agents, and the most important component of these patients' quality of life that was affected was their

emotions. The one [aspect] that was greater with targeted therapies was the emotional [one], probably because with the emotional component, you have many more toxicities affecting the face or areas of the body exposed to other people, and also because you have a greater incidence of itching and other symptoms that can decrease a patient's ability to sleep and just feel comfortable.

Moderator: Would you be able to share key takeaways from the phase II study[15] of EGFR inhibitors that compared preemptive versus reactive skin toxicity treatment in patients with metastatic colorectal cancer?

Dr. Lacouture: The most important two points of this phase II are the following: number one, that by using a prophylactic regimen within the first 6 weeks of treatment with an EGFR monoclonal antibody and chemotherapy with topical corticosteroid to the face and chest and an antibiotic such as doxycycline, 100 mg twice daily during the first 6 weeks, you are able to reduce grade 2 or worse skin toxicities by more than 50%. You are able to reduce grade 3 skin toxicities, or eliminate them altogether, with the use of this prophylactic regimen of the topical steroid and the oral antibiotic. Point number two: you are also able to improve upon dehydration, neutropenia, and diarrhea if you start patients on this prophylactic antibiotic regimen and topical steroid, likely because you maintain an intact barrier of the skin and you alter the intestinal flora with the antibiotic, preventing the diarrhea that was associated with these agents.

Moderator: What are some of the most mentionable irAEs seen with the checkpoint inhibitor nivolumab? Also, are there any differences with respect to AEs seen with ipilimumab versus those seen with pembrolizumab?

Dr. Lacouture: With nivolumab, the most common irAEs are colitis or gastrointestinal toxicity, manifested usually by diarrhea and abdominal pain; also, pruritus or itching of the skin, a maculopapular rash, as well as endocrine alterations. In terms of pembrolizumab and nivolumab, they appear to have a very similar toxicity profile.

Ipilimumab has a similar constellation of irAEs as PD-1 inhibitors, but more severe and frequent. Conversely, with pembrolizumab or nivolumab, you have another toxicity that you do not see with ipilimumab, pneumonitis, which occurs in less than 5% of patients with PD-1 inhibitors, but you do not see it with ipilimumab.

Moderator: What role does patient communication play in management of these adverse events? How best could this information be communicated to the patient in your opinion? Should it be all at one time or as the treatment progresses?

Dr. Lacouture: Because adverse events do not always appear simultaneously, it would be good to focus on the most immediate and severe toxicities, on the first visits. If one is seeing a patient every month or every six weeks, focus on the most likely or severe toxicities that can occur during that time period, so that patients can report their symptoms if and when they do occur.

And it's important to indicate to patients that if they experience toxicities, [they should] communicate with their oncologist or their oncology team, as soon as they feel them, and not wait for the next visit to report on these. And even in between appointments, it's important for patients to know that they should communicate with their oncologist.

Moderator: What effect does combining checkpoint inhibitors have on irAEs?

Dr. Lacouture: There are lower incidence of dermatologic toxicities when you combine a BRAF inhibitor with a MEK inhibitor. But, when you combine immunotherapies, for example ipilimumab and nivolumab, you will have a much greater toxicity profile with 55% of patients having grade 3-4 AEs, and 30% of patients will have AEs leading to treatment discontinuation. When you combine nivolumab and ipilimumab, for example, in this study published by Dr. Larkin, in *New England Journal* in 2015[16], the combination of ipilimumab and nivolumab resulted in a higher number of toxicities. More commonly, what was seen was diarrhea, fatigue, pruritus, rash, as well as, nausea. Importantly also, endocrine abnormalities occurred in about 20%, but the most important grade 3 toxicities were diarrhea, fatigue, and rash. Interestingly, because these drugs combined appear to be so robust and effective, 70% of patients who discontinued the combination of nivolumab and ipilimumab, due to AEs, did have a response in terms of their tumor. So, it's important to know that most patients did not receive the full cycles of dosing, but even after receiving only a few cycles that led to a greater toxicity, they did respond to the drug in a beneficial way.

Moderator: Do irAEs have an impact on overall survival? Do we have any data from published studies evaluating this?

Dr. Lacouture: Yes, there is data in melanoma, a paper published by Dr. Jeff Weber's group, in *Clinical Cancer Research*, in 2016[17]—the first author is Freeman-Keller—which shows that melanoma patients, when treated with nivolumab, had an improved overall survival when they developed rash or vitiligo, which is the depigmentation of the skin, both of which are considered to be irAEs. So, it's important to know this, because it also helps in counseling patients. It helps them to better cope with these side effects if a discussion is held indicating that they may experience a rash or vitiligo, but, that usually when these things happen, it means that the drug is going to work better. So, it at least helps patients find some comfort in these untoward events.

Moderator: What special considerations need to be kept in mind for management of dermatitis and pruritus?

Dr. Lacouture: [An important point is that] usually interrupting the drug, interrupting the immune checkpoint inhibitor will not be sufficient. One needs to intervene or treat the pruritus and the rash. Another important point—what I usually see—is that the use of topical steroids is, of course, not easy because patients have to apply this all over their body; and, usually they are prescribed a

topical steroid of an adequate potency. So it's important in these patients, because of the implications of this in terms of impacting the dosing of the drug, that a high potency topical corticosteroid is used in a vehicle that is easy to apply to large parts of the body, for example, coming as a spray or as a foam, something easy to spread all over the body, to apply it twice daily and to continue applying it even after the rash has resolved for at least two weeks in order to prevent this reappearance upon re-challenge with the immune checkpoint inhibitor.

I would also like to emphasize that, as I said, it needs to be treated, and not only the drug needs to be held, but, also, oral corticosteroids need to be used whenever the rash is of grades 2 or 3 in severity. Another thing that's important to know is that some studies have shown that the use of corticosteroids to manage irAEs did not result in a negative impact in clinical outcome. So, using oral corticosteroids is better to manage these events and does not appear to have a negative impact on outcome. And finally, with pruritus, it's important to keep in mind, that in most patients, the pruritus is not associated with a rash. So, one needs to find other ways to treat this pruritus, which will include oral antihistamines—topical antihistamines are not very effective—oral antihistamines, and other agents, such as GABA analog agents like pregabalin, gabapentin. Aprepitant, the NK1 receptor inhibitor, has also been found to be effective in pruritus, and those things can be considered.

Moderator: How should GI adverse events, such as diarrhea and colitis be managed in patients taking checkpoint inhibitors?
Dr. Lacouture: Diarrhea and colitis usually is treated with antimotility agents and modifications in the diet when there is no bleeding or pain associated with it, and when it's mild in severity. So counseling from a nutritionist or dietitian is helpful. When it's moderate, in other words, there are 4 to 6 stools a day greater than baseline, one should withhold the immune checkpoint inhibitor and start oral corticosteroids, about 0.5 mg/kg/day of prednisone or the equivalent. You continue those steroids until the severity of this diarrhea goes to mild, or it resolves, and then you resume the immune checkpoint inhibitor at a reduced dose according to the package insert.

If the diarrhea is severe or life-threatening, with 7 or more stools per day over baseline, one should also consider an evaluation by a gastroenterologist for a possible bowel perforation or for an endoscopy. Steroids are recommended at a dose of 1-2 mg/kg/day of prednisone, or the equivalent, until the diarrhea improves to grade 1 or 0. Patients should continue to be evaluated. It's important to obtain, in these patients—always when they do not respond—a bacterial panel of their stool to make sure there is no other infection. And, also, if patients do not respond to steroids, the recommendation is to use an intravenous tumor necrosis factor (TNF) alfa inhibitor such as infliximab; only about two cycles of infliximab are needed.

Another important thing is, that whenever there are signs of pain suggestive of perforation, to perform imaging studies such as a CT scan, and, also, I strongly recommend an evaluation by a GI doctor in case there is a need for endoscopy and to rule out infections that they would do with a stool sample.

Moderator: How frequent is the occurrence of pneumonitis in patients on checkpoint inhibitors? How could this be managed in clinic?
Dr. Lacouture: Pneumonitis, thankfully, is not very common, and occurs in less than 6% of the patients. The incidence appears to be increased in patients who have lung cancer and in patients who receive combination immune checkpoint inhibitors. It's usually a clinical diagnosis, so patients present with dyspnea, cough, fever, and chest pain. So, it could progress or could be reminiscent of acute pneumonia or acute respiratory distress syndrome. It is a clinical diagnosis; so, in imaging, you would see the infiltrates and you would see hypoxemia in these patients. The treatment usually consists of admission of these patients, and also depends on the severity.

So, for example, for a grade 1 pneumonitis that is asymptomatic and there's only radiologic changes, one would investigate with a high resolution CT of the chest. And, usually, with grade 1 pneumonitis, you continue immunotherapy, but monitor for symptoms every 3 days. And, then, you would repeat the CT scan at every cycle of therapy. If the patient has a grade 2 pneumonitis with mild-to-moderate or new symptoms, it's important to also image them with a high-resolution CT, and, whenever necessary, do a bronchoscopy to see if there is any infection. It's important to withhold immunotherapy. Patients should be monitored daily for a moderate-to-severe pneumonitis. Prednisone, at a dose of 1 mg/kg/day or equivalent, should be given, and if the pneumonitis persists for more than 3 days, the notion is that one would discontinue immunotherapy altogether because of the severe implications of this.

So, for grade 3 and 4 pneumonitis, and, of course, patients who are hypoxic, it is important to also, again, follow the patient with imaging, microbial assessment where necessary, and to consider a pulmonary and infectious disease consult for possible bronchoscopy. For a grade 3 or 4 pneumonitis, discontinuation of immunotherapy is mandated. Patients need to be hospitalized, and the steroids should be given by IV at a dose of 2 to 4 mg/kg/day of methylprednisolone, and patients should also be given prophylactic antibiotics. If the toxicity worsens after 48 hours, consider additional immunosuppression such as cyclophosphamide, mycophenolate mofetil, or infliximab.

REFERENCES

1. Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol.* 2015;7(2):122-136. doi: 10.1177/1758834014566428.
2. Niezgoda A, Niezgoda P, Czajkowski R. Novel approaches to treatment of advanced melanoma: a review on targeted therapy and immunotherapy. *Biomed Res Int* 2015. 2015:851387. doi: 10.1155/2015/851387.
3. American Cancer Society. Targeted Therapy. http://www.cancer.org/acs/groups/cid/documents/webcontent/003024-pdf.pdf. Ac-

cessed April 19, 2016.
4. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol.* 2015;33(17):1974-1982. doi: 10.1200/JCO.2014.59.4358.
5. American Cancer Society. What is cancer immunotherapy? http://www.cancer.org/acs/groups/cid/documents/webcontent/003013-pdf.pdf. Accessed April 19, 2016.
6. Quinn DI, Lara PN Jr. Renal cell cancer – targeting an immune checkpoint or multiple kinases. *N Engl J Med.* 2015;373(19):1872-1874. doi: 10.1056/NEJMe1511252.
7. European Society for Medical Oncology. Managing the Side Effects of Novel Cancer Immunotherapeutics. http://www.esmo.org/Oncology-News/Managing-the-Side-Effects-of-Novel-Cancer-Immunotherapeutics. Accessed April 19, 2016.
8. Planchard D, Groen HJM, Kim TM, et al. Interim results of a phase II study of the BRAF inhibitor (BRAFi) dabrafenib (D) in combination with the MEK inhibitor trametinib (T) in patients (pts) with BRAF V600E mutated (mut) metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2015; 33(suppl; abstr 8006).
9. Hirsh V, Blais N, Burkes R, Verma S, Croitoru K. Management of diarrhea induced by epidermal growth factor receptor tyrosine kinase inhibitors. *Curr Oncol.* 2014;21(6):329-336. doi: 10.3747/co.21.2241.
10. Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. *Semin Nephrol.* 2010;30(6):591-601. doi: 10.1016/j.semnephrol.2010.09.007.
11. Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Transl Lung Cancer Res.* 2015;4(5):560–575. doi: 10.3978/j.issn.2218-6751.2015.06.06.
12. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol.* 2015;33(18):2092-2099. doi: 10.1200/JCO.2014.60.0379.
13. Ruiz JN, Belum VR, Creel P, et al. Current practices in the management of adverse events associated with targeted therapies for advanced renal cell carcinoma: a national survey of oncologists. *Clin Genitourin Cancer.* 2014;12(5):341-347. doi: 10.1016/j.clgc.2014.04.001.
14. Rosen AC, Case EC, Dusza SW, et al. Impact of dermatologic adverse events on quality of life in 283 cancer patients: a questionnaire study in a dermatology referral clinic. *Am J Clin Dermatol.* 2013;14(4):327-333. doi: 10.1007/s40257-013-0021-0.
15. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010;28(8):1351-1357. doi: 10.1200/JCO.2008.21.7828.
16. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373(1):23-34. doi: 10.1056/NEJMoa1504030.
17. Freeman-Keller M, Kim Y, Cronin H, et al. Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res.* 2016;22(4):886-894. doi: 10.1158/1078-0432.CCR-15-1136. [Epub 2015 Oct 7].