IMMUNOTHERAPY

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Our next session is on the Advances in the Use of Immunotherapy in Oncology. Please welcome two wonderful speakers, Ms. Laura Zitella of Stanford Healthcare, and Dr. Anthony Olszanski of the Fox Chase Cancer Center.

DR. OLSZANSKI Welcome. We’re going to talk a little bit about immunotherapy. You’re going to hear some of the same topics as Brianna had just discussed about melanoma and about the management of some of the patients because immunotherapy is the new beginning of medical oncology, and it’s changing the way that we think about patients. It’s changing the way that patients are behaving in our clinics, and it’s producing what we didn’t think we would necessarily see, which is these wonderful, durable responses with patients who are staying alive years and years after their treatment, participating in community, and having all the love that they deserve from their families and their friends because they’re around and they’re feeling well. Why don’t we get started?

LAURA We’re really pleased to be here to talk about immunotherapy again. As you know, this is one of the most major breakthroughs in cancer therapy that we’ve seen in our lifetimes, and it’s been touted on the covers of many mainstream magazines.

It was really nice that the previous presentation gave us a start in talking about immunotherapy. And we’re going to try and focus on some pearls for
treating patients across different tumor types because these therapies have the potential to be beneficial for patients with a variety of different diseases.

Our main learning objective is to manage the treatment plan for patients who are treated with immunotherapeutic agents factoring in the concept of pseudoprogression, and then we’ll also touch on the slightly controversial issue of PD-L1 testing.

These are our disclosures.

DR. OLSZANSKI We’re going to talk relatively specifically about what we call the checkpoint inhibitors, and we’re going to describe a little bit how they work, why they work the way they do, and some of the toxicity managements again. But I want to make sure that you understand that immuno-oncology is something that’s an old topic. Immuno-oncology was first described back in the 1800s when there was something called Coley’s toxin. A doctor had started trying to get staphylococcal infections and injecting them back into patients because he had seen a couple cancers regress in that situation. Coley’s toxin was probably the beginning of what we would consider to be normal immuno-oncology, but now you can see that we have IL-2 and interferon as part of the cytokines, as checkpoint inhibitors.

We heard a little bit about T-VEC. CAR T cell therapy is something of vogue these days. Vaccines -- we have a lot of vaccines that are still in development. Vaccines for the most part have been relatively negative in the oncology setting, although we have one or two seem to be working and we’re still looking at that, and then tumor-infiltrating and lymphocyte therapy.
Immunotherapy is a big, broad topic; it’s much broader than what you see here on the slide. And we’re going to focus on the checkpoint inhibitors because those are the things that we’re going to be using in the clinic today most commonly.

LAURA Here we go again with another refresher of the immune system. The immune system is extraordinarily complicated, so hopefully it is helpful to you to hear this several times during this conference.

The immune system consists of highly specialized cells that are designed to detect and destroy pathogens. There are two interrelated interdependent immune systems; there’s the innate immunity and the adaptive immunity. The innate immune system is readily available. These cells are nonspecific; they generate an immediate immune response.

In contrast, the adaptive immune system is unique. Every B cell has a unique B-cell receptor, it has a unique T-cell receptor, and generating this adaptive immune response can take days. It’s activated by a sequence of events in order to engage a clone of specific B or T cells in order to fight a pathogen.

The two immune systems work together very effectively, but the T cells also have an additional role, and T cells can recognize cells that are diseased or cancerous or old or worn out. The remainder of this presentation is going to focus on T cells and how T cells can destroy cancer cells.

How do T cells destroy cancer cells? We’re going to go through this step by step. The tumor releases antigens; antigens are taken up by antigen-presenting cells. The most effective antigen-presenting cell is the dendritic cell, which takes a little piece of the antigen and associates it with its MHC molecule.
This antigen-presenting cell travels then to the lymph node, where it encounters resting T cells. The T cell that has the T-cell receptor that's specific for that antigen will bind to the antigen associated with MHC on the dendritic cell; this is a first signal. But in order to prevent autoimmunity or reactivation of the immune system unnecessarily, T-cell activation must have a second signal; that second signal is the binding of B7 and CD28.

Once that happens, the T cell’s activated, it expands into an army of clones that can attack the tumor, they travel out of the lymph node, through the bloodstream, to the tumor, where cytotoxic T-cell activity occurs by releasing perforin and granzyme to kill the tumor.

Moving onto to CTLA-4 and PD-1, they have very important normal functions. When you turn on the immune system in order to fight an infection, you don’t want to keep the immune system turned on. You have to have a way to turn it off; it’s part of the natural feedback loop. And CTLA-4 and PD-1 are an important part of normal function, so they turn off the immune response or as we say, they’re the brakes.

You have a situation here where you have activation of T cells, but after T-cell activation, your body automatically upregulates CTLA-4 on the cell membrane and that suppresses the immune system. That will turn it off, and that’s something that occurs normally.

Another checkpoint, or another possibility of brake on the immune system, occurs right at the action between the T cell and the tumor cell, and that’s between PD-1 and PD-L1. PD-1 is expressed on the T cells and it downregulates
T-cell function and it prevents the T cell from releasing perforin and granzyme and continuing cytotoxic activity.

Cytotoxic CD8 T cells are the most potent tumor-killing cells, so these are the cells that we want to engage. T-cell activation requires two signals and immune checkpoints exist as a normal function, so we can exploit this in the treatment of cancer. But they are important to protect cell from inflammation, autoimmunity, allergy, hypersensitivity, pregnancy, allograft, and they also can allow tumors to evade the immune system by inducing self-tolerance.

Because immune checkpoint inhibitors operate at different stages of immune response, we have several opportunities in which we can exploit this. The anti-CTLA-4 antibody that’s approved is ipilimumab, the anti-PD-L1, the newest one that’s been approved, is atezolizumab, and the anti-PD-1s are nivolumab and pembrolizumab. As you can see, since they operate in different areas of the immune system, they also can be combined as in the treatment of melanoma to have greater effectiveness.

DR. OLSZANSKI Laura’s already gone through a very good description about how there’s an interaction between the immune system and our T cells so that they’re upregulated. All of us have immune systems and we have innate immune systems, which are always keeping us relatively healthy. I think it’s really important to recognize that tumors are mostly normal tissue, right? One of the situations that we get ourselves into in the clinic is patients say, “Well, doctor, what’s wrong with my immune system? Why did I develop cancer?” And I think it’s really important to go to those patients and say, “There’s probably nothing
wrong with your immune system, but rather, the cancer is evading the immune system just like our normal cells evade the immune system.” If our normal cells didn’t have that capacity, we would all be subject to many, many autoimmune toxicities. As well as Laura did to describe all of the mechanism of action of the PD-1 and CTLA-4 inhibitors and the PD-L1 inhibitors, we have to recognize that there’s many, many receptors and ligands on each of the cell surfaces. What we’re describing is a very simplified form of what probably happens in the cell.

This cartoon shows that there is a receptor and a ligand match and some of the receptors might be upregulated, while the ligand might be downregulated, and there’s going to be many, many of these interactions that actually occur. While we’re excited by CTLA-4, while we’re excited about PD-1, it’s going to take much more understanding over the next 5 to 10 years before we can capitalize on what we consider to be immunotherapy and how we, hopefully, decrease the amount of adverse events.

It is a very complex interaction because we talk about a lot of positive interactions, but there’s also negative regulatory signals. We have tumor-specific mutations, which can sometimes play a role, and I want to also emphasize that there is a big component here that we usually don’t think about and that’s the stroma, all the surrounding tissue around the tumor itself, which is helping to protect it, helping it to grow. And there’s this concept of immune evasion, as well, as a concept of immunosuppression.

There’s been a number of FDA approvals. We’re really excited about this because we’ve seen over the course of the last 5 years or so that there’s been a
huge upswing in the amount of approvals that we’ve seen. Of course, ipilimumab was the first monoclonal antibody approved and it was approved for advanced melanoma. It is now approved in adjuvant melanoma, and if you haven’t seen it yet at ESMO this year, in the first trial that looked at adjuvant ipilimumab and melanoma, there is now an apparent survival advantage, so that’s really exciting.

Nivolumab was approved and you can see some of the indications there; pembrolizumab approved and you can see some of the indications there; and like Laura said, the newest one is atezolizumab. Atezolizumab is approved right now in second-line lung cancer as in bladder cancer, the most recent approval that we’ve seen. I had to update this slide just for you because pembrolizumab captured the first-line setting in non-small cell lung cancer if PD-1 expression is over 50%.

Immunotherapy has been effective in a wide range of tumor types, and we’re using a lot of immunotherapy on clinical trials these days. Small-cell lung cancer, which is a disease which is so hard to treat and now we have a 15% response rate and what’s really amazing about this is at least in some of the combinations, nivo plus ipi, we’re again seeing some durable responses in small-cell lung cancer; that’s really fascinating and you can see here, the gradation of the objective response rates. In colorectal cancer that’s microsatellite stable, we don’t see very many response rates, but in microsatellite unstable colorectal cancer, which accounts for about 15% of the general population, there is a 60% overall response rate; that’s really exciting. You have to find these patients that are microsatellite unstable.
This is an example of immunotherapy’s potential in chemotherapy-resistant disease. This is a patient in my clinic with metastatic hepatocellular carcinoma. If you treat HCC, you know that there’s nothing that works in the metastatic or advanced setting; it’s such a difficult and troubling disease to work with. The kinase inhibitor that we have, sorafenib, has a lot of toxicities; it’s very challenging.

But, you can see here, here’s a baseline scan from May of this year. This patient went on to receive a PD-1 inhibitor as compassionate use and three doses later you can see that this patient has had a remarkable response, not only in the size of that tumor up on the chest wall that you can see, but also look at the alpha-fetoprotein levels -- from 22,000 down to 250. Now, this makes the patient quite happy; makes me quite happy too.

We have, I already told you, great responses in microsatellite unstable colorectal cancer, although that’s still a relatively rare segment of the population. It’s really important to understand it, so I thought I’d briefly go through this cartoon about what MSI-high is. Here you can see what we call a microsatellite region. This is a DNA strand from the five prime to the three prime end and its matching strand that you can see right underneath it. The microsatellite region is that repeating region and it doesn’t have to be too nucleotides, but I made it two nucleotides so we can follow along pretty easily. It’s CA, CA, CA, CA and then from the other side is GT, GT, GT, GT. That’s the microsatellite region and we all have these. In fact, this is part of what’s used in DNA fingerprinting for science. A
microsatellite region is relatively unstable; it can flex, it can bend, it has a somewhat different makeup compared to the regular DNA.

And so you can see that in the bottom part of the graph, we have a part of this microsatellite region which is sort of looped up on itself. It’s now mismatched compared to the strand that’s trying to grow underneath it. This particular double-stranded DNA now has microsatellite instability. This is literally just another mutation. We know that in immunotherapy, the PD-1 inhibitors, the CTLA-4 inhibitors were recognizing that it might be the antigen load which is most important in patients. If they have a big antigen load, there’s more chances of finding that antigen that’s going to direct the T cell to kill that tumor. And so microsatellite instability is basically causing many, many thousands of mutations in a patient. That’s why microsatellite instability in a colorectal cancer patient is important.

Now, I said microsatellite’s the instability or we all have microsatellites, this is normal, but microsatellite instability is relatively uncommon in a patient who has colon cancer with MSI-high; they have problems with their mismatched repair genes, they can’t correct this. If you don’t have microsatellite instability, you have the ability to correct this dysfunction; that’s the difference. So these patients, they end up with a lot of mutations, and you saw really, really high response rates.

This is just a summary of that -- the mismatch repair deficiency -- well characterized. This is what we talk about when we talk about patients with Lynch syndrome -- up to 100 times as many somatic mutations compared to the stable
tumors. Prominent lymphocyte infiltrates, which sometimes suggested immune response, and this mutational load may, in fact, predict, PD-1 inhibition efficacy.

Laura, do you want to take it here? Is PD-L1 necessary for our testing?

LAURA That’s a pretty controversial topic right now. We do know that PD-L1 testing is helpful, and primarily we feel like it’s helpful for prognosticating which patients are going to respond to PD-1 inhibitors. The current data that we have suggests that if you have higher expression of PD-L1 you are more likely to have a response to PD-1 inhibition or PD-L1 inhibition.

However, there are patients that still respond even if they have low expression of PD-L1, and so it’s hard to know what to do in those situations because you don’t want to deny a patient a potentially effective therapy based on their PD-L1 testing. At this point, PD-L1 testing is indicated for pembrolizumab, so it’s being used in that setting and they’re certainly continuing research in that area.

DR. OLSZANSKI That’s exactly right. Remember that we’ve been using bevacizumab for a very, very long time as a VEGF inhibitor. And early in its days of life, we were struggling to find an adequate biomarker, and to date, 15, 16 years later after its approval, we have nothing and yet, it’s still a very effective medication. And I think that that’s where we are right now with PD-L1 testing, except in specific indications.

There are a lot of biomarker challenges with the PD-L1; the immunohistochemistry assays differ among testing platforms, so if I get PD-L1 tested at one platform versus another, I might get disparate results. Testing
confers positivity on tumor cells, but it’s not consistent, it might also be on tumor-infiltrating lymphocytes, although we presented a situation where PD-L1 is only between the tumor cell itself and the T cell. There’s PD-L1 all over the place, so it’s not just within that tumor interaction. There’s no standard testing threshold; again, pembrolizumab is indicated if PD-L1 testing is greater than 50%. It does not consider other immunoligands; we looked at that graphic where there’s other things that are at play here.

There’s a lot of heterogeneity in a biopsy too. I can perform a biopsy of lung cancer and a biopsy of the same lung cancer on the different side or a different organ and find out that I have different levels of PD-L1 testing in that same patient, same tumor, just different sites. And PD-L1 expression -- this is part of one of the clinical trials I’m running where we’re trying to change PD-L1 expression using gamma-interferon. So we recognize that this happens all the time from therapies.

The other thing that we should also talk about is whether or not these checkpoint inhibitors are in fact interchangeable. We now have three to consider: pembrolizumab, nivolumab, and atezolizumab. These monoclonal antibodies are exquisitely specific and this is true of all monoclonal antibodies. They are geared to go after one specific protein and that’s all they go after -- extremely specific. And the PK and PD seem similar within classes, so there’s this exquisite target specificity, very, very similar AE profiles, no apparent difference in overall response rates, but this is a between trial comparison; we haven’t seen a whole lot of head to head.
We’re struggling with the biomarker selections; how do we select between these? Sometimes we use the biomarkers. If I’m going to use pembrolizumab, for example, sometimes I use the infusion schedule because there’s q2 week scheduling versus q3 week scheduling. But from my standpoint at least to date, within the same tumor type, there’s no meaningful clinical differences that we can identify.

Laura, do you want to take us through this slide?

LAURA Now we’re getting into my favorite part of the presentation. When we’re thinking about what we wanted to bring to you today; it is the management of side effects. The side effects of immunotherapy are so different from chemotherapy. And for those of you who have been involved at the clinical trials, you probably feel very comfortable and have a lot of experience with this. But now that they’re all approved, we’re exposing thousands more patients, rather than hundreds of patients, to these drugs and we are seeing a wide variety of side effects.

To review briefly, activation of the immune system and jumpstarting the immune system to reeducate them against cancer cells, which are self-cells, can also induce an autoimmunity, or reactivity against healthy cells. And that’s where we see the side effects; it’s from anti-self-antigen recognition.

We have prepared for you a few case studies so we can walk through some of the management. After listening to the previous presentation, I expect that all of you will know all the right answers already, so this should just be review.
The first question that we have for you is what are the most common immune-related adverse events of PD-1 and PD-L1 and CTLA-4 inhibitors? Would you say that it’s rash and fatigue, diarrhea and colitis, hepatitis, pneumonitis, or endocrinopathies?

The answer is rash and fatigue are the most common across this class of drugs. But immune-related adverse reactions can affect any tissue. We really like this diagram because it shows exactly how it can affect every single organ. Of course, the most common side effects are rash, fatigue, dermatitis and pruritus, and diarrhea and colitis, and those are some of the things that Bri talked about in her presentation earlier. Infrequently, you can also see hepatitis, pneumonitis, and endocrinopathies, and then very rarely you see problems in other organs, like encephalitis or pancreatitis, nephritis, Guillain-Barré, and other things like that.

But as much as we talk about the side effects, I do want to emphasize that when we look overall at how many patients experience side effects, most of these side effects are very mild and these drugs are very well tolerated, especially when you compare it to the side effects of chemotherapy.

Your patient asks you, “When will I get side effects from immune therapy?” How do you respond? Do you tell them that they’ll probably have something this week? Do you tell them that side effects are very unlikely and you’ll probably be fine? Or side effects can happen any time, but they’re most likely to happen 6 to 12 weeks after therapy or any time after therapy, but the most common time is 7 to 14 days? Tony, how would you answer that question?
DR. OLSZANSKI I think that you’re going to be showing a graph very shortly about some of the side effects, and we usually see this sometime in the time frame of weeks. However, I don’t think that that means answer B was wrong because the vast majority of patients do extremely well from this particular therapy. I think that when we talk about side effects it’s important to disclose that if side effects occur, they usually occur after a 3-week period or so, but most patients tolerate it quite well.

LAURA This graph just demonstrates when you’re most likely to see the most common side effects. As you can see, the skin toxicity tends to happen first; it usually happens after 2 to 3 weeks on therapy. GI toxicity follows, then hepatic, and then endocrine. Immune-related adverse events are pretty rare after 24 weeks on therapy; however, when patients start therapy they’re used to expecting side effects immediately. It’s really important that they’re educated on what to report, especially if something happens 2 or 3 months into therapy.

The other group of professionals that require some additional education about this are consultants and also our emergency room physicians because they’re seeing patients. And the side effect profile is so different from chemotherapy that we need to make sure that they understand it needs to be in their differential.

This is a checklist that was published by a group from the European Society of Medical Oncology. We haven’t put together a lot of standards yet; all of these drugs are new. It’s been interesting talking to people from different centers and other clinicians across the country about how we’re managing
patients on these drugs. This is an extremely comprehensive checklist of things you might want to think about with patients who are starting immunotherapy.

First of all, you want to assess for autoimmune disorders. If a patient has a pre-existing autoimmune disorder, they are at high risk of having exacerbation of that disorder. However, in routine practice if you have a patient who has a life-threatening cancer with minimal treatment options and they have a certain autoimmune disorder that may or may not be exacerbated, there’s a discussion about risk benefit. I know most of us have successfully treated patients with autoimmune disorders on immunotherapy; it just requires extra vigilance and a lot of education of the patient of the potential higher risk of exacerbation, and then a thorough review of systems, physical examination. And then I think the area that’s a little controversial is the labs and the imaging.

This is a pretty comprehensive list of baseline labs, and what we’re finding in practice is most people do a complete blood count, they do a complete metabolic panel, and LFTs, and they definitely do a TSH. Some other centers do this complete list of labs, some do CT imaging at baseline. But over the next few years, we’re going to learn how to manage these patients most effectively, and Tony and I both agree that at the bare minimum before you treat a patient you should have a CBC and a comprehensive metabolic panel with liver function.

You can check TSH before each treatment or you can check it once a month, but you don’t need to hold the therapy waiting for the TSH to come back. We’re going to talk a little bit about management of the hypothyroidism that we see with the immunotherapy.
I think we both can take this one because both of us feel really passionately about patient education. It’s really important that -- and I know that Bri also mentioned this in her talk -- that patients have like a wallet card or something to alert other health care providers that they are on these drugs. Especially, I think that all of us share a similar challenge, particularly with your patients who have metastatic lung cancer.

We’re going to talk about this in one of our case studies, but a patient with metastatic lung cancer is at risk of a lot of different things; they can have pneumonia, they can have pneumonitis from their immunotherapy; they develop a PE; and they already have a generally not so good-looking chest x-ray or CT scan. So it’s really important when they’re coming into the emergency room that the emergency room physicians are aware that pneumonitis needs to be really high on the differential.

The signs that require prompt evaluation are diarrhea, blood in the stool, fatigue, weight loss, nausea or vomiting, any new rashes, shortness of breath or cough, any neurologic changes. We’re seeing that after patients have been on therapy for a while; some patients have been on immunotherapy for a year or two or more at this point. We’re seeing arthralgias and neuropathies happen as very, very delayed side effects.

The general management approach to immune-related adverse events is listed here, and we wanted to make this very simple. There are a lot of charts that are available for your review to help guide you in the management and there’s an entire page on what you do for hepatic toxicity or what you do for
colitis or what you do for pneumonitis. And we wanted to just simplify it as this: if it’s mild, then you treat with supportive care; if it’s grade II or above, then you use steroids; and if it’s grade III or IV and requires hospitalization, then you use higher-dose steroids and/or IV steroids. And that’s a very simplified version of the management approach.

DR. OLSZANSKI Let’s give you another case to discuss about. John -- John is a great friend of yours, a 70-year-old gentleman with stage IV lung cancer. You’ve already tested him for EGFR and ALK, which is important, and it’s negative. And he’s progressed after standard-line therapy, which is cisplatin based. His oncologist now recommends nivolumab in the second-line setting where you know it is approved. His baseline thyroid function tests were normal, and he begins nivolumab currently now at a standard dose of 240 mg IV q2 weeks; that is now what we give all patients; it’s no longer a mg/kg basis. And after two cycles, John presents to clinic and routine TFTs show a TSH of 0.03 and a free T4 of 3.76; ACTT, TH, and cortisol levels are normal.

Obviously, this is bringing out the endocrinologist in all of us; I’m not sure that I ever had that in me. However, what’s your diagnosis? And you can see some of the choices up there. We won’t belabor this; all we need to know is that TSH is particularly low and a low TSH might indicate hyperthyroidism, right? So this is likely going to be A -- autoimmune thyroiditis with hyperthyroidism. As we continue to follow this patient, John is seen in clinic for cycle 4 nivolumab, and he mentions he’s now extremely fatigued. You now get repeat thyroid function tests, and his TSH is now nine, and his T4 is very low at 0.2, and this is consistent with
hypothyroidism. This is just after you’ve already diagnosed hyperthyroidism, so what do you recommend to treat this autoimmune hypothyroidism?

Basically, he’s burned out his thyroid now, do we start him immediately on prednisone? Do we treat him with a thyroid hormone replacement and expect the thyroid function will recover? After we complete nivo, do we treat and tell him that it’s unlikely to recover or we don’t do anything? Thyroid function should recover completely after nivo. The first point is we might not stop nivo, right? If he’s responding really well, he might be on this for a year or two and maybe more. So we’re going to treat with thyroid hormone replacement, and most of the time both Laura and I would start that in clinic and then refer this patient to a primary care provider or an endocrinologist who knows what they’re doing.

But it is important to tell patients that his thyroid function is unlikely to recover, so they really need to anticipate lifelong therapy. This is a pill that they have to swallow, but I don’t think it’s a bitter pill if they’re having a great response from the immunotherapy.

LAURA A couple of clinical pearls from that example -- it is common to see a period of hyperthyroidism followed by hypothyroidism. The patient in that example was not symptomatic, so we wouldn’t treat the hyperthyroidism, we would just watch it knowing the natural course of what was going to happen. And that the hypothyroidism is one of the very few side effects that you don’t hold therapy for. So you continue to treat through and you don’t have to use steroids to treat it as opposed to all of the other side effects that we’re going to talk about.
DR. OLSZANSKI  In the prior session, Brianna had presented a patient with melanoma who started having one side effect after another side effect, and you’re probably thinking, “Okay, they stacked the deck,” right? “They’re making it so that we learn something out here.” But in fact, many patients present with more than one side effect oftentimes when these autoimmune side effects happen. In this poor gentleman, after five cycles of nivo, he calls, he’s short of breath now, it’s difficult to climb up the stairs to his bedroom; in clinic, O2 saturation was 96% on room air, so he seems to be doing pretty well at rest, but you no sooner get him up and walking around and he’s 83% when ambulating. O2 sats in the clinic are really important, especially with ambulation. And chest x-rays show -- this picture you can see the chest x-ray on the left showing a very normal silhouette of the heart and the mediastinum; you can see all the bones outlined really well there, you can see the costovertebral angles, which are really sharp; a very nice, normal chest x-ray without any masses or anything; as opposed to the chest x-ray on the right. He’s sent to the emergency room. He’s afebrile, heart rate is 112, blood pressure is okay, respiratory rate’s high, and his O2 sats are 86%, so what is the differential diagnosis, right? What’s the differential?

This is where we all have to put our medical hats on, and this is what I love about oncology. I used to do cookbook medicine in many respects; I’m a clinical trialist, so I got to use a really weird-looking cookbook. However, it was a lot of cookbook medicine, and now I’m using all of my internal medicine background again and that makes it so exciting and so damn scary.
LAURA And so hard. This is a situation that I find the most challenging. The answer is all of the above. This is a patient with metastatic lung cancer, and working inpatient as an oncology hospitalist, this is something that I see quite often. We’ll move onto the case study, and I’ll let you know what happens.

In this situation, there was no evidence of PE, so that was something that we could rule out right away. We did a bronchoscopy to rule out infection and obtain a biopsy, but in the meantime, waiting for those results we started the patient on steroids. And when in doubt, you need to start steroids and you can always take them off quickly later, but this is something that could be very severe, it could be life threatening, and so there’s no harm and there’s definitely a great benefit in starting them right away.

We started methylprednisolone 1 mg/kg IV daily for 3 days and then we started oral steroids. And the biopsy did show that there was a pneumonitis, and you can see the CT scan here. But you can see that CT scan, it’s not a subtle finding. And then you can see after 1 month the pneumonitis was greatly improved with steroids.

The immune-mediated pneumonitis is a very, very difficult clinical challenge. It can present, as you can see, radiographically in many different ways, so it’s important that any patient that presents with shortness of breath or dry cough, new or increasing oxygen requirements, does have imaging with a CT scan and you can always hold the immunotherapy to be on the safe side and start steroids. If patients are having a true immune-mediated pneumonitis, we
generally see a response fairly quickly, certainly within the first week or so, so it
does give us an idea at least if we are treating the right thing.

DR. OLSZANSKI    It’s also important to recognize that when we’re giving
high-dose steroids, we are suppressing the immune system of the patient, and
we have to remember that other opportunistic infections can happen to the
patient as well. It is not uncommon to have a patient to say, “Doc, I can't swallow
anymore,” and they have a lot of floor candidiasis. Or a patient has a rapid
response to the steroids and then a couple weeks later can’t breathe again
because they have PCP, so those are things that you really need to think about
when you’re giving these high-dose steroids. And so sometimes, especially if I
need to continue that course of steroids, we do give prophylaxis as well.

LAURA    That’s a really good point and that came up in a lot of
discussions that we’ve been having at this conference -- I came from a
hematologist background and I’m used to working with graft-versus-host disease,
and there’s a lot of similarities and parallels between that and [I’m] pretty familiar
with high-dose steroids.

But now that we’re moving into the solid tumor world with immunotherapy,
a lot of the clinicians aren’t as used to using high-dose steroids. And I think that it
is overlooked that you need to have GI prophylaxis against stress ulcers, you
need to watch out for thrush, and you certainly need to worry about PCP
prophylaxis.

DR. OLSZANSKI    Immunotherapy was appropriately held in this
situation; hypoxia resolved with steroids, he’s discharged 2 days later, begins
steroid taper, and it’s important that we continue in this particular instance with a long steroid taper of probably over about 4 weeks. He does get prophylaxis and he’s feeling well. He’s down to 10 mg per day and his recent imaging shows resolution of the pneumonitis. Now you have a treatment that may have been working for his lung cancer, if I remember what John had, and he’s had a pretty significant toxicity, where do you go from here?

We have a number of things that we could do, and it’s difficult to say that there is particularly a wrong answer of discontinuing the nivo because this was a potentially life-threatening event; however, he’s now controlled on 10 mg of prednisone, which is about physiologic levels of prednisone a day, and so we could consider restarting the nivolumab and considering continuing on the prednisone here. Remember, we’re dealing with disease, his lung cancer, which is a fatal disease. I think it’s important to recognize that in this situation we would start nivo at the prior dose of 240 mg. We do not tend to dose reduce immunotherapeutics; there is no information out there that would have suggested a dose reduction in some way decreased the side effect profile.

LAURA When do you consider restarting immunotherapy? If the side effect resolves and the patient is on the equivalent of less than 10 mg day of prednisone or the equivalent, in many of those cases you can safely restart immunotherapy. And another reminder is that if it’s an endocrinopathy that you’re treating, that does not require termination of immunotherapy.

We’re moving on to Sue, who is a 56-year-old woman with advanced melanoma and she’s treated with pembrolizumab 2 mg/kg every 3 weeks. After
cycle 1, she presents with a mild pruritic erythematous maculopapular rash on her arms, chest, and back; you diagnose autoimmune dermatitis. How will you treat the rash? Hold the pembrolizumab and treat with topical steroids? Continue and continue with topical steroids? Hold the pembrolizumab and treat with oral steroids? Or continue the pembrolizumab and treat with oral steroids?

Hopefully, I did hear most of you say that you would continue the pembrolizumab and treat with topical steroids, which is what I would do in that case as well. We continued the pembrolizumab and the rash resolves, and after 12 weeks, the response is assessed and Sue appears to have progressive disease -- would you continue therapy?

DR. OLSZANSKI What you’re looking at here on the left-hand panel is her inguinal area on the left prior to and at week 12, and I don’t think it takes any rocket scientist to figure out that she’s having progressive disease. You can see the CT images below, which show the liver, which appears to be growing with disease there as well.

This is a very common problem that we have; something called pseudoprogression, or maybe this is pseudoprogression, maybe this is real progression. Do you want to go through this slide with us?

LAURA This is a real challenge. Pseudoprogression is characterized by having an increase in the size of the tumor. And the reason why that happens, we’re still learning a little bit about it, but it could just be tumor infiltration with immune cells or inflammation. So when you’re assessing patients, it can be really difficult when you have a patient in front of you and you’re trying to decide if this
is progressive disease or if this is pseudoprogression. In the KEYNOTE-001 analysis, an atypical response like this, observation of an earlier progression followed by an eventual response occurred in about 7% of the patients. So we acknowledge the pseudoprogression occurs and it happens, but it actually happens a lot less frequently than -- it actually is not that common -- 7% is not that common.

One of the important things that came out of that was that even patients who had evidence of early progressive disease could eventually respond and some of them had very prolonged overall survival. We're going to talk about that a little bit more and talk about how we are assessing patients.

The traditional criteria of assessing patients for response is the RECIST criteria, and in the RECIST criteria you take a maximum of five target lesions and assess the size of those lesions. If there’s an appearance of any new lesion, that accounts as progressive disease. Researchers now are trying to figure out how are we going to assess response for immunotherapy because patients can have these atypical response? And they came up with the immune-related response criteria. It's a little bit better, but it still is imperfect in assessing response. And in the immune-related response criteria, they look at a greater number of lesions and they measure the overall tumor burden. They allow you to have a couple new lesions that are just added to the overall tumor burden, so progressive disease is assessed based on overall tumor burden rather than just a small number of target lesions.
DR. OLSZANSKI  The disease assessment for patients is becoming much more complicated because we have this idea of pseudoprogression. It’s a human bias to believe that if you’re the patient, you’re going to be the one having pseudoprogression, and if you’re the provider, it’s your patient who’s having the pseudoprogression, so how do you tell the difference between progression and not progression? You always start with a baseline scan and the baseline scan on this particular graph is at 0 even if they have a lot of lesions; that’s what we call baseline. Here we have a patient who is going through time point one 3 weeks later, time point two, time point three, and it’s pretty easy in this particular patient where every subsequent time point gets less and less and less, and you can say, “Okay, this patient is clearly responding to therapy.” But I’m going to remind you that you have a little bit more information oftentimes before you even get that baseline scan.

This patient had a partial response, but you can retrospectively look at how the patient was doing as well. I do want to remind you to always go back to the prior scans and try to get an idea of what the growth kinetics were. We’ll explain that a little bit better.

Here’s a patient; you have three scans and you’re looking at this going, “Well, I don’t really know, is this pseudoprogression or is this real progression?” Obviously, in a patient you can start graphing this, and it’s in this patient where we’re using a lot of our clinical attributes to decide whether or not we continue their therapy. If they feel like they’re doing pretty well, they’re not having any egregious toxicities -- I have one patient, true story, melanoma, 78-years-old, and
on cycle 3 of his nivolumab that he was getting for a mucosal melanoma of the nasal pharynx. The wife complained to me and I said, “What’s the problem?” She goes, “He’s starting to do pushups again. He’s too old to do pushups.” That is a wonderful complaint. So, this patient, I would probably give nivo at that time point too, but then it becomes obvious that the patient is, in fact, progressing.

This is a graph of what we might we see with pseudoprogression, so you’re going to see that those three time points are very, very similar to the one that we saw before. And, in fact, if we looked at this and looked at that third time point, we’d have to assume that per RECIST this is, in fact, progressive disease; this represents a 20% increase in the sum of the longest diameters. If we follow this patient a little bit longer, we can see that all of a sudden, despite an early apparent progression, this patient has a PR. This is a pseudoprogression and, again, if we take a look with our retrospective scope and look back at the scans that we saw before this patient and plot out that course, it might give us some information that would tell us that this patient might be pseudoprogressing. Because if you would have extrapolated that growth curve for this patient, you could see that at time point two, they were already a lot lower than you might have otherwise expected them to be. It’s a little bit of objective data with the CT scans and a little bit of clinical data, subjective data, from how well the patient’s doing.

You can look at labs, right? I showed you that AFP that goes from 22,000 to 250, that’s good clinical data to use. In melanoma, it might be using LDH; in a different disease, maybe a different marker.
LAURA We don’t have a perfect answer on how you determine pseudoprogression from progression, but we can tell you that in clinical practice, when you’re faced with a patient who potentially has progressive disease and has a metastatic cancer with very limited other treatment options, you want to give them the benefit of the doubt that this might be pseudoprogression. That’s what we’re seeing in clinical practice, that if a patient is tolerating immunotherapy well, it’s generally continued. In Sue’s case, that’s exactly what happened.

This is a picture of her baseline lesion. At week 12, this lesion looks much worse and it looks like she’s having progression. But her treatment was continued and by week 24, she had a partial response, and by week 96, she had a complete response.

DR. OLSZANSKI What do you think Sue’s feeling about now?

LAURA That was pretty fantastic. The responses to immune checkpoint inhibitors are difficult to assess. There are four patterns of response; there could be progression, stable disease, response, or pseudoprogression. But it’s really important to remember that as we talked about in the early pathophysiology slide, it takes time to generate a T-cell response, and so it’s going to take time to generate an effective response.

One of the things that we have to be careful about is imaging patients too early, because if we image them too early to find out response, we may be faced with a situation where it looks like progressive disease and we don’t know if this is pseudoprogression or not. So we try to wait at least 12 weeks before reassessing for a response.
Then the other important clinical pearl that we wanted to address was the use of steroids. As you can imagine, there was a lot of concern that using steroids, which diminish the immune response, would affect the effectiveness of immunotherapy. But at the same time, we had to use steroids in order to manage the side effects, some of which were life threatening or could be life threatening.

So they did a retrospective analysis of patients who had melanoma who were treated with ipilimumab, and they found that of those patients, most of them had some side effect – most of the side effects were mild -- and of those patients that had side effects, 35% of them required steroids. Then they compared the patients who required steroids and the ones that didn’t and, fortunately, they found that there was no difference in time to treatment failure and no difference in overall survival. This is really encouraging because it suggests that steroids do not affect the effectiveness of immunotherapy.

DR. OLSZANSKI We do recognize, also, unfortunately, that when we start immunotherapy and they have a partial response or even a complete response, sometimes patients do have progressive disease. So I thought I’d talk to you a little bit about some of the things that we think are behind this resistance that we’re seeing, because conceptually you wouldn’t think that resistance would actually occur; we’re not changing the immune system. What appears to happen is if you look at the tumor site, the important cells, the effector T cells, are still present at the tumor site, but there was a couple things that might have happened. Remember that we’re talking about a specific antigen, so if that
antigen has been eliminated from most of the tumor, but there’s a different antigen out there, those same T cells are not going to be able to exactly identify that antigen. There could be a lack of the tumor antigen that they initially went against.

There could be a loss of sensitivity. Remember we talked a little bit about the stroma interaction. The stroma interaction is quite important. We also talked about the fact that it’s not all about just CTLA-4 and PD-1, but rather, other ligands and bindings. There could be inactivation of the Janus kinase pathway, the JAK-STAT pathway, and this can lead to resistance to interferon gamma.

Interferon gamma upregulates PD-L1 and might make these immunotherapies more effective, so if we have inactivation of the JAK-STAT pathway, we can see decrease of the interferon gamma, decrease of the target, PD-L1. Then there is also this thing called loss of beta-2 microglobulin and loss of the human leukocyte antigen, so our T cells, our immune system, might not be able to engage in the tumors like we wanted them to.

There’s this concept about the immunoediting hypothesis, not a particularly old hypothesis, but a way of thinking about the way that our bodies probably handle tumors on a day-to-day basis that I want to make sure that you’re aware of. There’s probably active immune surveillance, potential tumors, right? All the time, and that might be occurring in this room even as we speak, right? That’s called the elimination phase. Those mistakes in the DNA will never turn out to become cancers; they will never have the opportunity because they’ve been recognized by the immune system and killed.
But there is also this weird thing called the equilibrium phase, a balance between both alkylation and evasion, and we see this lot. We give immunotherapy after chemotherapy, we know the patient had progressive disease, but there’s a point when -- I see this a lot in lung cancer -- their disease looks like it’s stable, but they’re doing okay and I can continue the nivo. I had a person who was on nivo for a year with stable disease; before the nivo, clear progression of disease. It stopped the progression, but it didn’t kill down the tumor. We think this is akin to the equilibrium phase.

Then there is also this concept of reduced immunogenicity, enhanced immunosuppression, and then you see a growth and we call that the escape phase.

LAURA We only have a few minutes left, and we want to leave time for questions. In summary, these are the pillars of immunotherapy management. Understand the toxicity spectrum, educate patients, intervene early so you can prevent severe adverse effects, and monitor.

Then we talked about what are our unanswered questions? I think there’s a lot of unanswered questions and things that we’re going to learn about over the next few years, but one of the biggest is how is response to treatment best evaluated? How long do we continue these drugs for patients? Are there biomarkers which will predict who will respond? How should immunotherapy be sequenced and combined with other treatments? I feel like every other month I have to update myself; I’m like, “What needs to be sequenced first and which disease?” Because it’s rapidly changing.
Then is there a benefit to PD-L1 inhibitor after PD-1 inhibitor? Are these antibodies interchangeable? There’s still a lot of research to be done and a lot of questions to be answered.

DR. OLSZANSKI  Over the course of the next 5 to 10 years, we’re going to see a huge volume of new PD-1 and PD-L1 inhibitors that are out there that we need to know how to incorporate, but there’s also going to be a lot of other immunotherapies. Right now at my center, I’m investigating probably no less than 10 different molecules that you didn’t even hear us talk about today that are all part of this immunotherapy and checkpoint access. We’re at the cusp of the beginning of immunotherapy, and it’s really exciting times ahead.

[END]