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OMID HAMID: Well, good morning, everyone. Thank you for coming. I'd like to thank the organizers and my colleagues for the opportunity to talk on checkpoint inhibition and not just my metastatic cutaneous squamous cell carcinoma, but all solid tumors. I think when you come to one of these talks, you realize you're learning something about one entity that's relatable to almost all entities. And as an aside, I'll say that immunology has offered hope for curing cancer for over 100 years.

Coley's toxin and the spontaneous regressions of tumors for patients who've had viral infections, or who've had infections and then had come out, and gotten better, and we've seen that their immune system has resolved. Then like you hear in every movie, it's in you. But what's different now? How do we know now to grab the immune system and utilize it to target many different malignant diseases?

You know, for a long time, we've known tumor mediated inhibition of the immune system is responsible for progression, and that most of the issues that we have with solid tumors and liquid tumors, there is evidence of infiltrating immune cells on all of these solid tumors here. That is, that when you open it pathologically, you see inflamed cells, T cells, in those tumors, and there's evidence of tumor associated immunosuppression reported on the majority of these. And then the tumor immune interaction is known to correlate with prognosis. As we've gone further, we've seen that increased levels of T cells in a tumor lead to a better prognosis than a tumor that does not have it.

And I usually use to end my talk, saying that the promise of immunotherapy is that we could target almost all of these tumors and have a brilliant outcome, but I'll begin because that's true. Immunotherapy is approved for the majority of these tumors at this point, having just come back from Munich at the European meeting where even triple negative breast cancer has been shown to have some benefit with this type of therapy. You've heard a little bit about cutaneous squamous cell carcinoma. I'll get back into the background quickly, but the 2,000 deaths per year is under-reported.

As you've heard before, there are tumors that are cut off. There are tumors-- that are patients that are not seen. But although most are curable with surgery or radiation, about 5% metastasize. And the problem for a patient, with that metastatic or that locally advanced, unresectable tumor previously, that came to see me in my clinic, was that we didn't have much to offer. They were usually treated with platinum-based chemotherapy or EGFR inhibitors, and these epithelial growth factor receptor inhibitors and these platinums, these came from data from cutaneous squamous cell carcinoma but also head and neck squamous cell carcinoma.

The overall response rates were low. And although we gave them, we knew that their major role was to help palliate, but it would never give a long durable response. So with treatments not shown to have an overall survival advantage, we went and looked elsewhere. The blockage of pathways used by tumors to inhibit anti-tumor immunity is where we went.

Checkpoint blockade is based on the idea that, in our bodies the same way that we expel foreign bacteria and viruses, we should be interacting with foreign tumors. And that is that these tumors have specific antigens, specific proteins, specific things that are different that activate our T cells to notice them as being different, and then create an immune response, as you've seen here-- a stimulation and millions and millions of T cells out to attack the tumor, and we'll talk a little bit about this expansion. Here we bring in the checkpoint inhibitors and most importantly PD-1. Programmed Death 1 was cloned from an activated T cell undergoing activation induced cell death in a lab.

It does not directly activate caspases or cause cell death, which means it is not the thing that causes those T cells to die. What it does is it indirectly affects the immune system by reducing cytokines, which stimulate the immune system, and survival factors. What you can see here is a cartoon that's been put up a lot recently, and it shows the interactions between the T cell, and the tumor cell, and the dendritic cell. When I talk about this, I say that this is like a Shawshank thing. This is like a policeman bringing a part of the escaped convict, which is the tumor, into the bloodhound-- the bloodhound's the T cell-- out to attack.

And usually, what happens is when that piece of that escaped tumor is brought to the T cell, that T cell gets activated by a secondary pathway. Usually, when that bloodhound gets to that escaped convict, that tumor cell, that T cell destroys the tumor cell. But through PD-L1 interactions and through CTLA-4 interactions shown here, that T cell can become suppressed. How do we fix that?

Anti-CTLA-4 antibodies, which block that suppression pathway and anti-PD-1 antibodies, which we're going to be talking about, suppress that-- that block that suppression pathway between the T cell and the tumor cell, and then lead to T cell activation, tumor cell death. This is the first step that we're showing here, the antigen presenting cell and the T cell, and you can see here there are positive and negative signals. If you think back to your immunology classes, MHC and the T cell receptor connect.

And if you don't have a secondary stimulus, that T cell goes into energy. It goes into sleep mode. Usually, you have that second blockage.

Unfortunately, the negative, the inhibitory one, is a stronger secondary signal, and that causes the T cell to become suppressed. Why have these negative signals? I mean, it just makes sense that these T cells should be activated and attacking.

Unfortunately if that were true, I would have Crohn's disease. My colleague here would have another autoimmune disease, psoriasis, lupus, et cetera. So we have to find a way to shut off that in response. If you get a bacterial viral infection, it's OK to have the flu, but you can't have it for weeks, or days, or months. So it's to prevent a too strong immune response, damaging tissues, and to maintain immune tolerance, to allow us to have this immune system ready that can be turned on, but also turned off.

PD-1 and PD-L1 blockade, as they showed you in the second part, stimulates the anti-tumor T cell response. I'll take you through here again. This is the MHC from the tumor cell and the T cell receptor connecting together. That's the first connection. The second connection needs to happen, but when you have a PD-1, PD-L1 negative connection, you have this T cell inhibited by blocking with an antibody. With an infused antibody, that goes there, that blocks this negative interaction, you have those C cells awake and alert. You have that bloodhound ready to increase cytokines, and cause an inflammatory reaction, and cause tumor cell death.

So these immune checkpoints work in two places that I've shown you-- again, T cell priming, with the antigen presenting cell in the T cell-- early T cell activation that sends this army out into the tumor metastatic area-- and then the T cell activation in the metastases. By blocking the tumor cell and T cell negative pathway with anti-PD-1 and PD-L1 antibodies, you cause T cell activation, proliferation, and cell death. One of the other things we've learned is that we don't know everything there is to know about these pathways, as there are T regulatory cells in the tumor microenvironment that suppress the T cells themselves.

We've come to find out that tumor associated macrophages, they interact with the Tregs, and by blocking CTLA-4 here we can deplete T regulatory factors and allow those T cells to attack the tumor cells. Checkpoint blockade functions in multiple places, and this is another way to look at what I just presented to you. In the lymph node, CTLA-4 inhibition is important. And then in the tumor microenvironment, this is where PD-L1, PD-1 interactions become important.

So you can see that we are-- by just using one drug in activating multiple functions of the T cell and that in the tumor microenvironment. PD-1 pathways inhibit T cell activation. They lead to reduced T cell signaling, reduced cytokine production, reduced target cell lysis, altered lymphocyte motility, and the metabolic reprogramming. So you can see, as we sit here, and we talk about this drug, how involved and interactive it is, and how appropriate it is that the gentlemen who identified these two pathways are currently receiving the Nobel Prize in Medicine.

PD-L1 in cancer is not something that's just a construct. It's expressed on the surface of multiple solid tumors and hematologic malignancies. Even though it inhibits the anti-tumor immune response, we can stain, and we can tell that it is there. And we can tell a little bit more about how our therapies can work. Again, these are negative signals The CTLA-4 blockade leads to unopposed stimulation, Treg depletion, and ongoing immune response. But why doesn't directly stimulating the immune response cure our cancers?

In clinical trials and in early trials, we've seen a 20% to 50% response rate. How do we make this better? Well, PD-1 directed cancer immunotherapy is different from chemotherapy. Number one, it's well tolerated. This is not targeted therapy or chemotherapy. This is a therapy that I've personally given to people as old as 95 years old. There's no real blood count decline. There is no real hair loss. It's very safe, except for the side effects of immune stimulation.

Those autoimmune mediated like inflammations-- and I tell patients, anything that can become inflamed is inflamed. And you'll hear a little bit more about this-- inflammation in the lungs, causing a cough, and pneumoniatis, colitis causing diarrhea. But these severe toxicities are low in less than 10% of patients. And through education, like what you're doing here today, physicians learn more about how to identify those and treat those-- very easy to be done. And what's happened now is these therapies that you heard a little bit about are now disseminated throughout the community.

They have broad anti tumor efficacy. I told you, on one of my first slides that I show you, that the response rates are fairly beneficial in these tumors, and mimic the response rates, and, maybe even better than chemotherapy alone. I'd bring you to-- see here, Hodgkin's disease-- response rates greater than 50%, response rates in non Hodgkin's lymphoma, small cell lung cancer, kidney cancer, head and neck. And unlike when I first began my career, now we're going through immuno therapeutic talks and not even talking about melanoma. We're talking about common solid tumors we see in the clinic.

And I could just take this, and change the word melanoma, and put it down for almost any solid tumor. That PD-1 therapy is showing benefits in patients who have failed traditional response chemotherapy or targeted therapy, and is moving to the forefront as first-line therapy in a variety of solid tumors. We just came back from the European meeting again, and it has shown that PD-1 therapy is a standard first-line for head and neck squamous cell carcinoma. So you see now the paradigm is flipping, where we took the data from head and neck cancer and related it to our squamous cell carcinomas, this is now our squamous cell carcinoma skin data going to head and neck cancer.

We do need predictive markers to tell us who are these people that respond and don't respond? This is a slide, that's been shown over and over again, showing nivolumab, pembrolizumab now called atezolizumab-- durvalumab, the anti-PD-1, anti-PD-L1 antibodies-- and showing that response rate. You just need to go this way. And response rates are higher in those patients with higher levels of PD-L1, showing high immunosuppression, giving a drug that blocks that immunosuppression and getting response rates. But being able to select-- you know, these response rates are 32%, but if you take the PD-L1 positives you can tell someone that their response rates are about this much, as we go on.

And how do you do that? We've begun to find stains that can let us see them in intracellularly and extracellularly, and this is how it looks-- and be able to know. What does the immune system see, and how do we do that? How does the immune system recognize? When I said that that little piece of a tumor, that antigen, that neoantigen, is produced by the antigen presenting cells to the T cell, what is that? Well, tumors have multiple neoantigens that T cells can attack, and those new antigens come from mutations in a normal cell.

As you've heard before, normal cells turn into tumors by having mutations. Those express different neoantigens, and those neoantigens are immuno stimulatory. Your immune system says this does not belong here, just like a protein on a bacteria or a virus does not belong. We've seen that these neoantigens can be quantified, and the prevalence of these mutations across human cancer cells have been shown. And then what we've really found is these people at the end of the spectrum, who have the highest levels of neoantigens, they're the ones that respond the greatest to immuno therapy.

Well, where are we? Melanoma, lung cancer, bladder cancer, head and neck cancer you've seen here, these are the tumors where immunotherapy with PD-1 is becoming standard. But one thing you don't see in this, as it's been presented, that way out here is cutaneous squamous cell carcinoma. And in fact, you can see that higher mutational burden that any tumor type in the Cancer Genome Atlas belongs to squamous cell carcinoma of the skin. That's exceeded by that of other solid tumors, and in those patients that have the highest risks-- the immunosuppressed patients that have CLL, or that have had a transplant, that are immunosuppressant for something else-- those people's tumor mutational burdens are even higher. And that indicates, to us, higher risk disease.

And you can see that it makes sense to bring in a drug like cemiplimab and the anti-PD-1 inhibitor. And you can see, as the data was shown and will be shown again, durable complete responses, radiological responses, and long-term responses-- again, here's what I said. And this was just published. You're seeing the number of mutations to the objective response rate, and look what is way up here, cutaneous squamous cell carcinoma. Just as an aside, you don't need to have a high level.

Merkel cell carcinoma has high response rates. Melanoma has high response rates. But then as we go down, here is where we'll have to focus the most on-- improving immune response. These are the tumors where we're not doing, as well, but, as I've said to you, new data in breast cancer. So the future is bright. Again, there are two evolutionary processes that we usually talk about targeting. One is DNA mutations and driver mutations-- those are the BRAF mutations, the HER2, et cetera-- and immune invasion. What we have seen, and why the field is focusing on immunotherapy and looking at it compared to targeted therapy-- you can see here that there are durable, long-term responses and a survival curve that plateaus.

This is with anti-CTLA-4 therapy-- long-term anti-CTLA-4 with melanoma 22%, five year out presented by our friend Steve Hodi and Dana-Farber. And then you can see, with targeted therapy these are the BRAF inhibitors, you do get an early good response, but somewhere down the line you're losing. The early differential here, where the survival curves, they differ, is not what you see where there is no survival curve difference with immunotherapy. So what do we see here?

Targeted therapies work quickly, but over the course of time they run out. Anti-CTLA-4 and other immunotherapy targets, they start later. The benefits start later, but there's durable, long-term benefit. And some of the things we're doing are combining these. We're combining CTLA-4 and PD-1. We're combining targeted therapies and PD-1 or CTLA-4, and trying to show that those lead to better survival.

Again, the response rates in the mutation frequencies are bringing down. That, you can see here. As we're looking, prostate cancer and other cancers coming into use-- the data with cemiplimab showing locally advanced and metastatic cutaneous squamous cell carcinomas having a response in benefit. Every two-week dosing showed, again what I've said before, very, very tolerable side effects. As you can see here, the Grade 3 toxicities are low, and they're very manageable-- transaminitis, hypothyroidism, joint aches, nausea, and fatigue. And the any-grade toxicities are low.

So these are therapies you give to your patients that don't affect their morbidity much. They're not in your clinic for side effects, and toxicities, et cetera. And you're showing high response rates. And overall response rates-- those patients who had partial response, and those patients who had complete response showing 37.5%. But disease control, now another endpoint that is important here, because in a therapy where you have benefit, where you can control the growth, and you show long-term durability of that control may be just as good. And that was around 70%.

These responses do take time in certain people, but you can see the rapidity, and depth, and durability of these responses in a significant portion of these patients. This is in months. And you can have early response, and I've seen it in my patients, within the month. You can see, again, the tenants that we've discussed-- a PD-1 staining-- a PD-L1 staining showing those patients who are going to respond, and those patients who don't-- where those that have lower than 1% staining have a very low response. But we need to do better with our abilities. Why?

This is anti-PD-1 therapy in melanoma that has the longest experience, and you can see here this was presented to again by our friend Steve Hodi. And you're seeing here the survival of the original Topalian study at five years, now not 20%, but nearer to 30%. And at the 3 milligrams per kilogram effective dose that was approved, you're seeing the same thing. So this is what we can foresee for our patients with cutaneous squamous cell carcinoma. This is happening in the community, but we need to bridge the gap of getting higher response rates.

And as we began talking about the idea of checkpoints, there is more. There are not just PD-1 and CTLA-4, but there are other inhibitory checkpoints that we can block through antibodies, made in our labs, to give to patients. And there are stimulatory-- they turn up instead of putting the foot on the brake on the T cell, they slam on the gas for these patients. And guess what, when I used to give this talk three years, four years, five years, I would say this is a dream. But all of these targets, all of these drugs, are now in clinical trials available for our patients for multiple solid tumors. And now we're at the point of trying to decode who responds, and who doesn't?

Up until this point, this is how we've been working. We don't know the right tool for the right person. Which checkpoint is great? And we've just been blindly giving drug to our patients. We are now looking at combinations to improve the T cell infiltrating the tumor microenvironment, priming more T cells to come in by blocking multiple checkpoints, activating stimulatory pathways-- this was those pathways that I showed on the left side-- and administering those cytokines that we need like high dose IL-2, IL-12 together. We're working on targeting therapies, not like targeted therapies-- but figuring out which patient needs what combination or what drug?

I have had patients that respond to anti-CTLA-4 that don't respond to anti-PD-1. Why? How? Where?

And we're looking for prognostic markers. PD-L1 may be one of them-- heart markers predictive of sensitivity or resistance, and markers even predictive for adverse events. And this is one way. This is from a Christian Blank in the Netherlands, where we can take these new biomarkers-- LDH, glucose, absence of checkpoints, immune infiltration-- and target appropriately. And that's not just a dream. These are things that have been shown.

Here is Roy Herbst's data looking at immunohistochemistry of the T cells with PD-L1-- of the T cells, not just the tumor. Paul Tumeh from UCLA looked at the tumor T cell interaction. We've had mutational load. We've talked about it, right? The high mutational load tumors, they respond. The high mutational load tumors in each tumor type respond better. And you can figure out who needs combo and who doesn't? This is now data from Risby, in lung cancer, and others. This is all comers in New England Journal of Medicine. Interferon gamma signature has been validated to identify patients who have a high response, T cell, clonality, et cetera.

So as we end on time, the future is now, and here's where we are. We're now given the tools to give benefit to our patients, not just in higher response rates, but in durability and of course the holy grail of overall survival benefit. What we need to do-- those of us sitting up here and those of us in the audience-- is identify those who benefit-- only need one drug-- low toxicity. What happens when they fail to respond-- or they respond, and then they lose their ability to respond? What about the other drugs that we talked about?

How can we bring those T cells into the tumor? These are questions not just for cutaneous cell carcinoma, but for those tumors that were on the bottom of our x and y-axes. How do we get increased neoantigens to get an immune response? And then how do we find these resistant markers and overcome those?

But as I said before, it's a matter of time. If you were here three years, five years ago, you wouldn't hear this. And if you're here, hopefully, in a couple more years, you'll hear the answers to those dilemmas. And with that, I'd like to thank you for your time and thank the organizers again.