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IMMUNOTHERAPY FOR NON-SMALL CELL LUNG CANCER: WHERE ARE WE NOW, AND WHERE ARE WE HEADED?

PRESENTED BY: JASON NIU, MD, PHD

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Sarah Chart: Okay, so for our next speaker, Dr. Jason Niu will discuss the current treatment landscape and future direction for non-small cell lung cancer. Dr. Niu received his medical degree and completed residency training in general surgery at China Medical University before relocating to the United States to complete a doctorate degree in molecular pharmacology and, subsequently, a postdoctoral fellowship in pharmacology at the University of Illinois, Chicago. He is triple board certified in internal medicine, hematology, and medical oncology and joined Banner MD Anderson Cancer Center in 2016 where he's been focusing on clinical practice and research in lung, head and neck cancers. He currently serves as codirector of their lung cancer program.

Please welcome Dr. Jason Niu.

Jason Niu, MD, PhD: Thank you for your kind introduction. So I apologize, I'm going to talk about nothing but drugs and trials. So I have to say I felt quite proud before I listened to the talk. Now suddenly I feel deflated now because I'm keenly aware of the disparity, disparity at least in my field. So actually less than 5 to 10% patients or trial participants are patients 70 years and older. Actually, I did look at what I do because I'm a Phase I clinical researcher, so out of probably 200 patients I've enrolled, personally enrolled in the past few years, I look at actually their age. So 40% actually are older than 70 years old, at least in my own practice. So we're going to continue to do better.

So the topic I'm tasked with is talk about "Immunotherapy for Non-small Cell Lung Cancer: Where Are We Now, and Where Are We Headed?"

So these are my disclosures. Usually I quickly go through this before you can read.

So I want to touch basically four topics. First one for people who are not really involved in my field, I will talk about lung cancer briefly, in particular to touch upon the epidemiology of lung cancer. And then I'll talk about the background immuno-oncology. If you have heard this kind of pretty brief background, I apologize. And second, we're going to describe the current and emerging immunotherapy options and how to apply these kind of options in clinical practice. And last and not least, we'll talk about how to overcome so-called immuno-resistance, which is becoming one of the most important questions to answer for any clinical researcher and clinical care providers.

So lung cancer is common. If you're not aware of that, in 2023, although the cancer incidence is dropping, and particularly for lung cancer for men, starting from like the '90s, so lung cancer incidence is dropping. And for women, it's probably ten years behind that from 2000, so the incidence is dropping.

With that being said, we're still expecting up to 240, a quarter million new lunger cancer patients every year, and lung cancer can kill people. So it's actually lung cancer caused death is more than three I would say cancer types. Breast cancer or prostate cancer and colorectal, these are common cancers combined.

So the next speaker, Dr. Munoz, is a passionate, great speaker. He will try to convince you lymphoma is the most important thing on this planet. Actually not, it's lung cancer.

Well part of the reason so we're behind, so let's say compared with lymphoma because of diagnosis actually from other solid tumors. When you're diagnosed with lung cancer, and typically we're dealing with Stage IV, most of them end stage of lung cancer. And this actually is the most recent data from 2015 to 2019. So if you look at it, localized regional, meaning limited involvement and events, so up to almost 45/50% of patients among diagnosis were dealing with advanced cancer.

And then you look at on the right panel, so the five-year survival – I want you to remember this number because I'm going to come back referring to this number again and again – it's 7%. So if you are diagnosed with advanced lung cancer, your chance of surviving in the past and not remote past in the US is about 7%. It's not a great number, so that's why we're not proud of this number.

But I have to tell you if you are involved in general medicine practice, you're a general practitioner or family doctor, in the past few years, we have done a better job in terms of lung cancer screening. As a matter of fact, as I was preparing for this talk after a look at the new statistics, a few years ago when I was giving this talk to residents over here, so the localized actually five years before that, actually only 15 to 17%. So we have done a better job when it comes to early detection and early screening. We definitely need to do a better job. So the sober number would be only 4% -- 4 not 40 – 4% of screening eligible patients are being screened nationwide. So, definitely, I want it to go up to 80, 90%. Like breast cancer, we can definitely make a difference. Hopefully, five years from now we'll say actually advanced stage of undiagnosed is only 20% or 30% and this number can be reversed.

So another thing I think you're keenly aware of that's cancer related, so cancer mortality is actually dropping. So from 1990s, actually cancer mortality had dropped from 1% per year to 2% per year. This definitely has very little to do with the lymphoma actually, so it's largely driven by lung cancer, lung cancer treatment.

So if you look at lung cancer, in particular, so from 2014 to 2020 for men, the lung cancer mortality has been dropping almost 5% per year at a very rapid pace. For women, it's about 4.3%. And then if you look at the past 20, 30 years, lung cancer, actually the mortality has dropped by almost 60%. This is a stunning number. And for women in the past 20 years, about 35, 40%. So these for the most part, is due to the early detection of lung cancer. I mean you go to ER, you have a sneeze, they're going to do a CT, so you can definitely pick up some lung cancer. And then early screening it's very helpful as well. And another thing I would like to mention, which is related, obviously, to the talk today is the application of immunotherapy in advanced and in early setting as well.

So actually has been quite exciting in the past 10, 15 years also to be the medical oncologist in particular if you're involved in clinical research and medical practice in lung cancer. And these actually essentially depict what's happening in the past eight years. Starting from 2015, so we start to have the second-line therapy, then gradually move forward actually to first-line therapy, then in adjuvant setting, then in neoadjuvant setting. Now in 2023, we're going to have something available in perioperative setting. So it has been, you know, rightfully an evolving field.

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So if you have seen this, I apologize because I wasn't here this morning. These, in my opinion, really define the modern immunotherapy in solid tumor. So this actually is Dr. Jim Allison work when he was a young investigator at UC Berkeley in 1990s. So he's really interested in tumor immunology. So in this over here, so on the left panel over here when the antigen presenting cell, APC, present antigens to T-cells, T-cells got activated and then T-cell can further kill these cancer cells after a really complex circle.

But actually, there's something we call a checkpoint and he was most interested in. So in this particular one, we have two things over here. This is called costimulatory pathway and the other one, CTLA-4, is coinhibitory pathway. So these CD80 and CD86, also called B7 1 and 2, combine to either molecule to either stimulate the T-cells, so you enhance T-cell activation, or suppress T-cells.

So what he had shown in 1996, if you use a drug in that case similar to ipilimumab in mice – he cured a lot of mice actually with melanoma at that time – and then when you block the CTLIA-4, it can definitely enhance. So T-cell-mediated tumor killing. So based on this, we later on develop immunotherapy and, of course, Dr. Allison actually received Nobel Prize in 2018 as well.

So this actually is a landmark study, so that's why I want to mention it's not an actual lung cancer study, a melanoma study probably in 2010. When this was just published, I actually just graduated from fellowship program. I wasn't really impressed by the response rate. I think I was quite stupid. Didn't realize actually new era of immuno-oncology, it just started after this paper got published.

But if you look at the tail of the curve, so about 20% of patients they actually can stay alive years later. And that's why FDA approved in 2021. That actually was the very first agent in modern era, immunotherapy agent ipilimumab against CTLA-4 actually can be used and actually can cure patient with solid tumor; in this case, melanoma.

And we actually followed the patient for almost 10 years. So if you look at the curve once again, so 20% actually like the curve you usually see, come here basically everybody died after a few years. Ten years later, 20% of the trial participants are still alive and most of them are free of melanoma, so this is simply remarkable. It's unprecedented that with one single agent with reasonable toxicity you can potentially cure 20% of patients with metastatic disease.

And we also learned one thing which is also important, which is when you look at this, actually look at the tail not the head of the curve. So if anything you can take away today, it's actually look at the tail of the immunotherapy trial, which is very important because we are curing people, including lung cancer; we're going to talk about it in a few minutes.

So turns out CTLA-4 may not be the most important pathway. PD-1, PD-L1 pathway actually as another checkpoint is more important, at least for lung cancer and other solid tumors as well. So now we're looking at over here, so basically between the tumor cells, the T-cells activated T-cell came here trying to kill the tumor cells over there. You have PD-L1 with the ligand binding to the receptor PD-1. Over here it can actually suppress T-cell function. If you block this pathway and it becomes a very powerful tool, so T-cell on your immune system can kill the cancer cells, that's the very foundation of the most current therapy. And here at least about five, six different agents we're going to go through them briefly. So over here nivolumab and pembrolizumab and cemiplimab, which I helped developed, which are PD-1 receptor inhibitors

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or monoclonal antibodies. And the other three are PD-L1. The bottom line is we're targeting this particular pathway.

So, again, in the second-line setting, we're five years behind melanoma, but melanoma is a great solid tumor model. After that for the first time in 2016, we started to have two drugs that were available based on these three important trials. And these are outdated for sure. We barely use them in the second-line setting. You know, for the sake of discussion, when these three drugs were introduced initially, so to give you some perspective, in second line setting when you treat non-small cell lung cancer, the agent we have widely available is called taxane. The response rate is merely 7 to 10%, and nobody's going to survive. Most people are expected to die, and that's how I used to talk to them. Walk in the room, "I'm sorry, this is not curable. So this is all palliative. So by the way, you're expected to die in the next three to six months." There are exceptions, but the majority of patients will die within six months when you talk about second-line treatment.

So this is simply remarkable. Look at this response rate number one, and I told you it's not as important as the tail, so the response rate is higher. But when you look at the tail, some patients seem to do well actually years after. So in other words, I know medical oncology tends to use cured but how about let's be conservative, a lot of people can go into complete remission or stay in remission for years. I think by definition that's cured.

So we actually have three agents and Keynote-010 is another important trial as well. In this case, the difference is we actually have a biomarker. For the first time, we got a PD-L1. Using the PD-L1 level, we can define which tumor actually can be predicted to respond better to immunotherapy.

And then another agent, a PD-L1, so atezolizumab showed very similar results as well.

So when we follow the patients, so this is years later, five years later, for these patients who were treated either in the first-line or second-line setting, we are seeing long-term survival for the first time in history for lung cancer.

So look at this one here, you look at the treatment-naïve population, meaning at the time, so these guys were brave to be enrolled in a Phase I study. By the way, Phase I study, unlike what you used to think, I heard the comments just from previous speaker, actually I sort of disagree with that comment, so Phase I study I changed. In the past, we gave to the patient who had no options. Nowadays no. It's a very important part of anybody in clinical practice, including Dr. Munoz, who's going to talk to you who's one of the early investigators in CAR T trials we used actually to treat patients. Of course, you need to pick the right patient for the Phase I study as well but think about this is a perfect example these patients were not treated by anything else. But they took the courage to be enrolled in these new studies.

You know what, five years later, 23% they're still alive, and this has never been seen before. Absolutely unprecedented. And here if you have a PD-L1 over 50%, almost 30% are still alive. And I showed some data earlier, we were actually able to reproduce this data in the randomized clinical trials so telling you the strength of this Phase I study.

And same thing, you know, in the second line setting, we are seeing some long-term survival as well. That's why it's completely revolutionized what we do, what we can offer to patients with advanced non-small cell lung cancer.

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And can we push it to the first line and KEYNOTE-024 study is the very first study I have to say a lot of investigators were very nervous because chemotherapy has been our backbone to offer to the patients, suddenly you are offering patients without chemotherapy. I have to give credit to our trial participants. Actually they agreed to participate in this study, but you can see the difference. First of all, in the right population, PD-L1 over 50%, the response rate is higher. It's 45%, way better than 30%.

And second thing, again, I want to follow-up, but again and again, I think you remember, tail of the curve. Look at the tail of the curve. You can drive a truck through this, I think it's Tesla through this for sure. So there's a huge difference and some patients apparently actually kind of achieve long-term survival.

Now in 2023, we actually have three options now. So the first one, as I said, is KEYNOTE-024 study using pembrolizumab. Second one is called the IMpower110 study actually used a PD-L1 inhibitor, in this case, atezolizumab. And the third one is EMPOWER study. Like policy, I like politics, but I don't like powers essentially. Either IMpower or EMPOWER, but all these power studies show essentially the same thing. For this population, we are expecting up to 25 to 30% of patients to be alive after five years. So if you are seeing your patient, please stop telling your patient by saying, "You are diagnosed with Stage IV lung cancer and you are expected to die for sure." I'm not sure actually.

So I can tell you, I guess, that's part of my so-called antiburnout mechanisms. I have a long list of patients I have so-called cured over the years, Stage IV, brain mets; this list is getting longer every day. And I think we are able to cure some patients with Stage IV lung cancer. And in this case, of course, this is the best population with the PD-L1 over 50%. We're talking about 30% of patients actually five years later they are still in remission, or they are still alive at least.

What about adding chemotherapy? Would it help you because, you know, I'm a chemo doctor; I like chemotherapy. So, actually, there's a solid rationale to add this too. This also against what we have been taught at medical school or fellowship saying, "You give chemotherapy, actually you surprise patient's immune system" has not been true depending on what you give. And we actually tried. We are hoping for some synergistic effect. Right now I'm not sure we're seeing that. At least we're seeing some additive effect for sure.

And these are three trials. This is a subset analysis. So number one is so-called the KEYNOTE-189 study. It's also a landmark study when we use chemo plus immunotherapy versus chemotherapy alone in the first-line setting. And similar design was done in IMpower-150 study, in this case, is chemo actually plus anti-angiogenesis agent called Avastin. And the third one is KEYNOTE-407 study; in this case where targeting different tumor type is actually squamous cell carcinoma. Response rate is much higher. So, once again, this is unprecedented because for lung cancer I don't have, you know, lymphoma I don't have 80% response rate, but we are seeing that actually. When you use combination in the right population, you can get 60 to 70%. Majority of the patients are expected to respond.

But, unfortunately, when you look at, again, the tail of the curve, we're not seeing much improvement. As a result, it's very similar. So the consensus at this point for patients with PD-L1 is over 50%, for the most part, we're offering monotherapy to avoid unnecessary toxicities and, also, from overall survivor standpoint, it's not going to change much.

What about we add a second inhibitor, checkpoint inhibitor in this case CTLA-4? We have a few studies to address this issue. So the first one called the CheckMate-227, we actually use

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nivolumab with a PD-1 inhibitor plus ipilimumab, CTLA-4 inhibitor I just talked to you. It was the first approved agent to treat melanoma. Actually, we are definitely seeing some synergistic effect except that the five-year survival is not much better than single agent let's say pembrolizumab in this case. Of course, it's a cross-trial comparison. We add some chemotherapy. This is called a chemo-light regimen called 9LA. We give two cycles of chemotherapy then four, then you give these two inhibitors. Again, it's very similar. And, interestingly, when we use pembrolizumab as backbone, we add CTLA-4, in this case ipilimumab. This is called the KEYNOTE-598 study. We are not seeing any benefits in this case. Response rate actually absolutely the same, and the only benefit you get is toxicity.

So for this population at this point and, typically, we offer monotherapy. You have three options and I think pembrolizumab is the first kid on the block. We tend to stick to that, but I'll say the other two agents are equally effective. And then in some populations, we add chemotherapy. If they're very symptomatic, they have a lot of tumor burden, if they can tolerate, I'll just say I'm transitioning from my firm belief in the past I tended to use chemoimmunotherapy to monotherapy using one single agent in this selected population as well.

And, of course, you can use IO combination, although in my opinion, I'm not seeing much benefits in this case.

So what about PD-L1 less than 50%? Can we use immunotherapy mono agent? Has not worked out. So I didn't show data here, but using a similar approach, in this case, we have KEYNOTE-189, so for nonsquamous cell carcinoma. And then you will have KEYNOTE-407 for squamous cell carcinoma, so we are seeing a very good result. Not synergistic, at least I'm not convinced. So we're seeing some benefits as well compared with chemotherapy alone. But if you look at the tail of the curve, out of the five years follow up over here, so it seems to correlate with PD-L1 expression when you have a PD-L1 1 to 49%. So the five-year overall survival, and that's in both trials, almost reproducible, actually, in different histology is quite amazing. And we're talking about 20% survival. If you have PD-L1 less than 1% or negative, so you have about 10% chance to survive five years, it seems to correlate well.

And these two trials show a similar idea. It says that a combination does work, but the follow-up is a little bit shorter than the other one.

What about these short, you know, using combination of immunotherapy? Well I think it's an option, so if you look at the PD-L1 positive 1%, so you definitely see some better result. But I think I'm more impressed in PD-L1 less than 1% which negative population five years later, three years later at least we're seeing 25%. So I have to say in some patients with PD-1 negative, I tend to put them on a trial. If the trial is not available, I would offer them combination immunotherapy plus chemotherapy.

And this essentially is CheckMate 227, and it showed a very similar result.

Now there is one thing I didn't really talk about. For advanced non-small cell lung cancer, the most important thing actually when you see the patient first is so-called the next generation sequencing. To better understand the molecular operations, in this case mutations, and we have targeted therapy, this is a huge topic. Over here you can see we have up to 10 different targets, and we target them differently. Some are in the second-line setting, some are in the first-line setting. This itself is a huge topic, that's why I purposefully carved it out today. I didn't talk about it.

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But without knowing this data it's hard to offer patients this option PD-L1 expression reclassified non-small cell lung cancer but it has to work in conjunction with the molecular testing results. Otherwise, PD-L1, for example, you can have EGFR mutation which has been well established. You can have PD-L1 100%, but if you treat this patient with immunotherapy, the response rate is probably less than 3 to 5%. So these need someone who understands the both molecular testing result and PD-L1 is not as simple as it looks.

So, but let's say for the right patient over here, PD-L1 over 50% we are treating patients, for the most part, with monotherapy. Less than that we can use combination, or you can use immunotherapy combination in particular for PD-L1 less than 1%, although FDA approval actually it's for PD-L1 over 1% actually positive population.

Now what are the potential challenges and opportunities? So the biomarker-derived immunotherapy is the most important thing. I keep talking about PD-L1 giving the impression PD-L1 actually is perfect. Actually, it's far from being perfect. Number one, the response rate is not 100% for sure. Number two, and a lot of patients with a different mutation other than the targetable mutations, even they have higher PD-L1 expression, they do not respond. We need to have a better understanding and, hopefully, we can come up with better biomarkers.

A second thing actually is an ongoing topic in this field, how long is long enough? This is actually a good question to have, meaning patient's doing well, are you going to give patient immunotherapy forever, which is a huge burden. This kind of therapy costs about, you know, the wholesale price it's about $5,000 each time, and you know we charge way more than that. So let's say $20,000 for each treatment every three weeks you keep giving to one single patient for 10 years, can you imagine how much it's going to cost. And I told you my list is getting longer every year, so this is a big question. Right now we have an arbitrary cutoff of two years because all the trials are designed that way. So were designed that way, two years we stop treatment. My personal experience majority of the patients are doing well, but this question definitely should be answered in a more scientific manner instead of, "You know what, I don't have data, but I was going to stop at two years."

Have I stopped patient therapy before that? Yes, actually during pandemic, many patients afraid to come to see me to continue. I stopped so far and actually maybe only one or two patients had recurrence. You know, one patient I keep talking about with another patient who's on one of my Phase I studies in the first-line setting, again, he's part of my clinical practice, and he received combination. He only received one dose of therapy and he developed actually immune-mediated hepatitis. You know what, seven years later he's still in complete remission. So we really don't know the answer to this important question, but we need to understand this question so that the patient can get proper therapy without risking resources as well.

And the third one is how to overcome refractoriness or resistance. We will talk about that at the very end of the talk.

So for a patient with nonmetastatic, they come in traditionally to do surgery, but if have lymph nodes, I have to keep it simple. It's all we talk about on tumor board essentially. Just for the sake of discussion, if they have let's say lots of lymph nodes in the mediastinum, in that case, our approach is to offer chemoradiation. Or if they have less than one station involvement or no station mediastinal lymph node involvement, we can offer surgery if they're a good surgical candidate. And after that we offer chemotherapy. This has been in practice for almost 20, 30 years to the point you just feel almost uncomfortable talking to the patient because in the past 20 years we have done everything. You know, what's the chance? Will you talk to the patient,

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"I'll give you chemoradiation. Your cancer has not spread out to other sites." "What is my chance, doctor?" "Well 10%." So a potentially curable disease you are offering patient very toxic treatment and then 10% opportunity to survive. It's definitely not a number we want to stick to.

So to address the issue with the introduction of immunotherapy, I would say this is another landmark study. So this was a study called the PACIFIC study. So we designed the trial essentially, again, standard. You're eligible to receive chemoradiation. We'll give you chemoradiation. After that, we'll give the patient one year of immunotherapy versus placebo.

And this is the result. Number one, it's interesting, you can see we're giving the old therapy just like 20, 30 years ago. We're not giving anything fancy, actually, fancier. It's the same chemoradiation. It's definitely not 10%. Actually 30%. That means supportive care is important. If the doctor - we know what we're doing, even with a good old therapy, we can actually almost triple the result we used to deliver. Well I think the previous speaker's point was well-taken. If you look at these patients, their average age is 63.5 for sure. You don't have to look at trial actually. I'm not joking. Look at it, less than 65 for sure. But, actually, in real life, how many patients younger than 65 you're going to treat with this?

But if you look at this curve over here, when they receive immunotherapy for a year, you're definitely seeing a great result. So almost 43. Let's just round it up a little bit, almost one in two patients now compared with 10% five years later they're still in remission. As a matter of fact, this actually is more telling progression-free survival. Actually I like this curve. So 33% of patients will not have a recurrence. So five years for lung cancer, I do think we can say they're cured.

So, as a result, this is becoming a new paradigm to treat patients with concurrent chemoradiation. After that we will offer the proper patient; it is much more complicated than this. I would say for the majority of the patients it's appropriate to offer them one year of immunotherapy.

What about surgery? After surgery, we can offer chemotherapy coming off immunotherapy, yes. So this is called the Impower010 study, and the study is positive too. And I want to draw your attention to the hazard ratio, it's 0.66. So I know you may not be impressed by this. 0.66 translated would be you treat three patients; you can actually save one patient's life. But we're talking about a big population of patients.

So also, historically, the hazard ratio for any positive trial, you know, for lung cancer is 0.85. You have to treat seven, eight patients in order to save one person's life. So this is a remarkable result. So, as a result, this is definitely approved for patients. And, also, actually, I forgot to mention here, it seems to correlate with PD-L1 expression. Here they use so-called SP263. It's a different antibody but correlates well with 22C3, the one we're referring to PD-L1 expression. When you have PD-L1, just count it as PD-L1, over 50%, the hazard ratio actually is less than 0.5 which is unheard of for lung cancer. In other words, I treat two patients; I can save one person's life.

And this is absolutely worth it. If this patient develops metastatic disease, I can tell you everybody, you know, you can spend at least one million dollars on every single patient every year, so this actually is cost effective.

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And then we have another trial using pembrolizumab, and this trial, the result is very similar; hard to explain. Pembrolizumab has always been correlating well with PD-L1, but this one, for some reason it didn't. I don't have a good explanation, but the FDA also approved the use of pembrolizumab in this setting.

So in this setting, if a patient has nonmetastatic disease, they'd receive chemoradiation; the majority of the patients will receive one year of immunotherapy. If they'd receive surgery, we'll have two options essentially; we'll give one year of immunotherapy as well. You know, this is all arbitrary cutoff. We don't know if six months is better or two years is better, but in these trials, we're using one year as cutoff.

What about use in the neoadjuvant setting? We do have some animal study results. If you give patients immunotherapy earlier before surgery, they seem to do better. I can tell you when the trial was designed, we didn't know that in human beings. If it's true, well it cannot always be translated. We learn from animal models, but they are not human beings. So you can be a great mouse doctor, doesn't mean you're going to be a great human doctor.

But actually now, and in retrospect, we do have data now. So in the SWOG-1801 study, we actually treated patients, once again melanoma patient is a great model, for other solid tumors. When we give them neoadjuvant, meaning presurgical immunotherapy just a few cycles versus surgery first and then you give adjuvant – adjuvant is a Greek word means help – when you give this adjuvant chemotherapy, you know, the hazard ratio we just talked about is almost 0.5, meaning when you give immunotherapy earlier before surgery, it actually works way better. And I do believe this is where we're going as a field.

But this is the very first attempt, so we call the CheckMate816 study on our tumor board and we'll say, "Yeah, based on 816, that's what it means." Based on this study, we give patients chemo and immunotherapy. After that, we'll do surgery. So the result is quite stunning as well.

So if you give chemotherapy, the chance for a surgeon to go in, remove the tumor and don't see any cancer cells in lymph nodes and the primary tumor, that causes a pathological complete remission, PCR. In that case, if you give chemotherapy, we used to do 2%. But if you give chemoimmunotherapy, it's 24%. It's 20 times better. Okay, if you use so-called the major pathological response called MPR, meaning there are less than 10% of viable cancer cells still in the tumor, if you use that, actually it's also a good indicator, a surrogate marker to predict a good long-term prognosis. In that case, actually, 37% versus 9%. So this is a great result.

And if you look at so-called event-free survival, meaning without death, without progression of disease, if you follow them, you can definitely see a significant difference. So this, as of now, is becoming another standard option for patients. So that's why we give patients chemoimmunotherapy, again, in the right patient population. I didn't really go into details, but this is a great option in the proper patient.

And then as we speak, this new trial result, as far as I know, going to be becoming another option will be perioperative option is as you give it and after you give adjuvant therapy. We don't know which one is better, and the company already announced this is a part 2 trial. We are expecting another option in 2023 for sure.

So what about where we're going in this setting, nonmetastatic setting? So I touched upon that topic briefly the timing of IO. I do believe we are moving to the neoadjuvant, or at least our

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biased opinion, although we don't have data for lung cancer yet, learning from immunotherapy model. And in melanoma, I do think this is where we're going.

Second thing, so that's why are we going to offer patients neoadjuvant before surgery or after surgery or perioperative? The more the better. Of course, the industry cannot promote that idea, so the longer the better, the more the better. We don't really have an answer. But I have to tell you in patients who achieved PCR, pathological complete remission after these three cycles chemoimmunotherapy, we followed them for two years in 816 study. None of them has recurrence, so making me believe in that population for the first time in history, I was joking with our surgeons. I said, "Actually, for the first time in history, your surgery actually can save money." Because you do surgery, they achieve pathological complete remission. I usually don't offer them another year of immunotherapy anymore. I know this is relatively smaller trial, only 400 patients, but I think that's the best data we have, and I actually feel quite comfortable to offer patients. That way I think we can save money actually and the patients don't actually develop long-term side effects from immunotherapy, which is totally different topic.

So what about the patient after surgery, they actually don't need any therapy at all? Can we come up with a way to answer this question? Well in this case, we start other than using PD-L1, we can use so-called circulating tumor DNA and a lot of trials are ongoing. After surgery, we do know that some patients do not need any therapy. They don't need chemotherapy. They don't need immunotherapy either. And in that case, if we have a circulating DNA or something like that to direct our clinical practice, that would be ideal situation. Some patients we can ramp up the treatment, some patients we can de-escalate this kind of treatment. All these treatments are not free. Patients suffer from significant side effects, including financial toxicity as well. So I think if we can de-escalate this kind of treatment, that would be great.

On the other hand, if patients actually do have circulating tumor cells and you know these patients are expected to have recurrence, I don't really believe in that situation you just give a longer immunotherapy patient is going to do better. I think we need to come up with a smarter approach. In that case, it does make sense to ramp up the treatment. We have a few studies ongoing trying to address this issue.

So I'm going to spend the last few minutes to talk about resistance to immunotherapy. When immunotherapy was first introduced, as a simple medical oncologist, I thought, oh I think we're going to have a homerun now. We have been studying this for 100 years from Colley's vaccine back in 1908, so now 100 years later, we're able to see some creation of immunotherapy. You know, your immune system is adapted now; I think we can get rid of cancer. Actually, that has not been true.

Number one, the response rate is not 100%, as I mentioned earlier. Second thing, you look at the different side of the coin. So median overall survival about 30 months, you have 30% of patient is going to stay alive out to five years, but majority of patients what about the other 70%? They either died or they had progression of disease, or they cannot continue because they developed side effects. Obviously, this is a question we need to address.

In order to understand that, so we need to understand it is actually a quite complex process. So when cancer cells present antigen, I showed in the cartoon how T-cells get activated. And T-cell activation and priming is the issue. And sometimes they don't have antigens to present. And after the T-cell got activated, this is literally happening in your body. It's not like you give this and it's going to work. Your immune cells actually need to be activated in order to travel to where the cancer is. And actually for solid tumor, unlike liquid tumor, you need to infiltrate the

tumor and then, in this microenvironment, need to be engaged, latch on, and kill the cancer cell. It's definitely not one step. Actually, at least seven steps are involved and at each step you can have some hurdles so that immunotherapy may not work.

So we actually start to understand a little better there are some interesting mechanisms. For example, your patient cannot, you know, the cancer can suppress the so-called cancer antigen with other new antigens, and you cannot present antigen; there's a problem. Or in the microenvironment or some other checkpoints actually got involved, this T-cell can get exhausted and cannot penetrate, may not work. So all these need to be understood better and actually addressed properly.

So I'm going to talk about just a few things. As I said, I'm an early drug developer, so that has been my passion as a molecular pharmacologist. So I'm going to briefly talk about what I have been involved in in the past few years, not even mentioning the trial name to stay neutral. I'm not trying to accrue more patients over here.

So this essentially is how to present the cancer antigen, if this cancer doesn't present antigen what we can do. We can inject this virus. I know it's a buzzword in the past few years. If you inject this live virus and absolutely made in the lab, so you actually inject this virus into the tumor and this virus, so-called oncolytic, can infect the tumor cells and then cause inflammation and cancer death. It's more complicated than this, but the bottom line is suddenly the cancer antigen can be presented to T-cells. And this at least has been some great success in this. As a matter of fact, the first generation, so-called the T-VEC, has been approved by FDA to treat melanoma, and we are working with more sophisticated viruses. Essentially, were bioengineered as in the lab and these can actually express PD-1 inhibitor or CTLA-4 inhibitor or cytokines, so making it more complicated. So we call the next generation oncolytic virus.

So what about the T-cell priming? Well this is actually right now everybody is doing this. I have probably five/six different molecules I'm working with every day essentially to target this, you know, I give you basically two pathways. One is CTLA-4. Second is PD-L1/PD-1 blockade. It's way more complicated than that, so you have probably 20 or more than 20 different checkpoints over there and each of them is being studied.

I can tell you in my own experience by working with almost the majority of the molecules in the past few years we are definitely seeing an efficacy of different checkpoint inhibitors. We definitely need a better biomarker to select the patient population. Almost every molecule I work with I have one/two lucky patients they just responded and went into remission, but the majority of the patients simply do not respond. So we definitely need to do a better job. Not saying it doesn't work, but it doesn't work for the population at this point.

What about tumor microenvironment? So actually believe it or not, we're actually giving patient oncolytic virus infusion. So the patient comes in going to receive a bag of live virus, and I have to respect my patient's courage. And I'm definitely now seeing that. So I have many African-American patients and actually Hispanic patients as well; they do need to trust you. When they trust you, you talk to them, they absolutely ask to participate in the trial. They don't trust you they're not going to because you're not going to infuse virus into my vein with a bag of virus every few days. So that actually, one, we need to address this.

Second, I'm working with a company to develop a bispecific antibody against VEGF and PD-L1, so can act against two things. And another one we're currently working on actually again EGFR and NKG2D, so basically to target patient's innate immune system as well.

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And then about CAR T, so I basically set the stage for Dr. Munoz sitting there. I can tell you the bottom line is I've been involved in at least two TCR trials and CAR T trials. It has not been working, although we're seeing some early promise and, hopefully, we can learn from liquid tumor oncologists we can apply this in lung cancer as well.

So the bottom line is we talked about a few topics very briefly. I do believe this is definitely not the end. It's actually end of the beginning. Our future is bright, but we still have a long way to go.

Thank you for your attention.

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