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The Next Generation of Care: New Treatment Frontiers in Immunotherapy-Resistant Advanced Squamous NSCLC

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Dr. Peters:
Hello, and welcome to this educational activity. My name is Dr. Solange Peters, and I'm working as the Director of Oncology in Lausanne, in Switzerland. Today, I will be discussing emerging strategies in immunotherapy-resistant advanced squamous non-small cell lung cancer. So let's begin.

We had the opportunity with colleagues to publish this integrated framework describing the specific biology of squamous cell carcinoma. First of all, the somatic DNA alterations. On the contrary of non-squamous non-small cell lung cancer, unfortunately, it's not possible to identify actionable alteration in squamous carcinoma. However, the exonic pattern of mutations include a lot of tumor suppressive genes like p53, PTEN, PIK3CA, KEAP1, really leading to a biology of aggressive disease. We also are able to describe a certain number of altered copy numbers, segments, as well as structural variations very typical of squamous cell carcinoma, but again not actionable.

Then you're able to describe how the signaling pathway, the cellular signaling pathway, presents aberrations, right, through the oxidative stress response to the squamous differentiating signaling, as well as inflammatory signalings; all of them creating a malignant phenotype in this cancer cell.

Unfortunately, also in squamous cell carcinoma, the tumor immune microenvironment has to be told to be a cold tumor microenvironment, despite the high copy number variant burden and composition of immune cells which are strongly immunosuppressive with Tregs with Th1/2 ratio being in favor of Th2, as well as the composition of the expression of immune checkpoints like PD-1, PD-L1, CTLA-4, TIM-3, TIGIT. So all of these describe this microenvironment.

This is also well portrayed when you look at the proteogenomic of the tumor immune microenvironment, with, for example, the canonical WNT signaling promoted pathway, which is strongly expressed here and promotes not only tumor proliferation but also describes an immune evasion.

And last but not least, all of these considerations lead us to try to identify where we can potentially create new treatment strategies. So, of course, we are moving faster to potential cellular therapy, cancer vaccine, because of the very high number of mutations targeting the checkpoints that we have not sufficiently exploited, and maybe some cell surface biomarker.

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And today, we will focus a bit on the checkpoints that we can potentially target a new mechanism of immune strategies.

We were used, when I started oncology, to describe squamous cell carcinoma as being connected or associated with a very strong negative prognosis as compared to non-squamous. Since that time, we have moved to immunotherapy. So all patients, most of them receive an immune component, an immunotherapy, and while the prognosis is still better for non-squamous as compared to squamous, the difference has become slightly lower. With non-squamous having a median OS in Flatiron databases of 24 months and squamous 22 months. So while they're separate, they separate less than was described before the era of immunotherapy. Median PFS 7.5 versus 6.7, and when you look at the 1- and 2-year survival, there is a difference. But I think the way we sequence treatment, but more than anything, the presence of immunotherapy has erased a bit of this difference we had historically. But always stressing here an unmet need, we need to improve these overall survival curves in both subtypes of cancer, by the way.

In terms of what we do, big strategies—and my idea is not to cover or review the ESMO guidelines—usually, we classify our patients according to the PD-L1 expression. Regardless of the PD-L1 expression, you can always give immunotherapy and chemotherapy. When you are in a high PD-L1 expression, you can skip the chemo and allow yourself just to give immune components. And while you are negative PD-L1 which is really an unmet need because here the chemo anti-PD-1 and anti-PD-L1 does not work well. When you are in negative PD-L1 you'd like to add a dual checkpoint inhibition with the CTLA-4 and I think most of the colleagues in the field are now agreeing that this unmet need is partly addressed adding a CTLA-4 with all the toxicities it means. But that's what we have usually in the guidelines. So where can we go from there to better survival curves?

So we have tried, and this is also a very nice *Nature* review we did with the colleagues and Martin Reck being the first author, showing the very strong rationale supporting phase 1, phase 2, and phase 3 trial. But unfortunately, this long list of negative phase 3 trial. And you can see here that all of these trial end up with hazard ratio for survival, which are not significant. And they target many pathways, right? Anti-angiogenic pathway, TAM pathway, some ADCs also trying to complete what can be done at chemo and IO resistance. And recently, an ATR inhibitor, the ceralasertib plus durvalumab versus the usual docetaxel. All of these trials have failed to show significance. So it means that fighting against docetaxel in second line in an environment where you already have to face chemo resistance and immunoresistance leads to that, right? Whatever you do, TAM TKI, IO combination with anti-angiogenic, you cannot significantly and meaningfully improve PFS and overall survival versus docetaxel.

So we need better ideas, right? This is a long list of failure, and this is basically what is left. So in adenocarcinoma on the left, what we like to focus today on squamous cell carcinoma, this is what we have left: docetaxel plus/minus ramucirumab, and some other variants of chemotherapy. So what I wanted to stress here is really the unmet need because when I show this slide to my colleagues, oncologists, nothing in this list is really exciting. So we need to find new ways to move.

Here we wanted also to maybe rationalize some things that we sometimes do, and I'm the first to have tried, is when you fail chemo IO front line, when you come to the second line, should you continue the immunotherapy? So, is there evidence for a PD-L1 or PD-1 inhibitor after failure of this agent? So the answer is unfortunately not. If you look at the prospective rechallenge, response rate is less than 10%. When you try to switch from a PD-L1 to a PD-1 or the other way round, there is a progression on the first CT scan. And when you look at meta-analysis, there's no meaningful response rate or benefit. To use IO after IO, let me be more precise—to use PD-1/PD-L1 after PD-1/PD-L1 failure. So really, we are a bit hands empty of good options.

We try always, and in all of these trial, we try to do that to understand what it means to be resistant to IO. So here you can classify, and that's the classification of the Immunotherapy Society between primary resistance and acquired resistance.

What we call primary resistance is refractory to immunotherapy. In that setting, the patient never presented with a response on their IO, and if there was a stabilization of the disease, it was less than 3 months. And in that environment, and we made lots of preclinical studies today. I say lots; it's hundreds of patients, maybe 200, something like that. But we were able to show a pre-existing immune exclusion or immune suppression in this patient subgroup, and even to describe what was mechanically involved here.

On the contrary, acquired resistance means that you had a benefit, a response, or a stable disease of more than 3 months. And here you potentially really have this mechanism of T-cell exhaustion, T-cell dysfunction that you can counteract and activate the immune system. And maybe these two scenario define different potential for re-engaging the immune system.

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So it's quite important in every trial to really keep in mind what is the population you treat with, of course, for immunotherapy probably a better potential for acquired resistance versus refractoriness.

So in all and all, what remains in terms of mechanistic, is these three categories that I would like to show you. First of all, we are trying and we continue to try to enhance immunogenicity. But for that, you need to have some kind of immune response possible, of course. But you can enhance immunogenicity, for example, using vaccines, which has become very fashion again, or antibody-drug conjugates, but maybe not in late lines, but earlier, or radiation, or some targeted therapy.

You can also try to reinvigorate the immune T-cell function, which would also potentially work in immune-refractory kind of tumors. And here we go back to these immune checkpoints. But you can also imagine to engineer CAR-T cells or TILs or go to co-stimulatory pathway.

And of course the most difficult is to target the immunosuppressive tumor microenvironment. And here we speak about the TAM receptor, but I have shown you how much we fail with sitravatinib, cabozantinib. We speak about the adenosine pathway, but with today no evidence really of efficacy, even if rationally it makes sense. Anti-angiogenic have limited activities. And today I'd like to speak to you about a checkpoint, but also a Treg component of the drug, gotistobart, which is really one of the first data of management of treatment, looking and focusing on the tumor microenvironment, which is successful. So there's always a development to think about targeting the immunosuppressive environment.

Targeting Tregs is not a lost idea coming right now. It has been exploited using many strategies. We know how Tregs are modulated by all these immune checkpoints, and you can see here that many failed. Right? The anti-GITR, for example. The anti-TIGIT will also modulate the Tregs present systemically and in the tumor microenvironment. The TNFR2. So all of this describe many ways to potentially modulate the quantity and the quality of Tregs in the tumor microenvironment. But of course, today I'd like to focus on one: is to use the CTLA-4 which is expressed on the surface of Tregs, so anti-CTLA-4 to try to modulate the presence of Tregs.

Of course, just to speak about the environment of potential Treg modulators, I just would like to make two slides about something again very fashion. I hope is going to be successful. Is a CCR8? CCR8 is targeting the Tregs—that's the chapter we discussed—but has a specificity of being expressed on the surface of Tregs, specifically when the Treg is engaged in the tumor microenvironment in an immune suppression of the attack to the cancer cell. So it's something which constrains or confines the Treg suppression in the tumor microenvironment. So there is some rationale for that preclinical, where you can inhibit when you give an anti-CCR8, you can deplete the Treg, you can activate the CD8, you can observe in a phase 1 trial or some phase 1 trial some specific responses, but it's a bit early in non-small cell lung cancer.

Today, one of these compounds is going at an expansion cohort with an anti-PD-1. So we'll see if this very large class of compound will lead to evidence, because that's maybe what Tregs might also be targeting. And I must tell you, there's a list, and I have read on recently the slides of potentially 20 anti-CCR8, I would say, elements and drugs which are being developed. But let's focus today on where we have data because we don't have data on CCR8 in lung cancer today.

CTLA-4 has data. We have tremelimumab, we have ipilimumab. We know their toxicities. Keep in mind what Jim Allison was telling when he got the Nobel Prize, really telling you it's not the same to block PD-1/PD-L1 because here you focus on the effector phase of the immune response, so meaning that you need to have an immune recognition, but you reinvigorate your dysfunctional tumor-reactive T cells, so you make them active again. When you target CTLA-4 you are in the priming phase, so you create the repertoire of T cells which are able to identify cancer cell, expanding and diversifying the T-cell repertoire. You can even broaden it, so potential also options to be late in lines of treatment. And of course, some of the mechanistic around CTLA-4 is about Tregs because blocking CTLA-4 means also depleting Tregs systemically and in the tumor microenvironment.

So the challenge that we have is how much can you deplete Treg systemically without having too much side effects, and we know the side effects of ipilimumab and tremelimumab, which prevents many of my colleagues to use that. Can we potentially minimize this depletion of Treg systemically and focus on the Treg depletion mainly in the tumor microenvironment? And that's what I would like to share with you today.

Because thinking about using CTLA-4 broadening the repertoire in late lines, we have tried and we have failed. Adding the CTLA-4 at resistance, thinking about this broadening needs really a therapeutic window. You need to be able to really expose the immune system

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to enough CTLA-4 blockade to reactivate a T-cell repertoire and an immune response. And probably today, because of this therapeutic window, or because just of the strategy, we have no data about ipilimumab and various CTLA-4 combinations after resistance to anti-PD-1/anti-PD-L1. So we need new strategies, and that's where gotistobart is coming.

So as I was telling, the major obstacle for CTLA-4 targeting is the immune-related adverse event. So we see several toxicity when you add a CTLA-4 to PD-1/PD-L1, and we have been knowing this toxicity since the development of ipilimumab. Remember, in the early days of melanoma, we're using high-dose ipilimumab, 10 mg/kg. So now we know what it means.

So that's why I'd like to introduce the mechanism of action of a CTLA-4 targeting, aiming again at depleting Tregs, which is using a pH sensitivity parameter. So meaning that this antibody will not act in the same way depending on the pH of the microenvironment, because as you know, the tumor has a completely different pH than the systemic level. And here you will be able to see on this figure that this will result in a recycling of the CTLA-4 which is different at the systemic level as compared to the tumor level.

The pH-sensitive binding at early endosome is required to preserve CTLA-4 checkpoints and basically to be able to completely deplete the Tregs in the tumor microenvironment. However, at the systemic level, the endosome recycling will not happen, meaning that you will not have such a depletion of the Treg at the systemic level, allowing at least in terms of therapeutic window to enlarge your therapeutic window and give more of this anti-CTLA-4 with less toxicity at the systemic level and a higher toxicity at the tumor level. So really allowing you to increase the dose, which doesn't mean it will have no toxicity, but to have a better therapeutic window, sparing the systemic level, focusing and being more active at the tumor level.

So, anticipating how gotistobart can work, it's a selective depletion of tumor-infiltrating Tregs within the tumor microenvironment. We know that advanced squamous small-cell lung cancer are aggressive and have a relatively high abundance of Tregs, as I said initially. So that's a good target tumor. And the pivotal phase 3 clinical trial is ongoing to evaluate and certify that this strategy is feasible and active in squamous cell carcinoma.

There are some regulatory milestones that you can see here with some NMPA breakthrough designation in China and a U.S. FDA Fast Track and Orphan Drug Designation this year.

So this is again how gotistobart works. It's a pH-sensitive anti-CTLA-4 which optimizes the dissociation intracellularly preserving CTLA-4 recycling, and enhancing Treg depletion specifically in the tumor microenvironment. So this is recycled and Treg depleting mainly in the tumor microenvironment.

This is a phase 1. So gotistobart was used in monotherapy. Remember my table. Remember how much I told you that IO doesn't work after IO. So these are the data after IO of gotistobart with this pH-dependent mechanism. Here's the response rate in late line, therefore, is 22%. Here, 1/2 of the patient had a squamous histology, so it's still way more than we describe with docetaxel usually. And I found the waterfall plot very impressive as compared to the ridiculous response rate you could observe with ipilimumab or tremelimumab, or even anti-PD-1 or PD-L1 in the same circumstances. If you look at the spider plot, what's interesting is the durability of some of these responses, which is really promising, right?

In terms of having the swimmer's plot, of course the patients were exposed previously to all of a variety of treatments, right? PD-L1, CTLA-4 inhibitors, TIGIT inhibitors. So you can really see some, even sitravatinib. So you can see that some responses and some durability are observed a bit regardless of the previous exposure or across previous exposures to treatment. So this is really the rationale to tell, okay, let's try to go in second line versus docetaxel, of course, with gotistobart monotherapy, and showcase that you can beat docetaxel in a controlled manner.

So this is a PRESERVE-003 trial where you can see that these patient have received platinum, have received IO, and in that setting they are randomized to gotistobart or docetaxel. There are two stages, right? The first stage 1 is a dose optimization stage where gotistobart is used at two different doses, but already comparing to docetaxel for the first signal and randomizing 1:1:1 the patient to 2 doses of gotistobart or docetaxel. And of course, once this first stage has been passed and it is the current status, we go to the formal phase 3 controlled trial with gotistobart with two loading doses versus docetaxel.

So I'd like to show you all the details about the stage 1. Right. In these two stages, the stratification was histology, squamous versus non-squamous, the brain metastases yes or no, and asymptomatic brain mets were allowed in this trial, the performance status, and the

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region. The primary endpoint is overall survival, of course also looking at response rate, PFS, and this will be blinded, independently reviewed by a group of radiologists.

So basically, I will focus on this stage 1. And as you can see in the manuscript, also with that, to focus on this further development is to focus on squamous cell carcinoma because there was an incremental and a real activity being still and confined to the squamous histology in the stage 1. Okay?

So this is where we are. We have the non-squamous subgroup, 120 patients that are described elsewhere, but I'd like to focus today on this unmet need of squamous cell carcinoma, where you can see 87 patients being treated with this dose, finally of 6 mg/kg with two loading dose that is continued further down the road. This is the disposition about the patients, right? They have squamous histology, so majority of them are smokers, previous or current smoker. In terms of PD-L1 expression, you can see that you represent the usual balance of PD-L1, but a certain number of patients have no PD-L1 being tested. But remember, we are in late lines anyway, it's not very important. And brain metastases are found in 13% of these patients. All patients had received prior platinum and prior IO, with 80% of them having received them concurrently, and of course some patients receive first the IO and then the chemo when the PD-L1 is high. Okay?

So this is the first very interesting slide where the response rate in squamous cell carcinoma after chemo and IO is 20% versus only the usual 4%-5% for docetaxel. The series today describes a response rate between 5% and 10%. We are more or less in the usual ranges of response rates to docetaxel. Very promising 20% response rate for the gotistobart.

Most exciting for me is the durability of this strategy, right? The median duration of response of 11 months was described. It's visually very obvious when you look at the spider plot versus 3.8 months with docetaxel.

And even more interesting is this 12-month PFS rate of 25% with gotistobart and the usual 0% at 1 year with docetaxel. When you look at the median PFS because of the crossing of the curves, that's probably where it's less obvious to see it, but you can see that later down the road the plateauing is within the gotistobart. The hazard ratio here was 0.69, and remember PFS was a secondary endpoint.

The primary endpoint is overall survival, and here the median overall survival was 18.5 months, versus 10 months for docetaxel leading to a hazard ratio of 0.56 with a *P*-value of significance.

Importantly, here we have now a kind of an interesting duration of follow-up of more than 2 years, making these data quite stable in time and not to change significantly later on.

Importantly, the toxicity. So, of course, because of the therapeutic window and the increase of CTLA-4 inhibition that we want to have in the tumor microenvironment, there are still grade 3 and more toxicities seen with docetaxel and gotistobart. By the way, the interesting thing is the proportion are more or less the same in the two treatment arms, and leading to discontinuation in more or less 13% treatment-related for gotistobart and 5% for docetaxel. So still, we need to be aware of toxicity and manage them. Seven patients, 15%, received gotistobart for more than 12 months.

When you look at the toxicity, docetaxel is chemo-related. Gotistobart, it's immune-related with of course what we know: GI toxicity, AST/ALT increase, and the other, fatigue and rash, what we observe with CTLA-4 inhibition. Just keep in mind that these are mainly low-grade toxicity, and some specific, very well-known toxicity can be grade 3 and more here in dark blue, with colitis and liver test perturbation being predominating here. So a profile we really know, but an efficacy which has an incremental as compared to what we know.

Immune-related adverse events occurring in more or equal of three patients with gotistobart you can see on this slide is diarrhea, colitis, and transaminitis, and that is why the close monitoring is essential, particularly for the colitis and of course the lung disease in this patient population, you have an immune-mediated lung disease that cause pneumonitis or ILD in 6.7% of the patients, but very rarely grade 3. But of course, it has to be taken into account in the follow-up of the patients.

So, after a median follow-up of 25 months, median overall survival was 18.5 versus 10 months of gotistobart versus docetaxel, leading to a significant hazard ratio of 0.56. The responses were more durable with gotistobart, with an amazing median duration of response of 11 months versus 3.8 months. The 12-month PFS rate was 25% with gotistobart versus 0% for docetaxel. The safety profile of gotistobart is

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consistent with CTLA-4 inhibition and with T-cell Treg depletion, and at a systemic level, but probably with a way increased efficacy of Treg depletion in the tumor microenvironment, leading to this efficacy result. The data indicate that the unique mechanism of action enables patients to tolerate this high dose and achieving therapeutic efficacy thanks to the mechanism of action.

The enrollment has reached the target for the pivotal stage 2 portion of the trial, and now we are looking forward to see how these data mature and might confirm at the global level the efficacy of gotistobart.

In terms of perspective, and for me, it's quite important to tell— and I've been working on many of these trial—how many failures, despite good rationale, we had to face for our patients and in the community. So having today such results, meaning that suddenly you almost double the survival in a specific unmet need with a squamous cell carcinoma, is really something quite fantastic to see. So I'm looking forward to see how the formal controlled phase 3 portion of the PRESERVE-003 will let us know about the further development of gotistobart. With such results, the community will be buying it without any problem. Managing the toxicity of CTLA-4 is well known to us because of melanoma and because also some non-small cell lung cancer data, and we would be very happy to use it would this be firmly confirmed.

With that, we will conclude today's activity. Thanks so much for listening, for your participation, and your kind attention to this presentation.

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