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What Are the Risks of Neoadjuvant and Adjuvant Immunotherapy in Resectable NSCLC?

Announcer:
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Dr. Peters:
My name is Solange Peters. I'm the head of Medical Oncology in Lausanne, in Switzerland. And I would like to discuss with you the potential risks of neoadjuvant and adjuvant immunotherapy in resectable Non-Small Cell Lung Cancer. It's a focus on safety of such strategies. We have been seeing this amazingly growing network of trials across companies as you can see. And using the usual compounds anti-PD-1, anti-PD-L1 in the adjuvant and the neoadjuvant setting.

We already have the reading of two adjuvant trials: The IMpower010 with one year of atezolizumab being given after surgery and chemo. And KEYNOTE-091 giving pembrolizumab for one year after surgery, plus minus chemo led to the investigator. We also have seen the wonderful data of CheckMate 816 which is pre-cycle of neoadjuvent chemo-IO before surgery, a short treatment which ends at surgery. And the landscape, as you can see, is going to be enormously larger. Is going to grow a lot with all the readings of this ongoing trials. Please be aware that the MERMAID program was closed but is still on that slide because of the historical construct.

We have been seeing these two adjuvant trials that I discuss in another recording, but very importantly, the IMpower010 and the PEARLS trial use adjuvant immunotherapy for a year after radical surgery for Stage IB to Stage III Non-Small Cell Lung Cancer, according to the 7th TNM classification. And as you can see, both reflect benefits of immunotherapy versus observation of placebo in these surgically resected patients. Of course, endpoint stratification factors are slightly different, but this strategy is beneficial. With now a registration trial of atezolizumab for one year in Stage II to IIIA positive PD-L1 patients in the US, China and Japan, and more than 50% on Non-Small Cell Lung Cancer in Europe. And potential intent to treat submission for pembrolizumab, which is ongoing. Of course, when you deliver immunotherapy in the adjuvant setting, you probably remember that in melanoma there was some suspicion that the profile of toxicity and even the magnitude of toxicity, the safety issues could be slightly different, even major and more importantly observed as compared to metastatic setting.

On this slide, you can see in IMpower010, the Grade 3 and 4 treatment related adverse event occurred in 10% of the patients with 28% leading to interruption. And interestingly, 8% being Grade 3-4 immune-mediated adverse events. So basically, in term of numbers for treatments rated Grade 3-4 as well as immune-mediated adverse event, it's very comparable with metastatic disease, maybe. So those interruption is slightly higher. But keep in mind that the adjuvant setting is a setting where compliance has always been shown to be way inferior to any kind of metastatic setting. And this is about the recognition of the fact that in the adjuvant setting, we do treat a certain number of patients who are already cured. And they have to be informed about it. But basically, no unexpected toxicities.

For the first trials of pembrolizumab trial, here I want you to show the adverse events, and particularly here the adverse events which you usually suspect for immunotherapy. And to make a long story short, I would say, if you look at the pembro and the placebo, it's quite interesting to see that when you deliver placebo, you also observe some toxicities, which means that the disease has its own impact,

right? And basically, again, absolutely no unexpected adverse event. And very importantly, the same safety profile as it was observed when pembrolizumab is used as monotherapy in advanced Non-Small Cell Lung Cancer. So, what do you do in the adjuvant setting when you have toxicities, you encounter toxicities? And now we can speak mainly about the adjuvant setting because we have a very low level of information about neoadjuvant. But anyway, think about applying immunotherapy in the curative setting. In the adjuvant setting, you need of course to be very conservative. Remember that the adjuvant definition means that you treat at least, if not more, one patient out of two without any impact because this is relapse anyway, or because the patient is already cured. So basically, it's about applying the guidelines. And on the next slide you see the ESMO Guidelines which are in pre-proof because they just were accepted. You need to apply exactly these guidelines which to me are the most, I would say, easy to use and recent guidelines, by the way. You have to apply that in the conservative manner. Remember that on the contrary of Stage IV disease, some of your patients will not need this immunotherapy or not extract any benefits. So, apply guidelines line by line conservatively.

Doing that, mortality should be close to zero if not 0%. So, first type I have shown is about, in general, the cutaneous side effects which happen quite often, I must the rash. But of course we always try to consider in lung cancers the risk of pneumonitis. So, lung cancer infiltrates particularly because you do follow up of these patients every three to four months. So, what to do if you have an infiltrate with a symptom of Grade 1 and so on and so forth? So very important guidelines on this slide on lung cancer toxicity. Let's move on the next slide about neoadjuvant strategy. Neoadjuvant strategy poses additional questions: The first question is to know if you take any risk of not being able to perform radical surgery. So, it's a very important question. Do you take any risk of ruining security intent, strategy and context? So, we have these two trials: CheckMate 816 against 3 cycles on NIVO + chemo versus chemo followed by surgery. We have another phase II trial: The NADIM II which is against 3 cycles of NIVO + chemo versus chemo followed by surgery but restricted to this very locally advanced disease Stage IIIA and IIIB.

So, let's look at what we know for this trial. So, we know that it's quite amazing. The pathological compete response goes from 2 to 24% with nivolumab in CheckMate 816 from 7 to 37% in NADIM II. So amazing pathological compete response. And amazing how that ratio for EFS 0.63, 0.48 respectively for CheckMate 816 and NADIM II. So really showing a super high magnitude of benefit. Just keep it in mind, one thing I did not present, is NADIM II has an additional six months, not one year but six months of post operative immunotherapy which is not the case in CheckMate 816.

So, let's look on the next slide at Patient Dispositions and Surgery. If you look at NIVO + chemo versus Chemo, in the NIVO + chemo, you have 94% of the patient completing the neoadjuvant treatment and only 85% in the Chemo arm, which makes you think that the addition of nivolumab is not a reason why patients would discontinue or be poorly exposed and imposed in term of the intensity to noeadjuvant treatment. Very interesting data. If you look at surgery, 83% had definitive surgery in the NIVO + chemo which is maybe worrisome because 17% did not.

So, what happened with this patient? Is it reflecting your daily practice? So patients are eligible, they start the treatment but they don't go to surgery, 17% looks a lot. But in that trial, look at the Chemo arm, 75% did not undergo surgery. So of course it's worrisome, but it's more prominent in the standard control arm with chemo only. Very interesting data. Let's go to the next slide.
So, if you look at what was described, what could be the pitfalls, right? The failures reason. So, the reason for not completing neoadjuvant treatment include, of course, disease progression. But only more or less one person in both arms. So, study drug toxicity, 6% in NIVO + chemo, 7% in the Chemo and an additional other 7% in the Chemo arm, which might be, we don't know why, but a refusal of the patient to continue which is not observed in the NIVO arm.

So, nothing unexpected here, and maybe in line with what we would have in the daily practice without measuring it. So, reasons for canceling surgery. The NIVO + chemo arm: 28 patients. In the Chemo arm: 37 patients. So, this is progression. NIVO + chemo: 7%. Chemo: 9%. So that is the reality of this disease. Adverse event NIVO + chemo, and chemo had 1% each. So, the question is what are the other reasons? So, we have patient refusal or fitness for surgery due to poor lung function after induction, unresectability.

This is for NIVO + chemo and more or less the same thing with chemo with probably a little more of a refusal or unresectability, but the same pattern. What I would mean by that is at least what you can conclude is that NIVO does not fragilize the concept of Neoadjuvant Chemo-IO. However, the question of neoadjuvant treatment beyond Stage III is: Is it the best strategy, for example, for Stage Ib and II? This question remains open. I let it to your scrutiny.

Looking at NADIM II trial on the next slide, you can see that patients with definitive surgery were 93% in the NIVO + chemo, 69% in the chemo. So again, we'd like to say that there are more definitive surgery when you give IO. And you can see that the reasons being adverse event is very low and only 1.7% in the NIVO + chemo. And not treatable for surgery, which can be refusal, disease progression, or unresectable tumors are way higher in the chemo. So all in all, I would say the benefit of tumor shrinkage related to the immunotherapy, looks like to make surgery easier to perform. So, let's keep in mind what we have on the next slide about neoadjuvent immunotherapy. These are the numbers for 7 to 18% of patients not undergoing surgery.

Remember please that it's also the case in the control arms meaning that the strategy is something to question in the tumor board and also to question with your surgeon who might not like it. And remember that there is a certain number of Grade 3/4 toxicity on the right column when you give neoadjuvent chemo or chemo-IO, which ranges between 10 and 30% of the patient, and has to be taken into account and very well managed, again, using the guidelines in place. So as a conclusion on the next slide, fragilizing/endangering the delivery of radical local intervention, namely, surgery here, might be a risk related to the use of innovative IO-based neoadjuvant strategies.

It doesn't look particularly today to be the case for anti-PD-1, anti-PD-L1 chemo followed by surgery. But with the new combinations, it might come. And we did more numbers and more data, particularly in the perspective of establishing new standards in early Stage Ib and II Non-Small Cell Lung Cancer. Immunotherapy rates of toxicity are as expected in early Non-Small Cell Lung Cancer and comparable to Stage IV. And in this early disease setting, it's very important to be familiar with toxicity management and to strictly follow the guidelines in a very conservative way. And with this, I thank you for your wonderful attention. And I hope I can meet you discussing this later down the road. Thanks a lot.

Announcer:
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