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Perspectives for Adjuvant Immunotherapy in NSCLC

**Announcer:**
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**Dr. Peters:**
My name is Solange Peters. I am the head of Medical Oncology in Lausanne in Switzerland. We will discuss today the perspectives for adjuvant immunotherapy in non-small cell lung cancer. There remains an unmet need in resectable non-small cell lung cancer as you can see. Up to half of the patients will have to experience a relapse with a very early non-small cell lung cancer of stage IB with up to 3 patients out of 4 having such a recurrence in stage III non-small cell lung cancer.

Here you can see the new opportunities for immunotherapy being developed. First of all, on the upper part of the slide the adjuvant approaches with the surgery being followed yes or no by chemotherapy followed by immunotherapy most often one year. And here we have already two trials having given results. But of course, the very vast potential also of neoadjuvant or perioperative immunotherapy we have one without which is a pure and the only pure neoadjuvant trial so CheckMate 816 giving three cycles of immune chemo before surgery and all of a series of immunotherapy plus chemotherapy followed by surgery followed by immunotherapy. We call it sandwich or perioperative. As you can see, several trials with only one partial without in a press release. But all of these trials will give us other additional insights into this opportunity in the very next future. Then at the end, the complexity will be of course to decide.

In the adjuvant setting because at the topic of today we have been establishing adjuvant chemotherapy as a standard. And this is true for stage 2A in the ACM classification meaning more than four centimeters to stage 3B with an absolute benefit of survival at five years of 5.4% as this established by the latest meta-analysis. The first trials having requestioned the standard of care in the adjuvant setting after surgery were the IMpower010 and PEARLS/KEYNOTE 091 trials. They had very similar designs. They looked at stage IB more than four centimeters according to the 70 nm to stage III and they look at patient having benefited from a complete resection of the disease. They have some differences. First of all, in Impower010 adjuvant chemo was mandatory at least one cycle.

In PEARLS trial it was left to the investigator. So, second difference is Impower010 is using one year of atezolizumab in the adjuvant setting in the experimental arm versus best supportive care. The PEARLS is using one year of pembrolizumab versus placebo - slightly different. And as you will see later on, the end points of the trial, very complex endpoints by the way, are slightly different. Last but not least the Impower010 is stratified according to many factors you can see on this slide. But the PD-L1 stratification uses an old scoring system which makes the stratification not very accurate, which is not the case for PEARLS which is decently stratified for PD-L1. But you will agree with me looking at the curves of disease-free survival stage IB to stage III in both trials, they look very comparable. And what is important to also conclude is we can observe a benefit of adjuvant immunotherapy versus nothing in these patients after this radical treatment.

You can see here the numbers. So, let's start with Impower010. You will see that we have approvals for Impower010 which are not the same at the time being across borders. For US, Japan and China, it is stage II to stage III PD-L1 positive, and in Europe it is only high

PD-L1 more than 50%, and you will see why.

So, the Impower010 has this design we have been discussing. It has a very complex hierarchy of endpoints as being defined as first looking at stage II to stage III positive PD-L1 population which is the registration in the US. And in Japan and China, would it be positive the hierarchy conserves the alpha to read DFS in all stage II to stage III population irrespective of PD-L1, would it be positive DFS in ITT population including the stage IB if would be positive of our survival? And as you can see on that slide here, primary endpoint US registration stage II to III, more than 1% PD-L1 is strongly positive hazard which was 0.66. If you get treat of the PD-L1, still you can see a benefit in all randomized stage II to stage III, but to a lower extent. And in ITT population these significance boundaries were not met.

So basically, this is what we have now.But when you look on the right-hand side of the distribution by PD-L1 it looks quite obvious that the benefit is first of all driven by positive PD-L1 tumors, but more than anything by highly positive PD-L1 the more than 50%. So, you will understand this registration in positive PD-L1 stage II to III in the US, and in Europe more than 50% PD-L1. And on the left-hand side you have this graph corresponding to DFS in high PD-L1 high, that ratio 0.43. At the time being we have been exposed to the first data about OS. Remember in the hierarchy it's exploratory because it should not be looked at currently and of course it's still nature. But as you can see in that next slide there is no overall survival benefit being observed in all populations except of course a signal that something can emerge potentially in high PD-L1 more than 50%.
Let's look at KEYNOTE-091. So, endpoints were slightly easier. Two dual co-primary endpoints meaning that if one endpoint with positive the trial is deemed positive DFS in ITT or DFS in PD-L1 high node more cell lung cancer. These are both the dual co-primary endpoints.

On the left-hand side, you have the DFS in the overall population, which is significant meaning stage IB to stage III. Regardless irrespective of PD-L1 one level hazard which was 0.7 this endpoint is met. But surprisingly in this subgroup where the benefit is supposed to be the best look for example at IMPower010 in the high PD-L1 more than 50% CGI co-primary endpoint is not met and the difference is not significant.

I had the opportunity to analyze this data. And as you can see the benefit of pembrolizumab is observed on the next slide in negative PD-L1 in one to 49 but the median is not reached, and the benefit is not seen in more than 50% PD-L1. The interest is to analyze why is it the case. So very reassuring that in the pembrolizumab arm you see this incremental efficacy of pembrolizumab according to PD-L1. So, the more PD-L1, the more benefit that is what is expected and it's really comforting in what we know from advance and early disease. The surprise comes from the placebo arm where there is a novel performance of the placebo arm in high PD-L1, remember usually PD-L1 one is not prognostic and if anything has a negative impact on the prognosis. So, we expect this arm to be as the other ones the high period one placebo are even lower. So, a NOVA performance which is unexplainable or multifactorial probably of the placebo arm. So basically, the conclusion of PEARLS is probably that you can use pembrolizumab in the ITT population and that might be where the industry will go for registration.

So, this is the portfolio of current trials. Looking at adjuvant immunotherapy we've been seeing IMPower010 and PEARLS but there are other trials to come. All of these trials will use one year of adjuvant immunotherapy. Is it correct? We don't know. And they all look at slightly different end points as stratification factor, but they will consolidate unconvinced the idea of adjuvant immunotherapy being an option in these patients. The competition with neoadjuvant and perioperative treatments will be the most complex debate we will have in the future in our tumor boards and in the lung cancer community.
So basically, adjuvant immunotherapy for non-small cell lung cancer, we are being defining new standards using neoadjuvant perioperative or adjuvant IO for resectable early non-small cell lung cancer. But this is of course in addition to what we know to the current standard of care we shouldn't take the short way to replace the radical surgery or even the adjuvant chemotherapy which are strongly established. Atezolizumab, improved DFS in stage II to III PD-L1 positive non-small cell lung cancer. In Europe, it's only registered in high PD-L1. Pembrolizumab improved DFS in stage IB to III mainly stage II to III respective of PD-L1 but it's still not registered, and we wait for long-term OS data. And with this, I thank you for your wonderful attention and I'm looking forward to discussing this data with you.

**Announcer:**
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