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Innovative strategies for resectable and unresectable stage III NSCLC (part two)

Prof Filippi: Okay, thank you and good evening. And welcome to this e-ESO session on innovative strategy for resectable and unresectable stage III non-small cell lung cancer. So, my disclosures. So, basically, we start with the first slide just reminding to us what is the frequency of stage III non-small cell lung cancer. It's around 25% of initial diagnoses. And it could be that screening, for example, will increase or decrease this percentage. This is actually what we are seeing currently. And for those who attended also the 2022 sessions, we are starting today from the very important insights into the management of the non-small cell lung cancer stage III. We are talking about today resectable disease and unresectable disease. And for resectable disease, last year, we had the data, important data, at the end of 2022, and then 2022, 2021, sorry, 2022, the data of the CheckMate-016 Study regarding the use of chemo-immunotherapy as neoadjuvant therapy before surgery. And we also added the data from two studies exploring the use of immunotherapy as adjuvant therapy. And there was a great discussion about that during the year among experts and also, results of the ADAURA trial using osimertinib as oral TKI after surgery stage III for resectable disease. And for stage III or III BC unresectable disease, our standard of care now is the PACIFIC regimen, at least for patients with one positive disease, in Europe, positive tumours. And we are starting from this trial to talk about new research drugs and new opportunities in this field. So, this was the last slide on my presentation in 2022. We are at a very, let's say, high-level in comparison with the past of disease-free survival for both neoadjuvant and adjuvant strategies. For sure, neoadjuvant strategy seems the most logical and the most promising in various settings. We'll discuss about that also with Dr Girard and Dr Veronesi. And, for sure, the use of osimertinib will, actually, is increasing a lot of disease-free survival. We can talk about that again. And from the other side, we will explore some new data regarding phase II studies exploring new strategies, and we have already ongoing many phase III also studies that are going to explore different combinations of immunotherapy and different sequences in order to improve survival in this setting, which is still already quite poor. So, for resectable borderline disease, I would like to present to you the results of the NADIM II study. The NADIM II study is important. It follows the NADIM study, and it was a study involving only stage III patients with also stage III B considered resectable and no eGFR or ALK rearrangement, eGFR mutation or ALK rearrangement. And the strategy was to compare chemo-immunotherapy with paclitaxel, carboplatin, and nivolumab to chemotherapy alone in a two-arm randomised fashion. And then, also for the experimental arm, nivolumab as maintenance directly versus observation. And the result of this trial has been presented by Dr Provencio at the IASLC meeting in August 2022. And as you can see, there was a very nice performance of chemo and nivolumab in terms of progression-free survival and also, in comparison, obviously, with the chemotherapy arm. And we have 66.6% at two years and 89.3% of PFS at 12 months. And also, the overall survival is very promising, even if obviously these are not conclusive data because we need more follow-up, but it is, for sure, it is a median signal reached. And as you can see, we have 85% of patients alive at 24 months. Therefore, this study seems very promising also in patients with stage III resectable disease in comparison to chemotherapy alone. So, it confirms and further, let's say, increased the evidence in favour of the

neoadjuvant chemo-immunotherapy for resectable disease stage III. There is also data about the down-staging, which is approximately 70% for patients undergoing chemo-immunotherapy before surgery. And thus, also the rate of definitive surgery is very good. So, I think the trial is clearly positive, and therefore, it opens new possibilities for patients with potentially resectable disease. The problem probably is that we still do not have clear criteria for potentially resectable definition. And so, what is hard sometimes is to decide what is the best strategy for, for example, stage IIIA multi-station N2 or stage IIIB with T4 N1 and 2 diseases. So, obviously, it depends also on many other factors, but the results are really, really good. There's another trial that I would like to show you. It is a phase II trial, randomised phase II, it's called NEOpredict-Lung study. And it's very interesting because this study does explore a strategy without chemotherapy and with the use of a new agent, an anti-LAG-3 monoclonal antibody, which is called relatlimab. And the combination of nivolumab and relatlimab has been tested in this study for patients with early-stage disease IB up to IIIA, so IIIB were excluded in this study. But as you can see, there is a very nice overall response rate to this combination without chemotherapy, 27%, with a very promised one-year disease-free and overall survival rate, and also with a very good resection rate, which is around 100% for both arms. And the feasibility was very good and also the toxicity, I have to say, was very good. So, this is a preliminary efficacy signal, so it's nothing conclusive, again, but I think it's very interesting to discuss this kind of chemotherapy approach. We will see a few data also, for example, for unresectable diseases in this field. And it is interesting especially for a group of patients that, for example, cannot tolerate chemotherapy or only which, if we will have a biomarker-driven strategy, for example, could be very good candidates for immuno-alone induction. And I remember to ask questions if you want using the QA button. Another study I think is very interesting, even if it's a truly aggressive approach to stage III and that's why the criteria were limited to cT3-cT4, M0 N2 disease. It is approached with chemotherapy plus a doublet immunotherapy, anti-CTLA-4, anti-PD1, ipi-nivo, plus radiation therapy, and from the second cycle, chemotherapy plus nivolumab, plus radiation therapy, and then, six weeks after surgery. And so, it's a kind of a new version of the classical chemo-radiotherapy approach. I mean, it was not shown definitively to be superior to chemotherapy alone, and that's why it is not used very often, at least at the European level. But this is a strategy that can obviously improve, I mean, obviously, the hypothesis is that this strategy can improve the response rate and also, the number of pathological complete response and major pathological response. From this point of view, this aggressive strategy is able to increase the complete response rate, even if we don't have a comparator arm in this study, but the pathological complete response percentage, even if, obviously, in a small sample size where 24 operated patients was 63% and major pathological response 79%. So, it's a very good result in terms of response. Well, obviously, the problem here is that this strategy is not so well tolerated. I mean, okay, it's feasible, with promising anti-tumour activity, management, safety profile, but if you look at the data regarding serious adverse events and the rate of grade three-four treatment-related adverse events is around 70%, so therefore, obviously, we should take with caution these results even if this strategy could be, for example, very interesting for patients with aggressive disease, highest stage. I think we need to compare also this option, even the fact that these patients have truly locally advanced disease, we need to compare these strategies with other strategies. For example, chemo-radiotherapy without surgery. But I think it's not a problem about surgery regarding tolerance in the combination of two immunotherapies plus nivolumab. So, we're going to maybe discuss a little bit about that. Another interesting study is the update of the ADAURA study, which is so well-known in the field of lung oncologists. It's a study randomising patient after surgery with stage I and II-IIIA disease, to osimertinib maintenance versus placebo. The study was already being shown to be positive for disease-free survival. These results have an updated follow-up, as you can see, we have at 36 months 84%. What is interesting is that, after two years, the discontinuation of osimertinib, we don't know, probability this is the effect of discontinuation of osimertinib. As you can see, the curve drops down to 70% at 48 months. So, in one year, you can see, there is, even if, obviously, you need to see the whole curves, so it is very positive for sure, especially with regards to placebo with or without chemotherapy because it was allowed to do adjuvant chemotherapy or not. And it's, for true, for sure that it is positive, and even if there is something that we need to watch for the next update of the study is what happens to patients

after three years of osimertinib and probably a strategy prolonging osimertinib, for example, could be explored in the future. In any case, it is something that we need to take into consideration. These are the results of CNS disease-free survival, I think that they are very important because obviously the brain is one of the most common sites of relapse in these patients and it is very important to protect the brain, and osimertinib seems to have a very nice, let's say, efficacy. And I think, for many reasons, this is very important data. Then, regarding the PEARLS/KEYNOTE-091 study testing after adjuvant chemotherapy, the use of pembrolizumab versus placebo, again, in operated patients IB to IIIA, I would like only to say that one of the primary endpoints was to explore the efficacy of this strategy in patients according to PD-L1 expression. And again, because we already saw this tendency in the very first presentation, we see that in patients with PD-L1 expression, apparently, there is no clear benefit of these strategies over placebo. And it is something that is surprising. And I think it was important to mention this update of the study, and probably, there was another performance of the placebo arm that can explain that this result was, obviously, unexpected. However, regardless of PD-L1 expression, the safety profile was good and the efficacy was good in completely resectable stage disease. So, therefore, we'll see what would be the decision also for regulation authorities about the use of pembrolizumab adjuvant therapy. We have the possibility to offer now to patients atezolizumab according to the results of IMpower010 and then, we'll see what would be the decision about pembro. There is also an interesting study regarding circulating tumour DNA. I think it's very important because it is a study performed before the use of osimertinib as adjuvant therapy. Therefore, ctDNA samples were collected longitudinally in patients between 2015 and 2017. And what this study showed is that in a quite large sample size we have clear data regarding the molecular response, because patients obtaining a molecular response being ctDNA negative after surgeries has much more high probability of being disease-free survival, of being disease-free from disease, sorry, at 36, 48 and 60 months. And on the contrary, patients with positive DNA, let's say, have a lower probability of being disease-free. So, this is, again, a study confirming what we are hearing from many trials. For example, we also have the molecular data, for example, CheckMate816 and also, NADIM I and II And all these studies are suggesting that obtaining molecular response in the blood, it's a clear prognostic factor for these patients. But I think it is very important also to have this kind of demonstration of the usefulness of a liquid biopsy for monitoring disease after surgery, but also after chemo-radiotherapy because we have initial data about unresectable disease for designing a new trial for a more personalised approach to stage III that we need a lot also to address patients to the right therapy, given the high number of options that now we have in comparison with the past. On unresectable stage III disease, we closed last year a presentation with a lot of ongoing trials, and all these trials have been designed with the idea of, let's say, of increasing results of the Pacific study, which, as you know, tested a concomitant chemo-radiotherapy approach with durvalumab [Audio Not Clear], which is now the standard in all the world. And the results are very good, but still, the progression-free survival is poor as well as the overall survival. If you look at historical data, it's very good, but it's still poor at five years, we have around 50% of patients who died and around two out of three patients relapsing. So, all these strategies are testing different approaches, for example, combination of immunotherapy doublet after chemo-radiotherapy or other sequences, or, for example, durva used with concomitant chemo-radiotherapy, or maybe ipilimumab or also a combination of immunotherapy TKI, KEYLYNK-012 with pembro olaparib, or anti-TIGIT, like, for example SKYSCRAPER-03, testing atezo tiragolumab, or the KEYVIBE-006. So, there are many trials, we still do not have data from these trials. So, I'm going to talk a little what have been, in my opinion, important data in 2022. At ESMO, Dr Nicolas Girard presented the results of the PACIFIC-R, a real-world study collecting patients treated with chemo-radiotherapy and durvalumab, either a sequential or concomitant in a real-life study, a prospective study with a very large cohort including more than 1000 patients. We have the results on 1154 patients, and still, we do not have mature overall survival data at the time of analysis, even if the estimation is to have more than 60% of patients alive at three years, we have results up to two years, very good, 72% alive, and at three years, 63%. These are data regarding the timing of the use of durvalumab, the durvalumab administration after chemo-radiotherapy that confirms what was the trend in the PACIFIC trial for a better survival. We also have the updated progression-free survival, which is quite good, 50% at two

years, and 42% at three years. And again, there is a positive effect of the anticipation in the use of durvalumab, we are close to less than 42 days after the end of radiotherapy. And we also have very nice data confirming that sequential chemo-radiotherapy may have different, let's say, outcome, even if, obviously, from diagnosis, we need to take into account that the time-period of observation is a little bit different, however, it is very good also for patients undergoing sequential chemo-radiotherapy plus durva, according also to the results of the PACIFIC-06 study. And we also have a confirmation that patients with PD-L1 positive disease have better responses, also better overall survival and progression-free survival. However, as you can see, the results are very good also for PD-L1 negative patients, because it's clearly superior to historical series. So, at the end, the message, and I will have more time, sorry, for discussing these results also with Nicolas Girard. I think that, at the end, the message is very good for both populations. And again, there is a great debate on what to offer to PD-L1 negative patients apart from the regulatory aspect and reimbursement policies. Because apparently this is quite a good strategy, even if being PD-L1 positive gives you higher probability to survive, a numerically higher probability to survive because, obviously, this is not a comparison with a comparator arm, so, we cannot derive any other data regarding kind of superiority or consideration like that. That cannot be made from this study. There is also an update of the KEYNOTE-799. This is a study exploring a strategy, which is quite intense. This is in treatment intensification because it's one cycle of concomitant chemo-immunotherapy plus concomitant chemo-radiotherapy plus immunotherapy and immunotherapy maintenance, there were two cohorts in this phase II study, one for non-squamous and one for squamous tumours. And they updated, sorry, it's a little bit difficult to read, but what I think is very promising is the progression-free survival value at one-year. Because if you remember, in PACIFIC trial, we had 55%, now we are reaching like 70% of progression-free survival at one-year with a longer follow-up. And then, as you can see, there is a very nice kind of plateau. So, result is very good also at 24 months with a longer follow-up. And I think this is a very good result for this strategy that is being tested, is being investigated in KEYVIBE-006 study. So, like a similar approach but with the use also of the anti-TIGIT, is a core formulation of pembrolizumab and anti-TIGIT, but with the same strategy in terms of induction and chemo-immunotherapy one cycle plus a chemo-immunotherapy and radiotherapy approach. So, because basically this study confirms that this is a safe approach and with promising results, so, I think this strategy, for sure, it is very promising. Another small study, but I think very interesting in term of a scientific point of view, we have, in this population of patients, over-expressing PD-L1 and tumours over-expressed PD-L1 are more than 50%. This group in the United States tested an approach based on chemo-free approach, two cycles of, sorry, three cycles of pembrolizumab alone for patients with a resectable disease followed by a PET-based dose-painting radiotherapy. So, basically it is a different dose, different volume according to response to immunotherapy in a group of patients that are selected for being highly responsive to immunotherapy alone. And the primary endpoint was one-year progression-free survival and the secondary endpoints were safety. But we have very nice data in terms of progression-free survival, again, one-year up to 73% without chemotherapy. And, as you can see, also this approach of adapting radiation-dose and radiation-volume to response, in my mind, is very interesting. And we also have very initial data, but promising data regarding PET response. Because, for example, if you have a PET response, so you have a quite easy-to-perform marker of response in term of metabolic response to induction immunotherapy, you have an increased probability of survival without progression. And it is a signal of what we can think about for a new generation of trials adapting this strategy to the initial risk, and stratifying the patients to the right strategy, and according to response, which is, in my mind, very interesting. So, for all the research working on the field of induction chemo-immunotherapy, because some of the groups are trying to translate their approach, we are using as adjuvant therapy before surgery. So, for example, chemo-immunotherapy or immunotherapy alone, in some experience, and some groups are trying to translate this approach to the unresectable disease. And so, one of the ideas that can probably, in the future, being developed to compare this strategy with the PACIFIC regimen will be to test this induction immunotherapy plus dose-adapted, volume-adapted radiotherapy, which is, obviously, expected to have also a lower toxicity. So, I'm going to close very fast with another study testing the safety of radiotherapy plus durvalumab alone, concomitantly full-dose radiotherapy. So, this is

not a study... again, this is a chemo-free approach, but in patients that can tolerate chemo-radiotherapy. So, it's another approach, again, in order to avoid chemo. And, I have to say, that the progression-free survival is apparently very good, but the safety profile, for sure, needs to be taken into account because we had very good responses in terms of overall response rate, and PFS, and duration of response. But, as you can see, we have, again, grade three-four toxicity adverse events around 50%, 5.9% of grade five. So, toxicity and generally tumour adverse events were around 90% with serious adverse events being 40%. So, I think that probably that's something that we need to understand about the combination of five dose radiotherapy concomitantly with immunotherapy even if, at the end, was generally well tolerated because it's something that we can maybe also expect. In my mind, we need to be careful for testing, at least, this approach, needing to be tested, obviously, only in clinical trials and we need more data to clarify these aspects. And another study, which is a negative study, the last one I'm going to present to you today, is a study testing consolidation of nivo-ipi versus nivo alone after chemo-radiotherapy for patients, again, with unresectable stage III disease. So, this is one of the strategies that is also being tested by a phase III study, comparing nivo alone to nivo-ipi versus durva and in unresectable stage III after chemo-radiotherapy and it's CheckMate-73L. And unfortunately, this study did not show any benefit with the combination of nivo-ipi versus nivo alone. Results are very similar, as you can see, both in terms of PFS and overall survival. And again, we have more toxicity for the combination of ipi-nivo. So, even if, let's say, we can say that it's encouraging survival, there were higher rates of toxicity. So, this study, at least, is not particularly promising in my mind, in my opinion for these settings. We need probably, again, to individualise more the strategy or better select patients. So, in conclusion, I think that, for sure, at the beginning of a 2020 review, we can say that the introduction of immunotherapy and TKI for surgical patients offers consistent survival advantages, and we are still waiting for mature overall survival data, but there are very nice trends in favour. So, it's not only about complete response and about disease-free survival or progression-free survival, but still, probably, it's about overall survival, and I'm sure this strategy will change our approach to resectable disease. Still, we don't have any data to compare neoadjuvant versus adjuvant, so the peri-operative approaches, for example, neoadjuvant plus adjuvant. But we will see, we had these very nice results of NADIM II study that need to be, let's say, taken with caution because it is a phase II study. But, for sure, they are promising. And also, IO maintenance is a standard therapy for unresectable disease. We have new data from a phase II studies that indicate a possible benefit, but also higher toxicity. So, we need to be little bit careful in exploring strategy. Obviously, it's all about clinical research and not an employment of this combination in the clinics. We will have new trials for intersections on both res/unresectable disease, between a surgery-based approach, towards, versus a radiotherapy-based approach, but this trial is very difficult to carry out. So, I think that will be probably large, we need a large academic collaboration for showing possible benefit regarding one study versus the other. And then, new data conforms the very good prognostic value of molecular residual disease in the blood for surgical patients. But also, I will say, for a patient receiving chemo-radiotherapy, I think that this approach will help us in selecting patients for the future. Thank you very much for your attention.

Prof Girard: Thank you, Andrea, for the excellent presentation. Very comprehensive. We see that we have now many, many, many data both for the resectable and the non-resectable tumours. This is very complex, obviously. And actually, I have one key question. Because in my clinic, at the tumour board, this is always the same discussion about the resectability. Because on the one side, we have the resectable tumours with this neoadjuvant or peri-operative IO strategy. On the other side, we have CRT, possibly combined with IO at some point. But the first question facing a patient is actually, is this resectable or not? And I would like to share with you our experience in my centre, pretty well-known centre. At the end, we looked back at our stage III and II patients, discussing the case again at the tumour board six months after the initial presentation just to play and see whether we had the same assessment of resectability. And in one third of the patients, it is published in "Lung Cancer", we had a discrepant decision, a patient deemed resectable and who had surgery possibly with neoadjuvant treatment, at the second discussion, surgeon said, "no, this is a medical

patient, let's go for CRT" or the reverse. So, it shows how complex it is, even within one team, to define resectability or not. I don't know if you have any comment, Giulia, on this, Andrea as well.

Prof Filippi: Giulia, please.

Dr Veronesi: No, yes, I completely agree with Nicolas. It's one of the more difficult points to establish the resectability of cases, and sometimes, even in case of resectable disease, there is the preference, maybe because of very big lymph nodes or multi-station, to make the option for radiotherapy. And so, this is something that, of course, the data, the long-term survival, regarding the PACIFIC, are very promising, and however, you have not taken out the tumour, and so the risk of maybe persistence or recurrence, who knows, can be higher compared to chemo-immuno and surgery. So, it's difficult, however, sometimes, there's not only the resectability, but also the, let's say, general option for the non-surgical decision, of course, taking into account the other factors related to the patients, like comorbidities' risk and age. So, it's a good point. So, what do you say, Andrea?

Prof Filippi: Yes, the same for us. I think we are all in the same situation. and I think, I have to say one positive aspect is that, as Nicolas highlighted, we are discussing the patients a lot more because there are many options and many points of view, and I think we are going a little bit deeper in the staging, we are doing a more accurate evaluation because we know that it is a decision that, obviously, it matters a lot for the patients, a completely different strategy. So, even if in Italy, at the moment, we don't have approval for neoadjuvant chemo-immunotherapy, but, in any case, we can use it in some ways. And, for sure, there is a higher expectation from the surgeon about response, about complete response. And I have to say that the data on pathological response, major pathology on this has very good data, and I mean, this is something that it is impossible to show with chemo-radiotherapy. For sure, we can think about liquid biopsy as a surrogate marker of response in this case, but we don't have it now in our clinics, so...

Prof Girard: I agree with you, I agree with you, the issue with MRD is that this is not sufficiently sensitive. Because even in MRD negative, so-called negative, we have some relapses, so it's not a perfect biomarker. Obviously, if it's positive, well, you can expect the patient to have a relatively short event-free survival. This is a very good question. Another question is about the patient pathway. Because now that we have all these options, the pre-operative strategy, and so on, it means that we need to have a pre-operative biopsy for all the patients to have a diagnosis, but also, to do some kind of biomarkers. PD-L1, because, at least in Europe, adjuvant atezolizumab is only for PD-L1 above 50%. So, I know that if a patient had a PD-L1 high, I can go to surgery first and then IO. But if the patient has a low PD-L1, then, I will maybe have the only option to deliver neoadjuvant chemo-immuno. So, this is the first point. We need to test for EGFR and possibly ALK, ALK to exclude this patient from IO and EGFR because if you have an EGFR-mutant patient, well, it goes to an adjuvant strategy. So, to me, this is the way we are now working with pre-operative biopsy for all the patients, some biomarker testing. This is not NGS, this is only EGFR and ALK in my clinic, and PD-L1. I don't know what is your practise, Andrea?

Prof Filippi: Yes, we are starting to test in every stage III patients because it was something that we were not used to do before. Before deciding about the strategy, ideally, sometimes it happens that we don't have these data, but hopefully, we are trying to collect also the molecular, the genomic data. Also, in our cases, we are trying to implement NGS, but we are now using a classical PCR approach or for first immunohistochemistry and then, a FISH for ALK. And it's true, I did not mention that EGFR positive patients, at the moment, for unresectable disease are not receiving durvalumab, but in the ALK translocation, we don't have any... we would like to have a trial, but it's difficult, they are rare. For surgical patients, we are trying, and I'll also involve Giulia, but we are trying to have molecular data before because, obviously, you can talk to the patients and explore a neoadjuvant approach versus adjuvant approach with immuno, or either TKI, if you have a mutant patient. So, it is, in my opinion, it is an information that we need to have before presenting

to the patient the whole strategy, ideally, even if it is respectable. I don't know what is your practise in Milan, in San Raffaele, Giulia.

Dr Veronesi: Yes, this is... we all agree that it would be the best to have all the data before. There is a main, let's say, question-mark related to the reimbursement here. We still need to understand very well we pay NGS for all patients in early stage. I, today, discussed with the colleagues and medical oncologists to find the right way, and we have next week the meeting with the pathologists. I don't know in your place how it is managed, because we still don't have the coverage of the public system for all the NGS in every case. However, I have another question for you Andrea related to the concurrent chemo-radiation plus immuno in case of unresectable disease. Do you think there is enough data to propose this kind of solution outside the clinical trial today? Maybe, it's not reimbursed but let's say in terms of safety, do you think that there are still some doubts related to the possibility to offer it? Or we maybe must select a candidate in a certain way? Can you explain a little bit more?

Prof Filippi: So, for the concomitant approach we chemo-rad and immuno, yes. We still do not have enough evidence to offer this approach to patients outside the trial. Because we are still waiting for, let's say, phase III study results. We only have phase II data. In the KEYNOTE-799, the result is quite good. We have a slightly higher rate of pneumonitis, but it's only a phase II study with a small sample size. The other study is, let's say, other studies, for example, PACIFIC-2, still, we don't have any results, even if, obviously, this is a large phase III trial comparing chemo-radio, durva versus, not PACIFIC regimen but concomitant chemo-radio, durva plus durva maintenance versus chemo-radio alone. And when this trial will be published, I guess, we will have enough data. At the moment, I'm a little bit worried about toxicity and I will, probably, I will be careful. Also, because the other data I presented to you around the combination of radio-immunotherapy at high dose, without chemo, I'm not completely convincing myself about the safety of this approach for reasons that I cannot exactly understand. Because apparently, we have a lot of data in combining palliative radiation therapy, for example, in immunotherapy, and no one did highlight any safety signal around that. But when you combine first-line high-dose radiation with, for example, durvalumab, you can probably know if you had some patients. But it's still something that I will be cautious about it.

Dr Veronesi: Thank you, thank you very much.

Prof Girard: Yes, this is a very good question. And maybe, in the future, we will have more personalization with MRD to help in the discussion of adjuvant, especially post-neoadjuvant, if we have this kind of sandwiches approach with immunotherapy around surgery. But maybe, we can have also a kind of one-fits-all strategy with chemo IO for everyone. You start with two or three cycles and then, you choose between surgery and/or radiation, and then, adjuvant or consolidation for everyone. Well, I'm not sure this is what we want to do, but at the end, this is what we will do. Because the clinical trials, for sure, will show some kind of benefit. Still, it will be a matter then of understanding, after surgery, what should be done based on PD-L1, PCR for surgical patients, maybe MRD, if we have more reliable tools to use these two. So, the field is really changing towards IO for the majority of these non-metastatic patients, I would say.

Prof Filippi: Yeah, also because the response to induction chemo-IO also for surgical patients seems the driver of survival. And therefore, also for chemo-radiotherapy patients, it could be that probably if we test a kind of a small induction, we will have a clear idea what are the patients who are going to be cured versus others where we can test a more aggressive strategy. This is what would be a very nice personalization also in terms of risk of toxicity because, obviously, you are more likely to accept higher toxicity if you have a patient that probably do not respond to standard. If you have a patient with a very good response, you will. Even if there are some, just to close, I don't know what are your experiences in terms of radiological response to chemo-immuno and pathological response, because, for example, it is not perfectly clear in the clinic. Sometimes, you don't have super responses after three cycles, but when you operate the patient, you see complete pathological response or major [Audio Not Clear]. This is something that it is a little bit difficult to interpret.

Also, we have a question from the audience about that. For example, pathological complete, sorry, radiological complete response after induction chemo-IO. Would you operate, Giulia, the patients? There is a classical question arising.

Prof Girard: What I believe is that we cannot predict right now PCR, so, it's very difficult to predict. And this is an issue because even in CheckMate-816, there are some patients who had a pneumonectomy, even if they had a PCR. So, I believe that if we could predict PCR, if we have a major radiological response, well, these cases, they should be discussed for maybe non-classical surgery. I mean, maybe segmentectomy, maybe lobectomy plus wedge to avoid pneumonectomy if possible. So, I mean, for the surgical strategy, it may have many impacts.

Dr Veronesi: Yes, I agree. I would suggest maybe I would operate if I can spare at least one lobe and not if I had to do a pneumonectomy in case of complete radiological response, I would make a follow-up probably. Less than a pneumo, probably yes, because you have to prove that it is complete response at least.

Prof Filippi: So, there was another question, Nicolas, I think last one, we need to close, about pseudo-progression in neoadjuvant chemo-immunotherapy.

Prof Girard: It's a very good one. In Checkmate-816, we made some mistakes at least for one patient who had a kind of mediastinal progression. At that time, the data about granulomatosis or sarcoid-like reaction were not that much published. So, we did not go for surgery. And at the end, this patient is still alive. Actually, she has sarcoidosis. So, now, it's better-known, I believe, if we have a progression this is something that could be investigated a little bit more, because usually you have some kind of response, but we know that 10% of patients or 7 to 10% of patients may have a true disease progression, but usually it's outside of the thorax. Still, in case of mediastinal progression, this is a typical case where you need to think about sarcoid disease or inflammation and probably do a kind of re-biopsy EBUS, not to cancel the surgery in a patient who is actually showing a response.

Prof Filippi: Great, thank you. So, I think we need to close because it's 7:00 PM, and I would like to thank Nicolas Girard and Giulia Veronesi for the good discussion we had. Unfortunately, only 50 minutes, but we can maybe think about another session in the future. So, thank you very much, and again, I'd like to wish a very nice evening to all the participants and like to thank European School of Oncology.

Dr Veronesi: Thank you.

Prof Girard: Thank you so much.

Dr Veronesi: It was a pleasure to be here and discuss with you.

Prof Girard: Very good discussion, thank you so much.