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An update in partial breast irradiation for breast cancer

Prof Meattini: Thank very much, and it's such an honour to be here for the European School of Oncology and it's such an honour to have an outstanding discussant as Pierfrancesco Franco and Orit Kaidar-Person today, having these updates on partial breast irradiation and focus on techniques, results, and patient's selection. These are my conflicts of interest disclosure. I do believe that the first question that we should have when we talk about partial breast irradiation, all of us had, all the techniques are really the same. So, basically, over time, we have the results from main Phase III trial. The first two were based on intraoperative electron radiation therapy, and the first one was the ELIOT trial. As all of you know very well, intraoperative electron radiation therapy in single fraction, 21 Gy, and more than 1000 patients randomised to receive whole-breast irradiation or intraoperative radiation therapy. An equivalence trial of five-year, Delta, that could be discussed, Delta of 7.5%. With these results, quite notwithstanding, ipsilateral breast tumour recurrence of 4.4%, as compared to 0.4%, as Delta hazard ratio of 9.3. And these are the stratification for true recurrence, and no difference in terms of overall survival. However, when we observe the multivariate analysis and the five-year ipsilateral breast tumour recurrence of more than 10% in high-risk factors, we can account on more than 10% of patients that have large size tumours, or positive nodal status with more than four positive nodes in 15% of patients, 12% of patients Grade 3 tumours, oestrogen receptor-negative or triple-negative tumours, between 14% and 18% of patients. When the authors analysed the patients called low-risk with none of these high-risk factors, authors observed a five-year ipsilateral breast tumour recurrence that decreased from 11% to less than 2%. And here below, you can observe the stratification of patients and five-year rate of patients following the ASTRO and ESTRO recommendations, but they were basically not outstanding results. Important: toxicity and quality of life for our patients. Toxicity, of course, always in favour of partial breast irradiation. The TARGIT trial, TARGIT-A trial was another intraoperative radiation therapy trial, 50 kilovolt energy x-rays single fraction 20 Gy. There has been a lot of discussion of this Phase III trial. Patients were randomised either before the pre-pathology group, or after breast-conserving surgery, the post-pathology group, by reopening the wound, and TARGIT received a supplemental external-beam radiation therapy in case of unforeseen adverse features that are not clearly specified. Also, in this case, the first publication of this trial was published in 2014, when there was 15% of patients that received a supplemental of whole-breast irradiation after TARGIT and was published at a median follow-up of 2.5 years for the 3000 patients. And the main results show significance in favour of whole-breast irradiation, or 3.3% of local relapse at five years, as compared to 1.3% at five years. In particular, as we observe the post-pathology group where they reopened the wound, there was a 5.4% of patients with local relapse, compared to less than 2% in favour of whole-breast irradiation, although, there was no difference in terms of breast cancer mortality. So, the first two trials, basically, were absolutely not in favour of partial breast irradiation. Thereafter, there was a lot of attention in terms of selection of patients, and I would like to mention the GEC/ESTRO trial on brachytherapy technique, Stage I, IIA breast cancer, more than 1000 patients that received HDR 7-8 fractions of brachytherapy. As you can see, in this case, the ipsilateral breast tumour recurrence rate at five years was absolutely not different between the two groups. It's around 1% for both groups, and no difference in terms

of distant metastases and overall survival. In this case you can observe absolutely results in favour of partial breast irradiation. In particular, if you look at the Grade II, III late skin toxicity, Grade II, III skin hyperpigmentation, absolutely in favour of partial breast irradiation. And here, you can observe the summary of the toxic effects for the patient. So, this was a renaissance for the partial breast irradiation. And again, it's not only brachytherapy. The IMPORT LOW trial, that was a Phase III trial, not accelerated partial breast, but 40 Gy in 15 fractions using an external-beam radiation therapy, easy technique, more than 90% of patients with T1N0 HR+/HER2- patients, more than 1000 patients. And again, as you can observe, there was no difference in terms of ipsilateral breast tumour recurrence, distant metastases, and overall survival, as compared to whole-breast irradiation and partial breast irradiation using 40 Gy in 15 fractions. It's something like 1% of risk of local relapse at five years. And the authors analysed following treatment group and showed an average number of adverse events per person lower in partial breast irradiation and the reduced-dose arm, as compared to whole-breast irradiation, and overall, these results decrease over time in all groups. So, again, equivalence in terms of local relapse between whole-breast irradiation and partial breast, and quite results in favour of partial breast irradiation in terms of toxicity. In Florence, we developed and recruited in a small Phase III trial 500 patients that all received in a single centre accelerating partial breast irradiation using an IMRT technique, 30 Gy in five non-consecutive fractions, as compared to a historical whole-breast irradiation, 50 Gy and a 10 Gy boost in 2 Gy fractions. And we published, initially, five-years median follow-up results, and we show no differences in terms of ipsilateral breast tumour recurrence, less than 2%, both arms, no difference in terms of distant metastases and overall survival. As you can observe, 60% of patients enrolled were Luminal-A-like patients and ipsilateral breast tumour recurrence rate at five years was basically no different between groups, and less than 2%. And please, take in account that around 70% of patients received endocrine therapy, but 30% of patients did not receive any systemic therapy in this trial, where you can observe the true effect of partial breast irradiation, and this is the stratification following the ASTRO and ESTRO low-risk groups. The trial was then published two years ago on the JCO at 10 years median follow-up, showing basically persistent effect in favour of partial breast irradiation, as delivered 30 Gy in 5 fractions, in terms of acute, early-late and late adverse events, physician-rated cosmesis following the Harvard score and patient-rated cosmesis, all significantly in favour of partial breast irradiation. It was one of the last, if not the last ECCO meeting, in 2017, where we presented also the health-related quality of life assessment of the trial, using the C30 and B45, and BR23, at that time of this trial. As you can observe, we demonstrated, basically, an impact in favour of partial breast irradiation in terms of physical functioning, role functioning, emotional functioning, and social functioning for these patients, both at T1 and T2, at two years from randomization. And also, if you observe the symptoms' scales, you can observe a significant effect in favour of partial breast irradiation in terms of fatigue, pain, dyspnoea, insomnia, appetite loss, both at T1 and T2 at two years. And what about the breast module 23 symptoms scale? Again, it was in favour of partial breast in terms of breast and arm symptoms, and this was true both at T1 and T2. We observed a global health status trend over time in favour of partial breast irradiation, both when we use a five-point difference in terms of GHS scale but also, if we use a 10 clinically relevant point-difference, always in favour of partial breast irradiation at two years. This was true for patients age less than 50-years, for patients between 50 and 70 but also, for patients age more than 70-years, always in favour at two years of accelerated partial breast irradiation. After that, the RAPID trial and the RTOG trial were presented in San Antonio, then published in the Lancet, 2019. The RAPID trial showed the accelerated partial breast irradiation was not inferior to whole-breast irradiation but the schema was 38.5 Gy in 10 twice-daily fractions, and that's something to discuss about toxicity, that was really, and cosmesis, not in favour of accelerated partial breast irradiation. Conversely, there was excellent and equivalent results in term of toxicity in the RTOG trial, but the trial, again, 4000 patients, 38.5 Gy in 10 twice-daily fractions did not meet the equivalence in terms of comparison between partial breast and whole-breast. But I would like to show you that 10-year difference in terms of ipsilateral breast tumour recurrence between the two arms was 0.7%. So, basically, this was the 10-year cumulative incidence in the APBI group, and this was the absolute difference. Again, it was a negative trial, as designed for the primary endpoint. This was no difference in terms of distant-free survival and overall survival rates between the two arms. Adverse

events, absolutely nice and acceptable, both for accelerated partial breast and whole-breast irradiation, with good results in terms of Grade II toxicity in favour of accelerated partial breast irradiation, and not significant difference in terms of secondary cancer. And what about the RAPID trial? This is the rate of ipsilateral breast tumour recurrence over time. No difference, 3%, at eight years, as compared to 2.8%. However, there's been a lot of discussion on cosmesis and toxicity in this trial, but it was observed that the importance of the V95/whole-breast volume ratio, that is, when was it kept less than 0.15, was related to a lower risk of cosmetic deterioration, but this was related only for the 10% of patients. For all subjects, factors associated with adverse cosmesis at three years were the age, older age, the location of tumours, breast infection, smoking, seroma volume, breast volume and the use, of course, of partial breast irradiation. And these are the results in terms of acute radiation toxicity and late radiation toxicity. And in terms of adverse cosmesis, defined as fair or poor at three years, we observe an absolute difference of 11.3%. This was kept both at five years and seven years. But what we basically observed over time, it is that, over time, with a good selection of patients, ipsilateral breast tumour recurrence rate reduced, and reduced even more if you stratify patients in these trials following the ASTRO and ESTRO recommendation, or following the Luminal-A-like tumours, and it was also confirmed in the RAPID and RTOG trial a very long-term ipsilateral breast tumour recurrence rate equivalent and safety concern on twice-daily schedule. I would like to quickly remind that you can always ask questions or send comments using the Q&A tools of the e-ESO application. The second important question was related to maybe at a longer follow-up, this difference will change? And what we observed was... This is the Florence trial, 10 years of median follow-up, the 10-year cumulative ipsilateral breast tumour recurrence incidence was 2.5% as compared to 3.7%. This was the P, and no difference in terms breast cancer-specific survival, overall survival, and distant metastases survival. And this was the longer follow-up of the ELIOT trial, where you can observe at a median follow-up at 12.4 years that the difference was even greater than the first publication, with an ipsilateral breast tumour recurrence rate of 11% in the ELIOT arm, as compared to 2% in the whole-breast irradiation arm. This was the 10-year percent rate, 8%, as compared 1%, and the 15-year rate, 12%, as compared to 2.4%. So, basically, the longer follow-up confirmed the initial results. This is always the same, even if you observe the published TARGIT-IORT, as compared to external-beam radiation therapy, TARGIT-A trial with a 4%, as compared with 1% difference, with a difference of 3%, which crossed the non-inferiority margin set by the authors at 2.5%. So, basically, the authors concluded a delayed target IORT, and there's been a lot of discussion. Basically, it was not non-inferior and actually, significantly inferior, compared to external-beam radiation therapy, where the five years local recurrence rate using TARGIT was comparable to the no-radiation arm in the PRIME trials. So, not all the trials are basically the same, and probably, at a longer follow-up, this difference will not change. What is crucial? Crucial is patient selection at baseline. This is the real key. Patient selection is a factor that you can't change over time. And what is really important is the knowledge of pathology features at selection of patients. These biology and pathology features are the key for a well-adequate selection of patients. So, please, do not forget to question. Questions, comments, suggestions and at the end of the session, to be discussed together. So, again, patient selection. We've already seen this slide but please again, ELIOT trial, it is a negative trial, but you can't, currently, not at that time, enroll 20% of patients triple negative and give them accelerated partial breast radiation. Again, sub-analysis, low-risk patients, even using intraoperative electron radiation therapy, 1.5% of ipsilateral breast tumour recurrence at five years. Again, a problem in terms of selection of patients in TARGIT trial, pre-pathology, post-pathology, data that are not complete, and no clear stratification of patients and use of external-beam whole-breast irradiation in case of high-risk adverse features that have been not specified over time. Brachytherapy, positive trial. These are the selections of patients. As you can see, all Stage 0, I, IIA breast cancer, mostly HR+/HER2-, G1, G2. And again, the IMPORT LOW trial, again a positive trial, please, observe the stratification and selection of patients. More than 90% of patients T1N0 HR+/HER2-. Again, this is the leitmotiv, it's the adequate selection of patients. Florence trial, again a positive trial. These are our patients. Mostly, less than 20% of Ki67, 80% of patients Luminal-A-like, even patients that are not going to receive systemic therapy. Most of patients ASTRO suitable or cautionary, ESTRO low or intermediate, never unsuitable or high-risk. So, again, no risk for patients Luminal-A-like, ASTRO suitable,

ESTRO low-risk. Again, selection of patients. And again, the RTOG trial subgroups defined by invasive tumour size and risk group is summarised here. No differences in terms of treatment effects between any of the subgroups, except invasive pathological tumour size, for which accelerated partial breast irradiation was favourable in patients with invasive tumours size one-centimetre or smaller. And again, I will show you again this slide, as it really summarises as we improve over time, how we design the Phase III trial, taking into account not only the stage, but also the biology of our patients. Again, do not forget to question using the e-ESO tool. So, all the techniques are the same, maybe yes, although not all the studies were designed the same, using the same shape. We have got the keys to adequately select patients for partial breast. ESTRO and ASTRO are basically in agreement; been also updated in 2016 the ASTRO guidelines. Patients more than 50-years-old, margins more than two-millimetres, negative nodal status, T1, ESTRO also T2. These are basically in agreement, all the recommendations. Concerning the fractionation, this is the era of the 5 fractions partial breast irradiation. It's not twice-daily. If you take in account the Royal College of Radiology's repository of clinically advisory documents, you can already find that they offer 26 Gy after the FAST-Forward trial publication, in 5 fractions over one week also for partial breast radiation therapy. But please, consider the ESTRO-ACROP external-beam radiation therapy consensus statements that we published in January 2022, concerning the partial breast selection criteria. We reviewed delayed features and obtained Delphi consensus among experts of the field. This is the consensus of partial breast irradiation, suitable patient selection for external-beam radiation therapy. It was an exciting work that we performed last year. These are the low-risk features suitable for partial breast irradiation: Luminal-like subtypes, small tumour less than 3-centimetres, absence of lymphovascular space invasion, non-lobular invasive carcinoma, tumour grade I-II, even low to intermediate grade DCIS, sized less than 25-millimetres with clear surgical margins more than 2-millimetre, age at diagnosis 50-years or more, unicentric/unifocal lesion, node negative, no use of primary systemic therapy or neoadjuvant chemotherapy. So, please, follow the existing guidelines to adequately select partial breast irradiation. Concerning fractionation, we believe that partial breast irradiation dose of fractionation could be performed using moderate hypofractionated irradiation therapy, 40 Gy in 15 fractions, as per IMPORT LOW, and ultrahypofractionation between 26 and 30 Gy in 5 fractions, if you want to use the FAST-Forward, I'll do this in whole-breast or partial breast trial, or the Florence trial in 5 fractions that do represent acceptable schedules for external-beam partial breast radiation. We have still some concerns about the twice-a-day external-beam partial breast irradiation dose and fractionation, similar to that one used in the RAPID that should be not offered as first option. So, coming to my main conclusions, in order to start discussion, leaving some time for a quite active discussion, we should really assess every single patient in an individual, case-by-case manner, evaluating tumour characteristics, but also, comorbidity, frail scores, Charlson scores, we have a lot of tools, G8, patients' expectations and assess all the benefit and the risk of all the treatments, not only irradiation, also systemic therapy. Use the PROMS, use the health-related quality of life scales, validated, reliable. We should always offer partial breast irradiation rather than whole-breast irradiation, but following patient selection ESTRO, ESTRO-ACROP and ASTRO existing recommendations. We should always favour a multidisciplinary discussion. And where available, please, strongly consider to enrol your patients in an optimization, what we called until yesterday de-escalation, ongoing clinical trials, when you can reduce treatment. That is not always the local treatment, but could be also systemic treatment, such as endocrine therapy in very low-risk patients. With this, I would like to thank you very much for the attention. Please, do not hesitate to use the Q&A tools now, but also, contact me for any clarifications. Thank you very much.

Dr Kaidar-Person: Thank you, Icro. That was quite comprehensive and interesting. Thank you. So, I do not see that we have any questions in the chat.

Prof Franco: Don't be shy. If you have anything urgent, we'll happy to process the question, and Icro, for sure, will be very happy to answer.

Dr Kaidar-Person: So, I do have a question since we recently had the ASCO meeting. So, I'm very curious, Icro, what do you think of the LUMINA trial, with regards to what you presented today with partial breast irradiation? So, if you can tell a little bit to the audience about the LUMINA trial and then...

Prof Meattini: Thank you. Thank you, Orit, because this is a really important question that is basically the last sentence of my presentation. The LUMINA is a very nice trial, but it's a single-arm trial that, again, tests what we always tested over time, where we analyse de-escalation or optimization trials. So, the de-escalation of the local therapy. So, the LUMINA, basically, reinforces data that there are some patients that could easily avoid both radiation and endocrine therapy, when you have got very low-risk patients such as Luminal-A-like. So, ER+/HER2-, low Ki67. So, basically, patients with less than 5% of ipsilateral breast tumour recurrence at five years, even less. But that's still a main limitation, that we are still looking only using one perspective that is the perspective to decrease the local therapy. We need Phase III trial that analyses also the reduction of the systemic therapy burden of symptoms in our patients. Please, take in account that these patients are recommended for five years on endocrine therapy, are post-menopausal, usually receive an aromatase inhibitor for five years. Arthralgia, myalgia, vaginal dryness, a lot of symptoms, asthenia, osteoporosis and risk of bone fractures over time in maybe patients that are already fragile or older than 70-years old, for example, so, we really should take in account all the interventions for these patients. You can, of course, omit radiation therapy in selected patients, but we need data to select patients, where also systemic therapy, namely, endocrine therapy in this case, could be avoided. That's the case of the EUROPA trial, where you are one on the co-authors and co-investigators of the trials; you know that there is a Phase III trial that not only compare exclusive treatment with radiation, partial breast or 5-fraction whole-breast now after the FAST-Forward trial and endocrine therapy, exclusively, using ipsilateral breast tumour recurrence risk primary endpoint, but we have also a co-primary endpoint that is the health-related quality of life. The real question is for very low-risk patients, what was the real primary endpoint? I think that ipsilateral breast tumour recurrence was something useful to design a trial, but it's not our clinical primary endpoint, clinically relevant. I hope that I replied to your important question.

Dr Kaidar-Person: Yeah, it was perfect. I was also concerned. I liked very much what you showed about the ELIOT trial, and how the graph is opening for all those Luminal patients and we see the recurrences relatively late. We know that also from the CLGB trial. Are you concerned with regards to the LUMINA trial that we'll see the same trend, even though they highly selected a very low-risk population?

Prof Meattini: I'm basically not particularly concerned. The ELIOT trial really had high-risk features patients. If you imagine that one out of five patients were a triple negative, or more than four positive nodes, we really can't compare a very highly selected population as the Luminal, for example, with the ELIOT. But it was really a different time. We can't say that the ELIOT trial was... We can say that it was a negative trial, but they used a completely different Delta, for example, that was acceptable at that time, and there was not a lot of discussion of biology at that time. So, we learned over time how to optimise the design of these trials, so, I'm basically, not basically, much concerned in that sense.

Dr Kaidar-Person: And it's a much better population compared to the PRIME II also, even though the PRIME II was mainly Luminal, but these are smaller tumours.

Prof Meattini: Yes, of course.

Dr Kaidar-Person: Yeah, extremely limited.

Prof Meattini: Yeah, it is the main reason, because the PRIME II is a trial that we should always read and respect on the results, because you can observe quite high rates of local recurrence in patients that were stated as low oestrogen receptor. If you look at the San Antonio presentation that was being presented at 20%, 18% of local relapse in a category designed as oestrogen receptor low, without a threshold, in my knowledge. But really, it's not the same thing. If you consider Luminal-A or Luminal-B-like population in this

trial, I would never omit radiation therapy in such as a population where I can expect a 20% of local relapse rate. So, there really is a nice study, we should always think about it.

Prof Franco: I think, I mean, the main point is probably a matter of finding the right tool to properly select the patient, right? Because we've been knowing for years that if we stick to only like the clinical parameters that we normally use, meaning, being the size, the nodal involvement, plus also the receptor, this is, of course, very useful, but it's somehow limited, and that's why the omission trials still are testing genetic signature to be implemented in the selection, to properly select a low-risk feature. And probably, of course, we need to demonstrate that, with clinical result and long-term result. We might be able to find effectively a subset of patients with a very low-risk ipsilateral breast tumour recurrence, potentially even on a long-term. But then, of course, even in this patient, we would need to explore whether saying that the ipsilateral breast tumour recurrence at a certain time, 5 years, 10 years, is the same and it's very low, and so, it's okay, then, what kind of repercussion our treatment will have on the quality of life of our patient? That's, of course, the importance of having co-primary endpoints that explore also this, so, we can have also these elements to put into our decision algorithm to offer our patient the best treatment, not only in terms of prevention of local relapse, but also in terms of being less impactful on their quality of life. And that's why the EUROPA trial is very valuable in this.

Prof Meattini: Yes, Pier. I basically fully agree with you. That was the main reason, because the omission trials of radiation basically failed over time, until we keep the size, nodal, age only features. When we started including the biology, there, we observed that something was really changing. That's another point that maybe in the future could also be considered. There is the genomic testing that, actually, we are using only to de-escalate chemotherapy, as you know, but that's a lot of research in terms of genomic tests, also, in terms of de-escalation at all treatments, also considering radiation therapy. But I think that this is the future, and we are basically not concerned using the immunohistochemistry and the existing biology classification. That is cost-effective. You know that cost-effectiveness is also another important point that we should always consider for our patients. And I, really, I'm not concerned on de-escalate treatments in Luminal-A-like patients, with small tumours, of course.

Prof Franco: Yeah. So, Icro, you mentioned, you focused on selection, which is crucial, in general, in medicine, it's crucial in oncology, but of course, it is crucial in offering patients with PBI, and I was just wondering... Okay, we discussed about low-risk patients, but what are the main features that you would consider as high-risk, or let's say intermediate-risk? So, which are the features that you're worried about not to offer partial breast irradiation of a patient? So, when you, let's say, see a patient and you say, "Okay, this one is a low risk. I will offer him or her, a PBI, and for this reason in that patient, I wouldn't offer. I will go for whole-breast irradiation boost." What are the main features that you consider in your decision-making process?

Dr Kaidar-Person: I will even challenge Icro a little bit more, and ask will he differentiate according to the method of partial breast, because he mentioned earlier that there are different techniques, so...

Prof Meattini: Yes. Okay. Thank you for the question. Starting from the importance of selection criteria, basically lymphovascular invasion, inadequate surgical margins and lobular are the three features for patients that I would not offer partial breast irradiation, even more than G3. G3 can maybe influence me in being more aggressive in terms of systemic therapy, rather than partial breast or whole-breast. The size basically alone is not something that scares me.

Prof Franco: You mean within T2, or also...

Prof Meattini: T1, T2 When you have got...

Prof Franco: You not going for T3, right?

Prof Meattini: No, no, of course, not for T3, even because then why you use partial breast irradiation? I use partial breast irradiation, basically, if accelerated, was to reduce the overall treatment times, but now you have got FAST-Forward, so, it's not anymore, the main feature. What is the difference? It's the toxicity. It's the toxicity. So, if I have a T3, I have much higher chance to have a ratio between an involved tissue, an involved tissue that is unfavourable for partial breast irradiation. So, I could have higher late toxicity or adverse cosmesis. So, I lose the gain that I want, that I pretend with partial breast irradiation. Conversely, if I well-select patients, even considering the dosimetry of my patients, then, I can really obtain my result. My result is an equivalent local relapse for these patients with a favourable toxic effect. And this could be obtained with T1, maximum T2 tumours.

Prof Franco: Yeah, that's sensible. What about age, for example? 45-years-old with low-risk features, would you go for PBI? And no nodal involvement?

Prof Meattini: No, no, I think that we should start speaking about post-menopausal and pre-menopausal when we talk about treatments, because age, it's really meaning nothing. I can say more than 50 or less than 50, but then, there are too many features that you have to take into account that change completely the prognosis of these patients. So maybe...

Prof Franco: But age is in the guidelines, right?

Prof Meattini: Yes, of course, because we are human. We need the thresholds. But I think that post-menopausal is even more important, even because post-menopausal affects systemic treatments. Currently, post-menopausal never receive chemotherapy. Even using the genomic test and are endocrine-based therapy, there's a lot of implications and so on. And I would like also to mention Orit's question concerning technique that are even more challenge. I think that we demonstrate that technique is not the main point. Of course, even if you consider intraoperative radiation therapy, it's a technique that you, using electron, of course, because there you have got robust data, you should consider if you are able to well-select patients. The ELIOT trial problem was related to the selection of patients, not to the technique. The technique was okay. We know what we are going to do. We can say the same using the kilovolt IORT strategy. But then, you can use brachytherapy, you can use external-beam radiation therapy in 5-fraction. You can use intraoperative radiation therapy when you have got enough features concerning tumour and characteristics. I'm not concerned, 90%, usually, about technique. Of course, in my personal local practise, we go for the Florence trial, because we have much experience and very nice results, in terms of acute, late and cosmesis results, but it's not mandatory of course, I think that the experience of every single centre with a technique, it's really the expertise, it's really more important. For example, now we recently published, on Practical Radiation Oncology, the evolution of the Florence trial. We now use VMAT technique, and we use the 30 Gy in 5 fractions, using consecutive days, with very nice results, for example. So, we evolved over time with our technique.

Prof Franco: Great, great. Thank you, Icro. I have a question. I don't know if it's provocatory or if it's just a stupid question, but one of the... let's say when you mentioned the result of the ELIOT trial, and you nicely showed us that the rate of ipsilateral breast tumour recurrence for triple negative breast cancer was very high, around 20%. So, biology is important. Those intrinsic subtype should be something that we should look and avoid probably prescribing and offering patients with partial breast irradiation, and if you look at the guidelines, one of the exclusion criteria for PBI is having received primary systemic therapy, mostly because those patients are local advanced tumour or more aggressive tumour on biology. But I see, for example, sometimes, like now, the indication for primary systemic therapy is even for early-stage tumour, right? So, let's say you have an early-stage T1c triple negative breast cancer, that after primary systemic therapy would achieve a pathological complete response. So, do you think... And so, theoretically, it's a triple negative breast cancer, so, shouldn't undergo partial breast irradiation and receive primary systemic therapy. So, it's an

exclusion-criteria in the guidelines, but do you think it's something that crazy to think, at least in a research setting to investigate whether partial breast can be offered in this setting?

Prof Meattini: Thank you, Pier, because this is the next step of partial breast irradiation. So, investigating the intent. Pre-operative, post-operative or after primary systemic therapy. In the context of clinical trials, I think that we can further investigate the role of partial breast irradiation, even in case of primary systemic therapy. Of course, in the context of a clinical trial because you know that it's quite true that we, more and more, offer primary systemic therapy in a very early-stage breast cancer, but this is most of time for triple negative or HER2+ biology, that at the same time are still the quite highly aggressive disease. So, we need a trial, because I am quite sure that the ipsilateral breast tumour recurrence is not the main point for these patients. That when recur, recur in a systemic way. So, I think the partial breast irradiation, in the future, could be an option, even in the preoperative setting, if you consider high-risk biology, where you can perform radiation when the tumour is there, and you can obtain even an effect, a biological effect, and maybe increase also the effect of the immunotherapy, for example, in the triple negative. So, we need trials. We need trials including partial breast irradiation, even in the settings that currently are contraindicating by recommendations.

Prof Franco: Yeah, that's a good message.

Dr Kaidar-Person: Yeah, but I would say that it's maybe in trials, but there were some studies suggesting that whole-breast irradiation in patients with HER2, I guess, there is some kind of radio-sensitization by trastuzumab, an anti-HER2 treatment, so they might benefit from whole-breast. So, for those type of population, I will take it slowly within a trial, especially triple negative. Also, they sometimes have more focis. We know that they tend to recur locally more than in other cancers. So, I would be careful, and only have them within trials to try to understand. I think now, as Icro said, that with correct planning, we see much less toxicity in whole-breast irradiation. So, we need to work on that as well.

Prof Meattini: Of course, of course. We have to find the courage to say that sometimes partial breast irradiation is not indicated due to unfavourable dosimetry planning observations. But now, you have got the FAST-Forward, so, you can easily move from the 5-fractions to the whole-breast and say no to partial breast irradiation in those cases. But I always should prefer partial breast irradiation because you haven't got a Phase III trial that demonstrated you have the same toxic effect, but then, when you have observed that the plan is not good, you can easily offer 26 in 5 and use the FAST-Forward for the whole-breast. Now, it's even better and easier for us.

Prof Franco: Yeah, which is clinically sensible, but I think you also should be driven by the ALARA concept, so as low as reasonably achievable, so, if we can de-escalate the volume, we should go for it, if it's clinically safe.

Prof Meattini: Absolutely. Absolutely, Pier.

Prof Franco: Great. I don't know if there's any questions from the audience? Otherwise, I think it's time to close the session, and I want to thank Icro, of course, for the nice talk and the nice lecture, Orit, for the very lively and interesting discussion, all the audience for attending and of course, e-ESO as always, for hosting us.

Prof Meattini: Thank you very much. Thank you very much.

Dr Kaidar-Person: Thank you. It's always a pleasure. Thank you.

Prof Franco: Have a nice evening.