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Hypofractionation in breast cancer RT

Prof Poortmans: So, thank you very much for the nice introduction. I will share my screen. But it's a bit forward. So, I'm Phillip Poortmans, I, indeed, sorry, I needed to smile. Work in the GZA Ziekenhuizen, Dutch is very easy but difficult to pronounce for a lot of languages. Most of you know me, Radiation Oncologist, I made the tour of Europe in my career and had some other functions, among others, ESTRO and the European Cancer Organization. So, the topic of today is Hypofractionation in breast cancer. And I'm very happy and privileged that my good close friends, Icro Meattini and Pierfrancesco Franco will accompany me in this by taking care of the questions, notifying when you send them in, so, that we can handle them. Most of the questions will be discussed at the end of my presentation. However, if it is really topically related to part of my presentation, they will show a hand to me and we can discuss them even in between. So, what are the current trends in Hypofractionation for breast cancer? This is my disclosure; it's absolutely not related to this topic. A short introduction about Hypofractionation in breast cancer. We should not forget about improvements in technology. And when I started my training back some time ago, 35 years ago, it was all very rectangular and square radiation volumes that we treated. Just anteroposterior, posteroanterior and lateral, for most of those for breasts just tangential but over the years, we improved our techniques to a major extent and this facilitates hypofractionation, because now we know much better which dose we are delivering, where, in three dimensions. So, thereby I say that the 20th century was the era of field-based radiation therapy, and it went up to static IMRT. In the 21st century, stop speaking about fields. We are speaking about volumes. IMRT, VMAT, should not be based on fields that you put during the simulation. It should be based on the volumes and this is not yet over. We will move more and more to adaptive radiation therapy also, in breast cancer, to adapt our treatments to volumes that might change, to movements but also, to biological and functional modifications. So, techniques are important. However, techniques serve goal. It's not the other way around. So, the most important is to know what volume to treat. And for that, you, of course, know the Estro Atlases which offer you an excellent guide. To my opinion, I'm involved. I may be a little bit biased but they offer you an excellent guide to how to control the lymph node volumes, the breast and the thoracic wall and for the boost and partial breast radiation. We have other guidelines including the very good GEC-Estro ones. So, forget the fields, again. We also offer help from ESTRO with the Falcon workshops which is on contouring, and for breast, we do it several times a year, and just two weeks ago we had another very successful session with more than 40 participants worldwide. This is an example of not-so-old contouring differences. You can see that the heart is pretty homogeneous but even the breast, there are some differences but it's around the same volume and we can homogenize this even further. And only after contouring, we can apply the right techniques. An example of 3D conformal radiation therapy, free breathing, volumetric IMRT and this in breath-hold, 3D and volumetric IMRT. If you don't start from the right volumes, you can apply the best techniques but they will offer you very little help. So, again, remember to ask

questions, send comments at all time, use the Q&A button that you have all on your screen. What's the evidence? So, the evidence is not so young. Well, it started already 85 years ago, we spoke about the difference between the effect of radiation on the tumor and on the normal tissues. And the difference between that we call the therapeutic window. How plays hypofractionation in this? If you look at the basis, you get the impression hypofractionation is bad for the therapeutic window, but let's go into detail and let's focus on breast. And by the way, it's quite similar for prostate cancer. We look at the total dose and at the dose per fraction. Never change the dose per fraction without adjusting the total dose. We will not speak about also important overall treatment time, the time interval between fractions and the volume in cubic centimeters. So, this is more for the non-Radiation Oncologists among you. If you hit once with a very big smash hammer, it's not the same as giving 10 times a gentle tick to the same volume. In the same way, 1 x 20 Gray is not the same in Biology as 10 x 2 Gray. Already 50 years ago, Ellis, Frank Ellis proposed a formula to take into account changes in fractionation. And this, the use of this in Norway and in Sweden, led to a disaster. They had based on these calculations' other fractionation schedules for breast cancer and with a lot of late side effects. The early side effects were similar. The late side effects were very much different. So, this Ellis formula was a very nice recipe for disaster. But then, came already 45 years ago, the linear-quadratic model, which was based on just observation of dose fractionations on skin reaction in mice. And the linear-quadratic component has two parts. The alpha component which is the direct damage and the beta component which is doubled. You can explain it as a DNA, double-strand break so, a logarithmic effect. And the formula is a search. The linear component is a single hit, non-repairable, the quadratic component, the beta component is that you need two events to have the damage. This is sublethal and this can be repaired. And what is the alpha-beta value? It's the place where the alpha component is the same size as the beta component. So, in a way, the alpha-beta relation shows how tissues react to changes in fractionation, so, a sensitivity to fractionation, but this is not constant. It can depend on a lot of factors, including oxygenation, including the absolute dose volume, including, of course, the tissue in question. And in general, the alpha-beta is high around 10 for early reactions, is low around two to three for late reactions, and is high for tumors. However, it's not high for breast and prostate cancer. We now estimate it to be around 2.5 of an alpha-beta value. And this favors hypofractionation, because then, you are at the same level as late tissue reactions. So, based on this, the first trials were set-up, the START trial, for example, assuming an alpha-beta still very, very careful, of four to five, they had in the START a trial three-dose fractionations that should show that normally hypofractionation would lead to a proportionally lower effect on the tumor compared to the late normal tissue. So, in theory, the therapeutic ratio would become smaller but is this true? Now, the real trials, and there are several, showed, confirmed that the alpha-beta in breast cancer indeed is low, could be as low as below two. However, be careful that you have the right techniques to give a homogeneous dose distribution. Because sub-doses, to low doses and over doses might be more important for late effects, if you apply hypofractionation. So, when using larger fraction sizes, you have to lower the total dose. And if you have a homogeneous dose-distribution with higher doses, you have a double effect, double trouble. And if you have this in hypofractionation it could be even triple trouble. However, is this true? No, I will show that in reality, the differences are nearly inexistent. It is really a very low change if you go from 2 Gray per fraction, to 4 to 6, it's a very little change. So, the triple the double trouble and the triple trouble effect is not that important as thought, even not in patients with large breasts. Again, don't forget to have your questions formulated and Icro and Pierfrancesco will give them through. So, the English say the proof of the pudding is in the eating. First trial publishing long-term evaluation was the Canadian led trial, not all participants were Canadians, and you know they were randomized between conventional fractionation. Now we should rather call this old-fashion fractionation against moderate type of fractionation which now became conventional fractionation. And there is absolutely no difference for local control and also for skin and subcutaneous tissue there are no differences, even not at 10 years follow-up. So, the difference, there is a difference but it's the time since treatment, the age of the patients, the size of the tumor but the fractionation plays no role at all. Also, the English did excellent studies. You know the START B trial which is now accepted as the most attractive treatment schedule, 15 fractions of 2.67, delivering 40 Gray. And here, it even shows that it might be more

effective and more gentle for side effects. So, is there a difference? No, the P-value is non-significant. However, if there would be a trend, you can see that moderate type of fractionation might even be better. And if you look at morbidity, there is again the same trends that 40 Gray in 15 fractions is more gentle compared to 50 Gray in 25. Of course, there was a lot of criticism and reluctance to apply it because it was including very few chest wall patients and few boost patients, et cetera. Thanks to the Chinese mono-institutional study. We have one prospective trial comparing a more hot fractionation schedule with the conventional and they confirmed that there was absolutely no difference neither for local-regional recurrence as for toxicity. So, the comment is that this research added to more understanding. However, I was not so convinced of this comment, because for me it was already demonstrated why should it be as good, at least as good for the breast and not for the chest wall? Anyway, the pudding was excellent. Don't forget, I'm asked to ask you to invite you several times to have your questions. So, where are the limits? Because now I spoke about moderate type of fractionation. But we can go further, we can go to... you can call it how you want, ultra-effect hypofractionation, extreme hypofractionation, et cetera. The first is the FAST study in which the selection of patients, rather low-risk patients, with a median follow-up of three years were treated with either the conventional fractionation or 5 x 6 Gray once a week or 5 x 5.7 Gray once a week. So, this is in overall treatment time identical. And as you can see, the 5 x 5.7 Gray in five weeks is equivalent to 25 x 2 Gray, lower in acute toxicity and about the same non-significant in late toxicity. The 5 x 6 Gray, low acute toxicity, however, slightly more late toxicity at two and a half years of follow-up. So, the 5 x 6 Gray once a week seems to be a little bit more toxic. Breast shrinkage, again, no difference between 50 Gray in 25 and 5 x 5.7 but more breast shrinkage also on longer follow-up with 5 x 6 Gray. You all have read the paper, of course, the FAST-Forward study where the now conventional dose fractionation of 40 Gray in 15 infractions, was compared to 27 Gray in 5 and 26 in 5. And this is the acute toxicity. The acute toxicity is about the same in grade 1, but if you look in grade 2, if there would be a difference there is lower acute skin toxicity with the ultra-hypofractionation compared to the moderate type of fractionation. Ipsilateral breast tumor relapse, absolutely no difference and if you want to take a bad look, if you don't like, it it's even better with the ultra-hypofractionation. Disease-free survival, absolutely superimposing slopes. And then, late side effects, no significant differences at all for the 26 Gray in 5 fractions in one week. However, more changes in the chest wall or the breast with 27 Gray. So, you can see that it is really critical, 26 Gray is as good, but the 27 Gray is more toxic compared to the 26 Gray and to the 40 Gray in 15 fractions. Clinical assessment at five years, 40 Gray, 26 Gray, no significant differences, however, slightly more differences with the 27 Gray. So, based on this, new estimations have been made for the alpha-beta of breast tissue and it is around 2. So, this is nothing new, late side effects, you know, we assumed it to be in between 2 and 3. So, concluding for late side effects, 26 Gray in 5 Fractions is equivalent to 40 in 15. It has a clear benefit to patients also, to healthcare systems, maybe not to the pocket of the radiation oncology department. So, the UK adopted in October the 26 Gray in 5 fractions as the new standard for breast or chest wall alone. Don't forget to have your questions. So, let's bring it together in a kind of discussion. We reviewed this and as you can see it, Icro participated to this review and it's comparing moderate type of fractionation to the old-fashioned 50 in 25 Gray. We have sufficient patients and sufficient trials that showed that it is completely equivalent. However, you could be very strict and say it's only for the groups of patients that have participated. So, after mastectomy, only few patients were included in the original trials. But thanks to the Chinese trial, we have sufficient data to call this hard evidence. Lymph node irradiation. We agree that only a part of the patients receive nodal irradiation. Advanced stages most patients had early disease stage with a boost. In some trials a boost was given often but it was conventionally fractionated. For DCIS, thanks to the at San Antonio presented data by Bun Chua, we now know that it was a randomization between yes or no boost for DCIS and yes or no hypofractionation which could also be chosen by the center. So, it was a 2 x 2 design and one of the two could be randomized or chosen. Absolutely, no difference in local recurrence for DCIS. By the way, also note that local recurrences in DCIS also went down a lot compared to the older series. So, putting it all together in radiobiological model, linear-quadratic model versus the trial results, we are even for moderate type of fractionation, a little bit more gentle for the normal tissues of the patients compared to 50 Gray in 25

fractions. Don't forget to ask your questions. Okay, the discussion is still there because you can say we didn't include the lymph nodes there are not enough data on hypofractionated boost. There are a lot of excuses not to do it. However, why should it be equivalent for the breast or the thoracic wall and not for the lymph nodes? You can say, okay, for the internal mammary lymph nodes you include more lungs and hearts. So, let's take a look at the tissues outside of the target volumes. And I made some calculations for that. So, just an old technique that we used when we group patients in the internal mammary lymph nodes trial. This dates from quite some time ago, more than 10 years ago but you can see that it's pretty conformal, nicely including the internal mammary lymph nodes. And here, is also the coverage. And yeah, that's the important one. That's a close look at the heart, in green, and the lungs, in brown. If you treat the internal mammary lymph nodes, you don't give the full dose to the heart or the lungs, that's only a part. Most of the inclusion of normal tissues is in the range between 30 to 70% of the dose. So, if you treat with a conventional fractionation 2 Gray per day, most of the normal tissues that receive a dose receive fraction sizes of 0.5 to 1.5. Every type of fractionation, instead of 0.5 it's 0.67 and instead of 1.5 it's 2. So, you are much higher on the alpha-beta slope. So, calculating it and taking a bad example, the Canadian schedule, which is hotter than the current to be taken a standard 40 Gray in 15. Realistically, alpha-beta for late normal tissue is 2, and for breast cancer 3.5. Then, you can see that between the 50 and 70% isodose line the effect comparing 2 Gray fractions or 2.66 Gray fractions, you even spare dose. This is calculated using the alpha-beta formula with the fraction sizes that are with the 50 to 70%. But even if you go to the 90%, it's lowered for hypofractionation compared to old-fashioned fractionation. If you go to an optimistic scenario, alpha-beta is 3, both for late-normal tissues and for breast cancer, you can see that it's even better. You really spare normal tissues by using hypofractionation. And even if you go to the 95%, you'll spare even if you go to the 100% you'll spare. And the worst-case scenario, 1 Gray for late-normal tissues, 5 Gray for breast cancer, we know this is not the case. Then, it's about equivalent for the 70 to 50% isodose lines where part of the heart and the lungs can be included. If you go to the higher doses, you have a slightly higher radiobiological effect of hypofractionation, but not a lot at all. So, this matches, in fact, the outcomes of the trials. So, this shows that by introducing moderate type of fractionation, even to the internal mammary lymph nodes, you relatively spare normal tissues. So, what was the Dutch protocol? I still worked in the Netherlands. Then, in 2009, we assumed 2.66. The Canadian schedule was the highest dose in the target volume. There was no discussion for breast and thoracic wall and for simultaneous integrated boost. Below 50 years, we only included patients from 2011. January 2011 on, because the young Boosts trial was still ongoing and every center participated, and that would interfere with the standard practice. There were some doubts about regional radiation therapy and there are more doubts about combination with reconstructive. So, this was the old-fashioned conventional with the sequential boost. This is recalculated with a simultaneous integrated boost, did 2.3 to the boost reach and 1.88, 28 fractions to the whole breast. And this was the moderate type of fractionation with simultaneous integrated boost. 21 fractions, 5 fractions more in 2.17 Gray to the breast, and 2.66 to the boost volume. The current protocol, they switched to the UK schedule in 2020, 40 Gray in 15 but it's still not adapted in every country. And there are a lot of radiobiological reasons. There is re-population, redistribution, re-oxygenation, repair. We added the fifth R, resistance but the most important of all is the sixth R, which is reimbursement. Reimbursement determines current practice in most countries. Don't forget to have your questions. And how comes? Now, reimbursement has an implication for all treatments. We published this as the EBCC, European Breast Cancer Congress 12 Manifesto, very recently, as you can see. And this goes for pathology, for imaging, for medical oncology, surgical oncology, reconstructive oncology, and radiation oncology. And it is recommended, however, it is blocked by reimbursement. And we calculated the financial impact worldwide. As you can see, there are participants from all over the world. And from the respondents, in the majority of the countries, because we asked the reply per country. In 60% of the countries, 30 to 40% reimbursement decrease is caused by switching from 50 Gray in 25 to 40 Gray in 15, so, this is very impressive. Don't forget to have your questions ready. So, concluding, do we need more evidence for moderate type of fractionation? No, in country-wise, it's a standard for a long time, in the UK it is a standard, as I showed, for 12 years, in the Netherlands. And it is a standard in many other departments and

countries. And do we need to prove it for internal mammary lymph node irradiation? Then, you could also say we have a trial in head and neck cancer, in T3 laryngeal and then, we don't accept the results for T2 oropharyngeal. It just doesn't make sense. So, frustrating a little bit was what we wrote when we saw the Chinese trial. If you look at the Chinese study, it was good as a study and the outcomes were good, but it was a 2-D study. It was using 2-D radiation therapy, no real quality assurance. So, if you look at it, let's cut the crap and make a point on it. It was published in Lancet Oncology and we had our political comments. We didn't need this information. It should have been accepted already, long ago. Why do we as radiation oncologists need this kind of evidence to convince our colleagues? So, trust in hypofractionation but aim at homogeneous dose distribution. My first choice for breast-only, chest wall-only and partial breast irradiation is 26 in 5 fractions in one week. You can use once a week for frail patients maybe not the 6 Gray but the 5.7. And for locoregional, awaiting the results of the simultaneous integrated Boost trials, and I invite you warmly to the ESTRO Congress at the end of August, in Madrid, where the first results of the real prospective trial that evaluated this, the IMPORTI HIGH study, will be shown. So, when could we still use 50 in 25? When combined to radiosensitizers hypothermia or especially systemic therapy, if you want to have the interaction between the radiosensitizer and the radiation therapy prolonged, you have five weeks of interaction instead of three weeks. Consider it for re-irradiation, but I quit it. I went for re-irradiation to 40 in 15. Why not? It's gentler than 50 in 25, and else, it's completely outdated. It is a schedule that should be abandoned. And then, with the help of Icro Meattini, and many others, including also Pierfrancesco, in the extended Consensus Panel, we worked very hard on the new ESTRO ACROP Consensus recommendation, which is well underway to being written down as a manuscript which is currently circulating among the co-authors. So, this will be released soon and please use it. It's very practical, it really makes sense. It does not make research impossible. It even advisors to do research. And if I want to stimulate research, in one field, in breast reconstruction. I use 26 in 5 Gray in one week in breast reconstruction only treating the real target volume but this is absolutely not substantiated with evidence at this moment. So, a lot of people to be acknowledged, too many to list here, and now we go to the questions Pierfrancesco and Icro, all yours.

Prof Franco: Thank you, thank you very much, Phillip, always. Very nice listening to your talk. Very informative and very educational so, thank you. I think we have a question coming from the audience. And the question is coming from Jose. And Jose is asking, does it make sense testing in the setting of breast cancer that the DAHANCA accelerated radiotherapy fractionation, 6 fractions a week? Which is, I mean, we have even more accelerated schedule like the one-week schedule, but you think it makes sense or...?

Prof Poortmans: Well, it's-

Prof Franco: Is it both head and neck, hence?

Prof Poortmans: It is head and neck, of course, but it made sense when we used the 50 Gray in 25 because how comes that the 40 Gray in 15 might even be better than the 50 and 25. That's because you go from five weeks to three weeks. It's not proven, it's not real evidence but there is a very nice article from John Yarnolds and the Star group where they calculated that the loss of radiation between three and five weeks of treatment is 0.6 Gray per day, identical, completely identical to head and neck cancer. It sounds strange because they are completely different tumors, also, from radio-biological point of view. But nevertheless, it was for me a critical point to go over, already when I was in the Netherlands, to a very strict regimen, where the overall treatment time was respected. I remember patients in one of the centers where I worked, where 25 fractions were given in more than 50 days. I've seen quite some recurrences. If you go for protracted treatment schedules, you lose efficiency also, in breast cancer. The Netherlands, I know from my former place still there, it's very simple. All cancers, all indications, all treatments of five times a week points, irrespective of bank holidays, of maintenance, of whatever. However, it depends on the organization whether you are capable to do this. And it's an organizational issue which is to my opinion, very important. Once you are at three weeks of treatment and below, I don't think so, not for breast cancer. I'm not sure whether the re-population already starts earlier. Today, I had a patient just for only 26 Gray in 5 fractions, it starts on a

Monday, Tuesday, Wednesday Thursday, on Friday there is an update of the software of the Institute so, on Friday and on Monday we cannot treat because it's a major update. So, she will receive the 5th fraction on the Tuesday hereafter, I'm not worried because even then, the overall treatment time will be just eight days. So, I don't mind if you are below the three weeks overall. Of course, you also see the FAST study with 1 fraction a week. The tumor control is good in low-risk patients. So, take also the risk profile into account. A big locally advanced triple-negative is not the same as a small luminal A light tumor.

Prof Franco: Thank you, Philip.

Prof Meattini: Thank you, Philip. May have a...as for a comment, so, if your main comment is, and the conclusion is that, at least, moderate hypofractionation for all or for most patients, but the reimbursement, as you clearly stated, affects also our practice. Some comments on how to overcome this huge problem even thinking about the advent of the 5-fraction schedule. Thank you.

Prof Poortmans: Let me go to politics. I think that the most important is to speak with our patients and our patients' advocates. If you read the EPCC manifesto, you can see that I made the calculation for one European country. What it impacts of switching from 25 fractions to 15 fractions means for 1000 patients a year. It's huge, they are millions of euros. In Belgium, thanks to the COVID pandemic, it's the only good thing I know from the COVID pandemic. The FAST-Forward results have been applied nearly immediately. We switched to the FAST-Forward schedule initially for a limited group of patients but we extended gradually. Thanks to that end, the reimbursement has been waived. So, we get, for the time being, the same reimbursement as for 40 Gray in 15 fractions.

Prof Meattini: So, thank you. So, probably, the time has come to rethink the reimbursement system. And so, we did not receive any other questions. I have another question, more clinical, about breast reconstruction and the 5 fractions. Have you have got some concerns or not?

Prof Poortmans: No, I don't have concerns. My concern is that we don't treat right volumes. Please, read the ESTRO guidelines on that. And if you treat correctly the real target volume, then, most of the reconstructed material does not receive the full dose, but will receive between 50 and 70% of the dose, which is already much lower. And why should alpha-beta of an implant be different from normal tissue? It's of course the fibrous tissue surrounding the implant, the capsular, which gives the capsular contraction, but also, there, the alpha-beta should be the same as normal tissues. And even more important in homologous, otologist reconstructions the implanted material is not part of the target volume. So, start with treating the right volumes and then, the risks will be extremely limited. However, we don't have data about it. We do it and we will collect our outcomes, our results. It's still a limited number of patients, but we have some and it's our duty, of the community of radiation oncology and breast cancer to perform for the studies in this.

Prof Meattini: Thank you, Philip.

Prof Franco: Philip, what about boost in hypofractionation? 'Cause I mean, we know with mild hypofractionated schedule, the boost was not like strictly included in the treatment protocol. And it was like at the institute's discretion, in the Star trial, 60, 50 to 60% had a boost, but it wasn't in the protocol. Of course, we are waiting for the result of one American trial, RTOG 1005 and the in PRO, but how can we plan our treatment strategy when we want to provide a patient with a boost but at the same time providing hypofractionated whole breast radiation?

Prof Poortmans: Well, there are several aspects. First of all, how comes that some countries give 95% of the patients a boost and other countries only 15%? This is a factor of more than 6 in difference and the results are equivalent. It is because the boost is also supported by reimbursement. So, that's an important issue to know. It's not always the right incentive to advise a certain treatment. However, in high-risk patients the boost offers a benefit, it spares breasts, not lives. It spares breasts. I think that the first and most important

issue in the boost is to define the right volume. And now, we are faced with oncoplastic reconstructive surgery during the lumpectomy, we face sometimes boost volumes that we cannot limit, to let's say, 25 to 50 cubic centimeters, but we get a boost volume sometimes 200-250 cubic centimeters. In those cases, I speak with my patient and I say if we give a boost, you will have a reduction of the recurrence-rate, but your breasts will suffer a lot on the cosmetic outcome and maybe, even breast pain. If so, try to keep the volume as small as possible. Fractionation for the boost, there are trials ongoing, underway and the IMPORT HIGH will give us a clue to that. What kind of integrated boost we can give? We're working, you are both involved on a protocol for boost volumes and boost fractionation. It's a very difficult issue. Currently, if you ask me, what are we doing now? Because of the COVID pandemic, we still give a one-time 6 Gray boost to as small volume as possible. But once the COVID period is gone, we have to go back to our normal boost which was 5 x 2 Gray. And that doesn't make sense. Giving 26 Gray in 5 fractions and then a boost of 10 Gray in 5 fractions, does make sense. So, we are setting up prospective studies to compare the 5 x 2 with more innovative and creative solutions.

Prof Franco: Thank you, Icro?

Prof Meattini: Just a quick, quick another last question. Could brachial plexus be a concerning nodal irradiation using a moderate or 5 fraction hypofractionation?

Prof Poortmans: Well, we don't see with the nodal sub-study of FAST-Forward, which will be analyzed in two, three years from now. So, too early to say that. But if you recalculate by lowering the total dose, the fraction size is compensated. So, I don't expect it, but be careful. Of course, we have to wait for the data. Normally, 26 Gray in 5 fractions should go. And another thing is, of course, you don't need to include the brachial plexus in your 100% isodose lines. Use proper contouring, use the ESTRO Atlas and there will be little brachial plexus in your CTV.

Prof Meattini: Yeah, thank you. You have been really clear during your presentation. That's a point, okay, Francesco?

Prof Franco: Yeah, I have, I think, one last question. I think you touched upon that during your talk when to still use conventional fractionation. So, you mentioned the association with systemic therapy and I'm thinking about capecitabine. You mentioned radio-sensitizers so, let's say triple-negative, locally advanced breast cancer, primary systemic therapy not achieving complete response in the nodes or need for adjuvant chemo with capecitabine plus radiation. So, maybe that could be an option for conventional fractionation. But for example, another setting could be a HER2-like disease, primary systemic therapy. Again, no complete response in the node. Need for radiation and need for TDM-1, let's say. So, how to combine the need for hypofractionation with systemic therapy other than radio-sensitizer? So, can we still use hypo, do we need clinical data or studies? So, what's your approach on that?

Prof Poortmans: My advice is to collect data. I don't see an issue with the combination of, for example, TDM-1, depending on the fractionation because the total dose is lower. And I think that it's more related to total doses than to fraction sizes. Never mix both, never mix fraction size with total dose. They are different issues. And there is another example that you didn't mention, in BRCA carriers with PARP inhibitors, also then, you might like to give it for a longer time to have more positive interaction between the PARP inhibitors and the radiation therapy because that's really also very attractive combination.

Prof Franco: Yeah, that's true, that's true. I missed one. Thank you, Icro, do you have something else or...?

Prof Meattini: I think that the last points were very, very nice question. So, olaparib,trastuzumab and capecitabine are and will be the most used components in the future. So, yeah, thank you for the replies and for the nice discussion.

Prof Franco: So, Philip, just one quick one. So, the 5 fraction in one week, you would be very confident in using for whole breast irradiation, for chest wall without reconstruction, even for partial breast radiation but a little bit more cautious for regional nodal irradiation and reconstructed breasts, or am I getting wrong?

Prof Poortmans: You're right, but I know, and I assume that in a couple of years from now we will introduce it for locoregional as well. The nodal sub-study of FAST-Forward accrued very well and we will get soon some data about early side effects. And I assume that they will all be favorable. The 27 in 5 fraction arm was, of course, after the analysis of FAST-Forward, closed and it continued with the 26 in 5 fractions versus the 40 and 15 fractions. So, our current standard protocol is 26 in 5 fractions for whole breasts, whole chest walls, irrespective of reconstruction, all ages, all grades, all, continue please.

Prof Franco: Okay, that's perfect. So, it's quite reassuring that we are... for people that are using it, that tend to be a safe option to offer patients. And of course, like logistically for the department and for the patient herself, it's a very reasonable option to offer.

Prof Poortmans: This morning, on my follow-up, I saw a patient. It was in fact the first patient who had some side effects off the 26 in 5 but it was a very obese patient, BMI above 40. And, you know, with 50 Gray in 25 fraction you always from the third, fourth week on, you had issues with moist desquamation in the inframammary fold and in the axillary folds. That was, we were used to that. With the 40 in 15, it's less. And it appears after you finished the radiation therapy and this was the same here. So, she had 26 in 5 and two weeks after completion of radiation therapy she had the moist desquamation in the axillary fold. But again, this was a very obese patient and it's an acute reaction, it's not a late reaction. Independent of the fractionation schedules.

Prof Franco: Yeah, well, I was saying it mostly depends on the patient's characteristics rather than the fractionation. So, it makes sense, right. Icro, do you want to close the session?

Prof Meattini: Yeah, yeah, no, I think that it's a very nice discussion. I think that we have to rethink also, as you said, how we communicate with our patients by using this new schedule and fractionation duties. Acute effects and there's no more space, no more room for conventional fractionation. I think this is the main message of this session and a lot of open questions but in the right direction. I think that moderate and ultra-hypofractionation will be substantially the future, I think. So, thank you very much, Phillip and Pierfrancesco for this nice discussion and the audience, thank you very much, really.

Prof Poortmans: Male breast cancer, there comes in a question. What about 25, 26 in 5 fraction in male? I don't know, that's another that I would suggest to collect data prospectively, but the most logical is why should a male on this aspect be different from a female? I don't think so.

Prof Franco: Okay, right. Thank you very much, Philip. It was nice as always, and excellent. And thank you everyone for watching. And thank you, Icro.

Prof Meattini: Thanks a lot.

Prof Franco: Thank you. Bye-bye, take care.