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Q&A and conclusions

Dr Biganzoli: So, thank you to all the speakers for a very, very interesting morning. High quality level of your presentation. And hope the people are here with us spending their Sunday morning, no Saturday. Wow. I have the Sunday free. With us. I've enjoyed the presentations. So, I get some questions mainly focused on systemic treatment. So, let us start with some of these questions and then we will spare some time to discuss also surgical and radiotherapy issues with our guests. So, the first question, is for our medical oncologist, and is whether we should consider chemotherapy dose-reduction upfront for a person that is age 70 plus. So, they are not specifying the setting. And I prefer to give the mic to Etienne and Nicolo and add some comments if you have not pointed out things I'm thinking. But please, go ahead with your answers.

Prof Brain: Yes. Thank you, Laura, for this question. And I think my true belief is that given the fact that there is potential frailty in roughly 40% of our allcomers patients above a certain age, from 70, I would say that to consider adjusting upfront and slowly and in a stepwise-approach increasing the dose, if no issue of side effects is faced, is clearly correct for me. It is also supported by the fact that if you take some drugs like taxanes, even if you have very similar pharmacokinetics in these patients, in these old patients, you can get different spectrum of side effects, and this toxicity can be higher just because the functional results are different. So, adjusting upfront, for me, is a good attitude. It's very difficult to demonstrate. It has never been completely demonstrated as something which is a strategy-useful, but I truly believe that it's right.

Dr Battisti: Thank you very much for this question. Yeah. I fully agree with Etienne. Yeah, I think this is a very good strategy to adopt with all the individuals. You have to go more slowly and you can always titrate the dose in case of good tolerance later on. But you have to consider that these patients actually have less functional reserve, may have issues with organ function. And I guess it depends also on what is the specific setting you're treating the patient in, whether it's palliative or curative, what are the individual status of toxic agents that you are considering. But I agree that's a good strategy. And obviously you can also help better inform the discussion with patients perhaps with using chemotherapy toxicity prediction tools to actually tell them whether that person has a low, intermediate or high-risk of severe toxicities to understand also what are that person's views in terms of benefits versus the potential risk of side effects on the specific treatment. But yes, I fully agree using an upfront dose-reduction is good practice if you have a concern about the safety profile of these agents. And obviously, as I mentioned in my talk, use geriatric assessment, chemotherapy toxicity, prediction tool to really have a look at what is the individual overall health of that person.

Dr Biganzoli: Okay. I would like to comment because you're quite... your answer a little bit surprised me. The question was based only on a chronological definition of the patients, 70 plus. So, personally, I do not think

this strategy of dose-reducing upfront the dose, just because the patient is 70 should be advertised and supported. I believe that we can adapt this strategy to the performance of our patients, or to the health status of our patients. So, without at least a screening test for fitness or in case of chemotherapy tests looking at the risk of toxicity, why should we dose reduce? 40% are at risk, in the general population, we try... we risk it to under-treat 60. And this especially in the adjuvant setting, seems a little bit concern as strategy. So, can we agree that age by itself should not be a criteria for considering dose-reduction upfront, but was implicit in your answers that we have before to select the patient?

Prof Brain: I agree. You make a make a very good point, Laura, but what I meant answering is that just as a rule of thumb, because nobody... it's maybe half/half at risk because of a screening test for frailty, which is impaired. I think as a step-wise approach is okay for me. But I agree that if you proceed to some geriatric assessment and some screening, if a screening test is okay, you can go for standard-dose as in younger ones. But even in those with a fit test, I questioned sometimes the dose. And it depends vastly according to the age. Because taking this decision at 70 is one point, but at 85 or 80 or above, it's very, totally different. So, I agree. Chronological ages cannot be the sole criteria.

Dr Biganzoli: Okay. We have spoken about the risk of cardiac toxicity related to anthracyclines and then also to trastuzumab anti-HER2 agents. So, there is a question that is asking whether there is an age cutoff limit to use anthracyclines in the elderly.

Dr Battisti: So, should I make a start? No, I mean, I don't think there should be an age cutoff for the reason that we just described in our EUSOMA-SIOP recommendations, we made the point that, for example, even sequential combinations anthracycline-taxane could be used in very selected, carefully selected treat. Older patients with high-risk disease, for example, in the adjuvant setting. So, again, you should define what is the individual health, fitness, or frailty of that specific person. And I guess also what is the risk, what that person has to gain, for example, from using an anthracycline? If you think about, again, anti-HER2 treatment, on the other hand, I'm pretty much reassured by the data that I mentioned during my talk that obviously this type of cardiac toxicity is reversible. There are data, for example, from Persephone showing, again, shorter course of anti-HER2 may not necessarily be inferior from that of 12 months course in the adjuvant setting. So, again, you shouldn't be making these decisions based on the chronological age alone. But really look at what are the individual circumstances of that, for that person. And I guess, again, for example, for when it comes to using anthracycline, you can also consider, perhaps, again, in a metastatic setting, also drugs like Helix that are sometimes easier to tolerate, or again, weekly regimens of anthracyclines. And again, with the idea of minimizing the risk of adverse events.

Dr Biganzoli: Thank you. And as he said, the question was addressing all the AC combination for being used also in the adjuvant setting, I would say that generally I find AC to be a little bit old-fashioned regimen for elderly patients, because in any case for the patient at risk of toxicity, especially, in the presence of co-morbidities. And now, we have data showing that also in older patients, if we substitute the anthracycline with the taxane, with docetaxel, we can be more effective. And we do not expose the patient to the risk of cardiac toxicity. And I would like to link my answer also to another question, who was asking if we should consider the use of primary prophylactics with GSF, when we use a regimen like TC or AC in, essentially, in the adjuvant setting? I would leave to you, Nicolò, since you have... addressing the side effects of regimens to give an answer that I believe is quite straight.

Dr Battisti: Thank you very much, Laura. This is another very good point. Yes, I personally always prescribed primary GSF prophylaxis in this population of patients. I want to absolutely limit the chances of myelosuppression, not only to obviously limit the risk of side effects, but also, to ensure that if that person requires chemotherapy, again, that person is able to get all the benefits that, again, she or he can derive from that regimen. So, I can maintain the dose intensity. So, absolutely. Yes, I am a strong advocate for primary GSF prophylaxis, especially in these patients. I have to say that, for example, even for younger patients in the

context of what's been going on with the last 18 months in my hospital, we've been giving primary GSF prophylaxis to everybody regardless of age. And again, especially, in the QFT setting.

Prof Kunkler: Could I make a comment?

Dr Biganzoli: Of course, yes.

Prof Kunkler: It's kind of relevant, I think, to the issue of trying to reduce systemic toxicity of chemo-radiation. There's a very interesting paper recently published by Geng and colleagues in Nature, Nature Chemistry in relation to switching on prodrugs with radiation. And this is a kind of preclinical study in which they've used local irradiation in the clinically relevant dose range to activate pazopanib and Adriamycin as a form of local activation of chemotherapy to essentially bracing a paradigm of site-directed chemo-radiation. Which might potentially reduce systemic toxicity in the long-term. And that might be particularly relevant, if validated, in an older population.

Dr Biganzoli: Thank you, Ian. So, I take advantage of you being on the mic to ask you a question. So, you have shown to us that different societies are acknowledging that there is a subgroup of elderly patients at low-risk of relapse that may be spared radiotherapy after breast cancer conservation. Despite, we know that there is a higher incident of local relapse. Those studies were mainly considering whole-breast irradiation. So, my question is, based on the fact that there is an expanded use of hypofractionated radiotherapy, or partial breast radiotherapy, that could also reduce the frequency of patients attending the radiotherapy department, do you think we have still a group of patients in which we can upfront propose not to receive radiotherapy after breast cancer conserving surgery?

Prof Kunkler: So, I think the data on admission of radiotherapy identifying a subgroup of low risk of recurrences is pretty-well validated at 10 years, although, there is obviously a persistent risk of local recurrence. And I think the, I think probably the ultimate application of the 10-year results of PRIME II will support that. But actually, the comparators are changing, so, that we now have shorter regimes of external-beam irradiation. So, the 26th Gy in 5 fractions, which under the sort of COVID-19 pandemic framework have now been recommended for use in that setting. So, actually, the comparison between emission of radiotherapy and a very short-course of radiotherapy, are actually not that far apart. I think what we'll probably have to wait for, is probably the longer-term outcomes of FAST-Forward, which is the 26 Gy in 5 fraction. And patients may choose to have a week's regime compared to the risks of the emission of radiotherapy. So, I think that's, I think that's quite a finely balanced argument, which is actually now changing.

Dr Biganzoli: Olivia, I see the hand raised on your photo.

Dr Pagani: I wanted also to ask a question about the FAST-forward, because I think it's important, maybe, if you stress that as the most of the audience is from low and middle-income countries, if to deliver a FAST-forward or similar regime, you need to have a specific technology, or this can be done, you know, everywhere with all kinds of machines?

Prof Kunkler: I think that's a very relevant point that these are defined on very tight quality-control standards. And also, I have to say that there are uncertainties over these hyperfractionated regimes in terms of the impact of breast size, the role of the boost, and the safety of nodal irradiation. So, these are... these are issues where more work needs to be done.

Dr Biganzoli: Okay. Thank you. And now, a question also for Riccardo, otherwise he would get sleeping. So, Riccardo, we know that elderly patients are generally less asked for reconstructive surgery, and we also know from published data, that when asked, they tend to refuse, or there is less interest in respect to younger population. So, I would like to know which is your experience, because I'm concerned that possibly this less uptake is also related to the way you propose reconstruction to an older patient. So...

Prof Audisio: Thank you for asking Laura, and thank you for having me. You are definitely right, the number of younger patients who are interested in better cosmetic outcomes, by far exceeding the number of elderly ones. And the message that I would like to pass through, is that do not be shocked when an elderly patient expresses a vivid interest in maintaining or in improving, optimizing, the way they look. We are getting there. We are collecting larger and larger series of senior women with an interest. And I think we want to respect this. Sometime, most of the time is feasible. Sometime, it's too complicated, and risky for the patient, so, maybe, we want to discuss this. One of the risks, including one of the risks, which is delaying the beginning of adjuvant treatment. We should also be brought into the consideration, therefore, medical oncologists are involved as well. But going through the questions and answers that have been put through, I think I failed on passing my message on quite a few occasions. There is this Nanuli Ninashvili who writes breast cancer is widely spread, but not in the ages over 70. Now, my message is once forever that breast cancer is a disease of all the patients. We need to take these onboard. When you're 30 you've got 1 in 1000 chances of being affected. When you are 60, you've got 1 in 20. When you're 70 it's 1 in 10. So, let's bring this very clear. The other issue is surgery, no surgery. This patient is not fit for surgery. My whole dissertation revolves around the fact that there is no age limit for surgery. Breast surgery is, I wouldn't say it's a haircut, but something that it is definitely never impossible. Local, blocks, whatever, you can take it out. You need to ask yourself, is this advantageous for the patient, or can she do very well with endocrine manipulation for the next six months, one year, given that she had three strokes and she's a very, very high-risk patient for her general condition? Therefore, life expectancy is very short. And this is all I wanted to reiterate. And thank you for giving me the opportunity to clarify this, Laura.

Dr Biganzoli: Thank you to you. So, then, there are some practical questions. Olivia, have you the raised hand from a previous question or do you have a question?

Dr Pagani: No, no, no. I just want to disagree with my beloved Riccardo. Because I think it depends on where you live. In many low-income countries, the proportion is the other way around. They have a much more majority of patients with young breast cancer. Because for many reasons, we do not understand, they do not live enough to develop breast cancer at 70 or whatever. But so, this, the numbers you showed are in our rich, well, Western countries. So, but I...

Prof Audisio: You said it yourself, Olivia, there is no elderly population in those countries or...

Dr Pagani: Yeah. But for other reasons they have an excess of young women with breast cancer, for reasons we do not understand, but I wanted to maybe to stress what you just, what you said already in the presentation and what you already mentioned here. One of the reasons why, in my opinion, elderly women do not want to go for surgery, is because they are afraid of general anesthesia, and all these, you know, fake-news about cognitive issues. And you mentioned that maybe you need just to stress it again, that you have alternative ways of performing surgery in the elderly. And so, maybe, if you can just stress this a little bit.

Prof Audisio: Yes, indeed. I stressed it substantially. There is no patient who is not a surgical candidate. It does not exist. Every single breast cancer patient can undergo breast surgery. Period. Whether this is advantageous for the patient, we need to consider on every single individual case.

Dr Pagani: Also, because the side effects of endocrine therapy, in this subpopulation of patients, are much higher than in the middle age. So, I don't think that in some cases, or in most cases, the alternative of endocrine therapy is associated with a worse quality of life, than a simple surgery. And so, this is said by a medical oncologist.

Prof Audisio: You are right. Thank you.

Dr Biganzoli: Okay. So, let us continue with additional questions raised by our friends who are following us. So, one that was posed yesterday, and, Matteo, I believe is for you, can a neutrophil to lymphocyte ratio be used at biomarker of frailty and tolerance to treatment in elderly breast cancer patients?

Dr Battisti: Thank you very much. I do not use those specific biomarkers to be honest. I think again, when it comes to the risk of determining what is the risk of myelosuppression really want to, you know, again, evaluate what is the overall health of that person. I look at comorbidities as well, for example, patients that may have maybe a high risk of haematological toxicity, may have specific comorbidities, I'm thinking about the CLL, hematological problems, or again, polypharmacy that may again increase the risk of myelosuppression on cytotoxic agents, so, again, for example, CDK4/6 inhibitors, and so on. As I said, I do not, I do not look at that routinely. Obviously, if there are concerns about increases of myelosuppression, as mentioned, a good thing you can do, you can start with the lower dose and then, titrate it based on blood counts with cycle-1 one for example.

Dr Biganzoli: Okay. Is someone using in the clinics this ratio for detecting the risk of toxicity? I'm personally not. Etienne?

Prof Brain: No, actually, no, I do as just mentioned, Matteo, sorry. And so, yeah, no, no, I don't have this used very... Nicolò, sorry, by the way!

Dr Biganzoli: Both are correct. Both are correct.

Prof Brain: Sorry. But no, I don't use that very often. I think these, all these descriptions on predictive tools are quite important to bring some level of evidence that we cannot anticipate in some ways through algorithms, because, but as a practical use of these is very often shadowed by clinical implementation and how we practice. So, I think it's more a demonstration step to stress the importance of paying attention to these aspects.

Dr Biganzoli: Nicolò, do you want to answer?

Dr Battisti: I think there was an interesting question in the chat box about use of CDK4/6 inhibitors, and whether you should, for example, prioritize one of the over for older patients with advanced positive breast cancer. For example, I think when it comes to the risk of minor suppression, if for example, you have somebody that you deem at high-risk of haematological toxicity, for example, Palbo and Ribo, then you could use, for example, Abema which has a different safety profile, or, again, if you have concerns about risk of GI toxicity, then, use obviously Palbo and Ribo. For example, I have a couple of ladies that have CLL along with metastatic breast cancer, in these patients, I have been using Abema just to try and limit the risk of myelosuppression on Palbo. So, again, you can use the evidence available on whatever systemic agent you're considering, again, to direct your decision for the individual risk for each patient.

Dr Biganzoli: Okay. So, let us check other... do you know, the prevalence of CGA offered in daily practice to older adults in Europe? And/or in EUSOMA credited care centers? So, for the last part of the question I can answer. Since having a GA performed in elderly patients is not considered up to day, mandatory in breast units. We were pushing, we are pushing for having at least one screening test for frailty performed, but we do not have a quality indicator use for this. And for this reason, this information is not collected in the data warehouse of EUSOMA. And so, we cannot address this question. But there is, there has been a survey conducted by ESMO and SIOG looking at this point, do you have the figures, Etienne or Nicolò? And then I see, there's also Ian wanting to address this question. Okay. So, Nicolò.

Dr Battisti: Thank you, Laura. Thank you, Laura. I don't have the figures, to be honest, but I think you really have to understand what are your, you know, what would work in your specific setting to have access to a geriatrician or not, to have access to a multidisciplinary team, including obviously, for example, you know, nurses or other care professionals or not. And based on that, you can use, you can implement, let's say, the

model that would be fit best in your specific institution. Interestingly, the American society of clinical oncology guidelines published in 2018. They do mandate geriatric assessment for all the patients. Everybody aged 65 plus was being considered for chemotherapy. But yeah, as Laura said, this is something that again, is not mandated in breast unit. My recommendation very pragmatically is to, again, understand what is the model that would work best in your case. And again, use directly screening that perhaps in these oncology practices are quite useful to determine what dose patients actually require enhanced. So, onco-geriatric care.

Dr Biganzoli: Ian and then Etienne.

Prof Kunkler: I mean, I can't... use of CGA resulting in a 40% reduction in treatment plan, is a very powerful figure. And it's really a question to Riccardo as to what the way forward is in disseminating the use of some form of CGA on a routine basis within clinics. My impression is that it's often still confined to a limited number of centers and it almost raises an ethical issue. If there might be a substantial number of treatment plans that might be modified.

Prof Audisio: Yeah, you're right. CGAs' use is limited to a... It's an amatorial appendix. Similarly, to geriatric oncology, to be honest, in that most people maintain that they know the patients, they understand the patients. It's the rule of thumb that has been going on for 20 years. What can I say? We try our best. All I can say is that CGA is pretty easy. We have the down escalated the comprehensive assessment into five minutes question. Self-completion form that you give to the old patients, the elderly patients in the waiting room. And that.. this gives you a very, very clear indication of how to address the discussion, the negotiation, how to advise, how to push for some treatment and... bridge the gap is a wonderful example of how artificial intelligence nowadays can easily, really, advise or assist in advising. And I don't see why we don't use it, but I even take it onboard, once again, with probably for 20 years. Please use it, try to homogenize the way you record patients' frailty so that I can understand from you. And you can learn from me. We can discuss the same language, and this is the way I look at it.

Dr Biganzoli: Okay. Before having Etienne addressing this question, I would like also to read what to me is a really important question, because we are always discussing about our situation and which countries in which we can have a geriatrician that is helping us to interpret the results of the geriatric assessment. But the question is, what you can do, if in your country, there are no geriatricians? So, if you do not have this facility, how can you, as a medical oncologist or someone that is dedicated to the care of breast cancer patients, do your best without this facility? So, I guess a screening tool is an obvious answer, but I would like you to focus much more on also this aspect.

Prof Brain: Just a short comment regarding the ESMO-SIOG survey, the use of GATs was said to be, roughly, between 40 and 50%, or a screening tool, in such a general population, which is not bad, already in this community. But, the second point to try to answer your last question is, I think, I truly believe in the education. I mean, oncologists, whether a surgeon, or medical, or radiation oncologist, should learn to handle or to tackle with these different tools, light tools, sometimes, fairly limited, numbers, but in order to open the door to the discussion with the patients. And I think Riccardo said it very rightly. I think we need to stay very open to this kind of information that we are not used to treat or to consider in our standard practice. And that's the only way to change a bit the landscape and getting some education. Following some costs and things like that. And then, you can train and you can implement that progressively. It's not an impossible challenge. I truly believe that's not.

Dr Biganzoli: Okay. So, the discussion has been extremely interesting from my point of view. I would love you to stay here longer to face other questions that you have raised, but we have to conclude. I hope you have enjoyed these two days we have spent together. I believe we have learned a lot, one for the other. Not only the audience, but also the speakers. Because has been a really multidisciplinary approach to the problem of elderly women with breast cancer that we have done in these two days. I have not too much to add. I really would like to thank you, all the speakers for the high quality of their intervention. I would love to thank all

the participants that attended the course. And just, just give you a small message. A take-home message. We are very far to approach in the right way the older patients, as you've seen also among geriatric oncology, dedicated people, there is not an agreement on the best way to address this population. But I think what Etienne has said is extremely important. Even if you do not have facility in your centers, start. Start with some simple tools. Like for example, a screening tool for frailty, it's not going to solve your problems if the patient results to be frail. Because at that point you should theoretically go with a geriatrician. But in any case, you will be informed on whether you have to look at, with particular attention, and to monitor particularly carefully that given patient and, why not, possibly put in place this reduced strategy of starting dose of chemotherapy for the patients who are resulting unfit to this screening test. So, are small things, but I believe if we start to implement all these small things in our daily practice, step-by-step, we will become more confident in the treatment of our patients, and we'll reduce, sorry, the risk of under-treatment that is really important. And in the meantime, we will avoid also the risk of over-treatment that is still present if we evaluate in a very approximate way the strategy for our patients. So, thank you again. I hope you enjoyed and you come back with some important new ideas for treating and taking care of your elderly breast cancer patients. Thank you. Thank you so much.

Dr Pagani: Thank you, Laura. I would love also to thank everybody from the half of ESO. And what I learned is that, this is the first course but it should not be the last. So, stay tuned. We will come back. And have a nice weekend.

Prof Audisio: Yes, grazie. Thank you.

Dr Pagani: Ciao. Grazie.

Dr Biganzoli: Ciao.