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Different approaches to BCS and surgical criteria to select patients for NAST

Prof Knauer: Good afternoon. I will now start sharing my screen. So, thank you for inviting me to give this presentation regarding different approaches for breast conserving surgery and the criteria that we need to select patients for neoadjuvant chemotherapy, and how to do breast conserving surgery after neoadjuvant therapy. I'm working in St. Gallen, Switzerland, and we'll start right away. Here's my disclosures. We got some support for our TAXIS Trial. This is an axillary surgery trial in Europe. And the other things here have nothing to do with the surgery. So, it's important that you think of your questions, type them into the Q&A section below here. Everybody knows Zoom; in the meantime, so, please, think of your questions and Carmen Criscitiello will later discuss them with us. So, if we come to the extent of surgery, it's important to know the size of the tumour, of course. So, the extent of the surgery also depends on the extent of the TNM stage. Smaller tumours often do not require neoadjuvant therapy and go straight to surgery. Larger tumours are more often a topic for neoadjuvant therapy. But it's not only the stage of the tumour, it's also the biology that we have to think of. So, we all know that HER2 + and triple negative breast cancer patients respond exceptionally well to neoadjuvant therapy so that it has become the preferred option of treatment in the beginning. And then, we just have to look how the tumour reacts to this treatment if we have a pCR, if we achieve a shrinkage of the tumour or if the tumour just dissolves, which is sometimes problematic to plan surgery. And this is completely different from luminal breast cancer. So, we have exactly to look even at the type of luminal breast cancer, the Ki-67, the grading, et cetera. What can we expect from neoadjuvant treatment and what kind of treatment would we use? So, surgery today is just one of several disciplines at the tumour board. But it's still the first treatment option for the majority of breast cancer patients. But it's not only a therapeutic procedure, it's very often in the meantime a diagnostic procedure for subsequent systemic treatment decisions. For example, if we have to use the T-DM1 with HER2 positive tumours in case of a pCR, we don't need that. In case of a non pCR, we use that. So, it's also diagnostic. On the other side, you can say surgery is also able to provide a pCR in 30 minutes at very low costs. And this is an advantage for many patients to use that as a first procedure. We also have to discuss about omission of surgery. Can we leave surgery away after a good response of neoadjuvant therapy? But at the moment, we cannot consider it outside of clinical trials. I will come to that in a few minutes. So, when we come to breast surgery, we have conflicting trends here. On one side, we have the trend to more mastectomies. And this is because we do a lot of more BRCA-testing. We do the family analysis of all of our patients. We have the trends regarding contralateral mastectomies, especially in the United States, we discuss a lot about that, in large tumour centres, about a quarter of all patients receive bilateral mastectomy with the reconstruction. And this is due also to improvements in reconstructive surgery that we have seen over the past decade. On the other side, we have improvements in mammography screening. We have different techniques of oncoplastic surgery and, of course, neoadjuvant therapy to shrink a tumour to make it more prone to breast conserving surgery. So, when we come to types of breast conserving surgery, what can we do? We know that this is just an

overview that breast conserving surgery in combination with radiotherapy provides equivalent disease-free survival and overall survival compared to mastectomy. And we know this from randomised trials, 20 years ago. The main goal is to achieve negative resection margins. And here, we have had consensus conferences, they have taken place about nine years ago and included a lot of patients. Here you see 28.000 patients for invasive cancer with a lot of local recurrences. And we can expect a local recurrence rate of about 5% after this median follow-up of six years. And in DCIS, about 8.000 patients have been included in these studies with a local recurrence rate of about 8%. And the adequate resection margin nowadays is no tumour on the ink of the specimen for invasive cancer, and what we try to achieve in DCIS is a 2 mm margin. And we have learned that wider margins do not reduce the risk any further, not even in patients with a poor biology, young patients, lobular cancer, et cetera. So, what are contraindications to breast conserving surgery nowadays? It's of course a large tumour size in relation to the breast, extensive, diffuse microcalcifications, inflammatory breast cancer, and if you've tried, also several times, positive margins after breast conserving surgery. And we have left the contraindications of multifocal and multicentric breast cancer if it's possible to do so. And all local recurrences after breast conserving surgery haven't to undergo a mastectomy nowadays. And I will come to that in a minute. So, one big achievement in the last decade or two decades has been the implementation of oncoplastic breast conserving surgery. And if we look, for example, in Switzerland, we have overall a breast conserving surgery rate of about 70%, more than 80% in T1 cancer, and about 63% in T2 breast cancer. And several operation techniques have been developed and implemented to improve that these rates and of course cosmetic outcomes by using a spectrum of aesthetic procedures. And there are many papers and textbooks out there. So, we've seen a lot of publications here in the last years. And these techniques can be grouped either according to tumour location or quadrant or, what's my favourite here, to complexity level. So, there is low level-I procedures that include resection of up to 20% of breast tissue where you don't have to remove a lot of tissue and move tissue around in the breast. And then level-II techniques that include resection of about 20 up to 50% of breast tissue. And surgeons have lots of creative names for these procedures. We read a lot of different names for sometimes the same procedures like donut, batwing, hemicrescent, racquet, mammoplasty, et cetera, et cetera. And this, it sounds complex, but sometimes it isn't. So, I will go just through a few examples with you. Here you see what we call an Atlas, what we can do in what position, where is the tumour regarding to the size of the breast, for example. And I would recommend this paper even if it's more than 10 years old now. So, you can see in the inner quadrant, you can use round block techniques to avoid scars in the skin of the inner quadrant. In the lower quadrants, you use techniques where you shift the breast tissue around a little bit and reposition the nipple areolar complex. And if it's in the upper part or the lower part, you can use classical reduction mammoplasty techniques in combination with the tumorectomy. For example, a very easy technique that should be in the repertoire of every surgeon nowadays is the donut or round-block mastopexy. It's quite easy to learn. And you see here, you take away this part of the skin and then, you retract the skin and do the mastopexy. So, you can get into this part of the breast without putting scars here in this part of the cleavage. And here, I have some clinical examples. Here there was a small tumour here in the upper inner part. And if you take away the skin and open up the breast, you see quite a nice exposure of breast tissue. And you can close this here. And after all, you have just the scar around the nipple areolar complex. And this is another example of the same technique, a young woman, 32, she had the tumour here, after removal. You see some... The position is not perfect, but it's better than having a scar here. And after one year, all this wrinkling and wrinkles they disappear. Another technique, just as an example of a level II oncoplastic techniques, is the so-called V-mammoplasty. Because this here looks like an inverted V, it needs somewhat more experience and skills, because you need rotation of breast tissue, you remove some skin and you reposition the nipple to avoid deformities of the lower pole. And this preserves the breast, the shape. Here, this is an example you can take, if necessary, quite some tissue away, then you rotate the tissue here, you reposition the nipple. And after some time, this is quite acceptable regarding cosmetic outcome. When we come to in-breasts recurrences, this is also something, a development of the recent years. Traditionally, if you had, after breast conserving surgery and radiotherapy, an in-breast recurrence, mastectomy was the treatment of choice. But two years ago, for the first time, the

St. Gallen consensus conference moved towards recommending a second breast conserving surgery in selected cases, if it's possible. So, just here you see the examples of these voting results that took place. For example, here, more than five years after initial surgery and radiation therapy, if you can do another breast conserving surgery, is this an option? And here, this expert consensus of about 50 people voted, two thirds, yes, it's an option in selected patients. If you can do another re-irradiation as well. Especially if you go for low-risk tumours, you see this here, this means small or luminal A tumours, more than 80% of the panel thought, this might be an option for selected patients. Or if you have a longer interval. So, this means if you do a triple-negative cancer and then there's a local recurrence within a year or so, this is probably not the best option to do another breast conserving surgery. But if you have a longer time-period between the first diagnosis and the second, this is an option here in some patients. So, surgery after neoadjuvant therapy, how to do it? How to plan it? This is quite complex. And I will go through a couple of slides here with you. And what we saw in studies that have been undertaken quite several years ago, these are just three examples that in the beginning you saw that here you see always a control arm and the experimental arm. And although, the pCR rates, in all these studies, were higher in the experimental arms, if you use the taxane in HER2 and the dual blockade, et cetera. The surgeons obviously didn't trust or couldn't do it or whatever. But because the breast conserving surgery rates were the same in all these trials, and we had to move away from this perception of not being safe when doing breast conserving surgery here. So, we have several factors that influence our decisions and the patient's decision for breast conserving surgery or mastectomy. You see the breast to tumour relation, multifocality, the patient, of course, extensive microcalcifications, the kind of cancer and also the biology. And of those only we can influence two of them. For example, breast and tumour relation. We can influence this by the use of neoadjuvant therapy. And of course, we can talk to the patients about her wishes and expectations regarding surgery and also, cosmetic outcome. And here, we have switched a lot because always also, let's say it was four years ago in the St. Gallen Consensus Conference, the experts voted already that in triple-negative and in HER2 positive breast cancer, regardless if you can do a breast conserving surgery or not, neoadjuvant systemic therapy is the preferred treatment. And this was voted by 98% of the patients. So, most of the patients starting from stage II, undergo neoadjuvant therapy nowadays. And how do we perform safe surgery here in this context? And there is several time-points where we have to really work together as a team in the multidisciplinary treatment, it's the diagnosis before you start with the treatment, it's the assessment of the response. And then, of course, it's the pre- or intraoperative marking and assessment to avoid R1 resections. And here, we have had a consensus in Lucerne that took place in 21. And I recommend you to read this paper by Peter Dubsky. And there was an interdisciplinary content where we worked on several topics, what is important for the success of neoadjuvant therapy? What kind of diagnostic assessment is needed? How to assess tumour response, how to do a surgical plan, and how to localise the tumour? How to do the axillary surgery? This would cover a whole more session here and I won't go into axillary surgery at all tonight or this evening. And what about quality assurance and indicators? So, an interesting paper and I recommend to read that. And still, we find some cases like this. For example, here we have a luminal B cancer. It was quite large and we had three positive lymph nodes. So, everybody says, "Well, let's undergo, let's use neoadjuvant therapy." And then, you do a second MRI. And this says, "Well, it's fine, and responded well." We don't see any suspicious contrast enhancement anymore. We see the tumour bed here and the clip inside here. So, let's undergo, let's do a clipectomy or tumorectomy or whatever you call it." But after all, again, microscopically it was still 7 cm in diameter and we still had positive nodes with only a marginal improvement here. So, on the other side, if we see exceptional responses and we don't see any tumour left at the imaging before surgery, can we omit surgery? And I can't go into a lot of details here regarding these studies. But four prospective studies have been conducted from Germany and United States and to Korea, et cetera. And they have been presented a couple of years ago at the San Antonio meeting in a quite nice session here. And they attempted to undergo, to do biopsy instead of surgery. But of course, they did surgery in the end to look if they were right with the biopsy or not. But all of these studies had high false negative rates of 18 up to 37%. So, this means in a substantial proportion of patients, you miss the residual tumour when you do just biopsies. And so, just

currently, we cannot omit surgery outside of clinical trials. However, some trials are still ongoing. And I will show you the one we do in Switzerland. This is a trial of Vacuum-assisted biopsy before surgery. We do it as a multicentre interventional cohort trial. Christoph Tausch in Zurich is the PI. And several centres also in Austria and Germany will join here. And the workflow you see here of this called Vision-I trial is, we have a breast cancer, we do an MRI, we clip the tumour, neoadjuvant chemotherapy, we assess the response again with an MRI and then, just before surgery, you do either stereotactic or mostly ultrasound-guided Vacuum biopsy. And then, normally you do it immediately after in the same surgery you do the breast surgery, you look at that. And then, we use also a machine learning tool to look at what are the factors that could make omission of surgery safe. And we have started and included several patients, and we are looking to the results of this study. When we come to multicentric or multifocal cases. This used to be an indication for mastectomy, but it's not anymore. And we have looked here, Ataseven et al. had looked into this in the German database, the GBG trial of several thousands of patients and included also 163 multicentric and more than 400 multifocal cancers. And they showed clearly that if you can achieve R0 reduction, the local recurrence rates after breast conserving surgery are not worse here. And also, if you have a pCR, of course. So, the St. Gallen consensus again, looked at this, regarding the residual invasive breast cancer after neoadjuvant therapy. And already two years before the panel suggested that the no-tumour on ink was also applicable here in unifocal disease after neoadjuvant therapy. And then, four years ago they asked the question, "What about multifocal residual disease?" And here the panel said, "Well, if you can achieve it", no-ink on tumour, more than 80% of the panel suggested this could be an option. So, I'm coming to the take-home messages here. So, we have seen a clear indication that the indications for breast conserving surgery are expanding. And we should try to do more and more because in most cases, breast conserving surgery is way better than a mastectomy and a reconstruction, even if it looks quite nice. But the sequelae, the complication rates are higher after mastectomy and reconstruction. And you also see that the sensation of the nipple is gone and you have, sometimes, you have to change the implants or you have to go to free flaps, et cetera, et cetera. So, we have to do quite some brain, invest some brain to look how can we reduce it, what is the extent of surgery, and we are strongly dependent on the success of the neoadjuvant therapy here. We have implemented oncoplastic surgical techniques and I would say these are the current standards if needed. There are always people that do a lot and do maybe also too much. Always ask the patient what she wants because many patients are of course happy with the size and shape of their breast and also ptosis. And they probably might want only to take out the tumour, tumorectomy and not always a bilateral procedure including mastopexy or reduction mammoplasty. So, if needed, this is what I added. In some cases a second breast conserving surgery might be an option in local recurrence. And I strongly recommend that you discuss this in your tumour board before you plan the surgery. Because normally local recurrences should go into your tumour board and radiation oncologists have to be a part of this discussion and maybe also to discuss it with the patient before you do the surgery. It can be of course considered in multifocal and multicentric disease. This is what I have shown before. And when we go to the target volume, how to resect and how to plan surgery after neoadjuvant therapy? We have to look at the imaging, of course, the preoperative imaging. And we have to use these methods that were helpful at the beginning. So, it doesn't mean that you need, absolutely need MRI for every patient. So, you take these techniques that were helpful and then, use them again and then plan your surgery and the volume of your surgery, and the technique of your surgery according to the imaging immediately before surgery. And you should not excise the whole tumour bed that was present before the start of neoadjuvant therapy. All detectable residual disease should of course be removed. And in case, if you think of a pCR, if you see a clinically complete remission, remove the centre of the tumour bed, include the clips, and then, of course, place some new clips for the radiotherapy. We have to learn, I would say, we have learned that neoadjuvant therapy is not a risk factor for local failure. You just have to plan it accordingly and you can do the resection within the new margins. And this seems to be safe and it is even a major goal of multidisciplinary treatment of our patients. And no patients should be excluded from breast conserving surgery as long as you can achieve negative margins here. And we have learned, or the residual ones of us who didn't believe, we have to learn to trust in the

capabilities of neoadjuvant therapy to reduce the extent of surgery. Also, for better cosmetic outcomes, but always without any oncologic compromise. And I hope we have collected a lot of questions. Here, this is the last slide. I think I'm still in time, yes. The involvement of the multidisciplinary team and the surgical oncologists is quite crucial, in these three time-points I have shown you. And this might be different in a different setting if you are working in a university hospital or what kind of localization techniques you have. I didn't go into the details of what kind of clip you should need or do you need intraoperative mammography or ultrasound or do you still need guide-wires, which is not a favourite of mine. So, you have to develop your in-house standard for these localization techniques and also for the margin assessment. In many countries, it's not acceptable, it's not feasible to use a pathologist for intraoperative margin assessment. In other countries you can still do it if you have it. For all of these standards of localization, the level of evidence is still quite limited. And the last thing I would like to add is that all these surgical questions should be included into clinical trial planning. And I made this remark also in the recent St. Gallen conference in Vienna, a couple of weeks ago, that if neoadjuvant treatment studies are planned, always consult with the surgeons to see what kind of questions can be easily included without doing several separated studies here. And I would like to thank you, everybody, and recommend here a different thing. This is Madama Butterfly at the Lake Constance here, at the borders between Germany, Austria and Switzerland. And this will be on stage this summer again. Thank you very much.

Dr Criscitiello: Thank you very much, Michael, for this interesting lecture on breast surgery. I would invite again attendees to ask questions in the chat or they can also raise their hands if they prefer. Are there any questions? Okay, I will start then. Of course, neoadjuvant treatment in the beginning started to make operable what was inoperable and to allow more breast conserving surgery for patients who were initially candidates to mastectomy. But now we know that neoadjuvant treatment should be preferred over adjuvant treatment. So, systemic treatment should be the first step of the treatment before surgery for many patients, because, as you said, biology also matters a lot. So, very likely if we have patients with HER2 + or triple negative disease, we will go for a neoadjuvant treatment and then surgery. And also, I would add, as a reminder for oncologists, medical oncologists and surgeons, that, actually, in the beginning we were used to say "if you have to give chemo, you can give it either before or after surgery because the outcome is the same." But actually, this is what we know with the chemotherapy. But now that we have biologics, immuno-therapeutics, anti-HER2 agents and new treatments, actually, we don't have this proof. And what we know is that giving the systemic treatment before is better, because, of course, as you said, we can achieve better responses for surgical procedures as well. But we can also increase the probability of improving the final outcome of our patients. And also, we can test in-vivo drugs and understand if we need to do something different in terms of systemic treatment afterwards based on residual disease or pCR. But most of these trials, which have been actually conducted in the neoadjuvant setting, despite demonstrating an increased pCR, have not translated into an increased rate of breast conserving surgery. What's your opinion about this?

Prof Knauer: I think this is absolutely a pity and I have shown some trials that have been conducted several years ago and in the beginning I think many surgeons were sceptical. But nowadays, that we have immunotherapy and anti-HER2 therapy, which leads to a pCR rate of up to 70% in many cases. I think it would be absolutely crucial to undergo for breast conserving surgery. So, one reason not to do it is, of course, extensive DCIS. So, if you have DCIS around this tumour and you see either microcalcifications or you see it in the MRI as DCIS, I think this is not an option to do, even if you have a pCR. But you have different definitions of pCR and if you look at the total pCR, these are also very high and you absolutely should undergo breast conserving surgery. And I'm not sure if it's a matter of education, I hope not because the topic has been around for quite some time, and I see it in the tumour boards from time to time, even in other centres that, "Well, let's do what the patient wishes" or "We want to be safe." And these are all... It has nothing to do with oncologic safety. It's perception, it's wishes, it's the wrong information of the patient. And if you really trust that and you see that pCR patients have the best outcome, you should convince your patients to undergo breast conserving surgery and that it's no risk. So, the fear of the oncologic risk is a major driver I would say

in patients. And in other settings, it might also be that some surgeons are quite fast to opt for mastectomy and reconstruction because patients want it sometimes and it takes a lot of time and enthusiasm to convince them to go back and say, "No, let's undergo breast conserving surgery." And I don't see a lot of contralateral prophylactic mastectomies in non-mutation carriers here around, at least in Switzerland, it's only a few. And we always try to talk patients out of that. But if we look at other situations like in the US in this, we see that it's up to 25 or even 30% in large tumour centres.

Dr Criscitiello: Yeah. And actually, I have two more comments/questions for you. You have showed us some nice slides on reconstructive techniques. Do you think that the improved reconstructive techniques may have somewhat improved the rate of mastectomy because of the excellent aesthetic outcomes that sometimes are even better than conservative surgery?

Prof Knauer: Exactly. So, if you use oncoplastic surgery, one disadvantage is that you lose some volume and this is what many patients do not wish. You have a little higher complication rate than traditional breast conserving surgery and you have quite large scars that sometimes are visible. So, this is the downside of that. And reconstruction has indeed become an easy procedure. So, nipple-sparing mastectomy is done as a routine procedure weekly in every mid-size to larger tumour centre. And the standard for reconstruction in most cases is prepectoral implant reconstruction. You put a mesh or an ADM around it and it's a quite safe procedure compared to 10 years ago. But there's still the disadvantages that you don't have sensation anymore and you have complications, sometimes, you have to change an implant. if you have an infection, it's a disaster. And especially, what I didn't go into is the combination with radiotherapy. So, if you have a mastectomy, it's, in many cases, not possible to avoid radiotherapy. Especially if you have involved lymph nodes or a larger tumour or a tumour that's in the medial part of the breast, you still... the tumour board recommends to undergo post-mastectomy radiotherapy. And this has a high complication rate in combination with an implant reconstruction of up to 50%. So that the experts and the literature says, well, free flaps are the standard for these patients. But when you look around, it's not being done as often as it should be because micro-surgeons are not growing on trees. And you have to have a really high expertise to offer this to your patients with a high success rate. And this can't be done in many settings and all countries around the world.

Dr Criscitiello: Michael, something else I would like to discuss with you, since we are, having a MTB now, multidisciplinary tumour-board. Now, you know that we have data with the adjuvant olaparib for patients with high-risk HER2-negative breast cancer, both triple negative, and HR+ HER2-negative breast cancer. Of course, to get access to olaparib, patients should be diagnosed with a general BRCA1 or 2 mutation and after six cycles of either neoadjuvant or adjuvant chemotherapy, they can receive olaparib. In the case of neoadjuvant treatment, they need to have either residual disease, triple negative and residual disease plus CPS-eg score of at least three HR+ HER2-negative disease. So, we will have the whole course of the neoadjuvant chemotherapy to assess the germline BRCA1 and 2 mutational status. And very likely, we will have more patients with that known BRCA mutational status at surgery. Do you foresee that this could increase the rate of mastectomy instead of breast conserving surgery and also, potentially of contralateral mastectomy for patients with this germline BRCA1 and 2 mutation known at the very first diagnosis, let's say?

Prof Knauer: Absolutely. And I think this is a major issue, and thank you for this question. We have quite liberal recommendations for testing or we have had them, and you have a catalogue of features that have to be present to undergo testing. So, at this moment it's young patients, it's several breast cancer patients in the family, it's triple-negative patients below the age of 60, et cetera, et cetera. And this varies from country to country a little bit. So, this is what we used to do. But we have seen studies where we miss maybe up to 50% of all mutations if we stick to these criteria, and we would have, excuse me, many more patients with a mutation. And since the time to do the testing gets smaller and smaller. So, in the meantime, we do routine genetic testing in three weeks or up to two weeks if necessary. It doesn't take six months anymore in many

settings. And of course, we absolutely should find these patients who would benefit from olaparib because the survival benefit is 8% in the study and this is major and this is the same amount of benefit as we have seen with HER2+ agents, with trastuzumab in the beginning, in the HERA trial, for example. So, it's absolutely necessary to identify all of these patients. And this also depends from country to country, but here, in Switzerland, at least, if we have some consequence for the adjuvant treatment, it should be paid so the reimbursement for the genetic testing should be there. And we are about to start to do this as a routine procedure for our patients. And then, we see more and more patients having olaparib and then, these, of course, have a BRCA1 or 2 mutation. And this will definitely lead to more mastectomies. About 12 years ago when I started to do genetic counselling and testing only about a third or so of these mutation carriers opted for bilateral mastectomy. But now, since the techniques have evolved and become much safer and the cosmetic outcome is much better, I would say, it's more than 50, even 60% undergoing bilateral mastectomy. But maybe I have a bias because I'm a surgeon and people come to me because they want surgery. I'm not sure.

Dr Criscitiello: Yeah. But what's certain is that we will now have to deal with BRCA as a predictive biomarker because now we have the potential use of olaparib for these patients. So, we will need to ask for this biomarker that can be asked also to patients with no family history because it's something that now it's not only related to family, to prophylactic surgery or relative to something that may impact the patient outcome because, as you said, adjuvant olaparib significantly improved invasive disease-free survival, also overall survival. So, this will be more and more important and we will see that this will change a lot I think also the approach to surgery for these patients.

Prof Knauer: Carmen, may I ask you something back? If we test a lot, a lot of more patients, how do you think you would cope with genetic testing? Because in several countries it's only the geneticists can do it. Here, in Switzerland, if you have some certain amount of training, the gynaecologists or surgeons or medical oncologists can do it as well. But still, it's a huge workload that we have to deal with. How do you foresee how we do this?

Dr Criscitiello: Yeah, sure. It will be a huge work because we will have more and more patients undergoing the test, so it'll be a huge work. But here in Italy, for instance, the National Society of Medical Ontology has actually changed the indication to do the test. So, before it was just the genetician who could ask for the test. Now, every specialist involved in the therapeutic aspects of the patient, for instance, the oncologist, can now order the test. Because if I asked for this drug, olaparib, and I can give olaparib to a patient with these and these characteristics provided that she has a germline BRCA1/2 mutation, I, as oncologist, can order the test without sending the patient to the genetician. Of course, if I will get back a positive test showing a mutation, of course, then, I will have to refer that patient to the genetician because this will have also impact on her future and on the future of her family. But as a first step, oncologist will be able to ask for the test. This is something that can at least reduce the overload of patients that are always sent to genticians. But this will not overcome the problem of overloading laboratories because of course tests should be done there. But I think that now we should really think at germline BRCA1 and 2 mutation as something completely different as we have thought of until very recently. Because it's a predictive biomarker, for instance. So, we need to know that mutational status in order to not under-treat patients who could have potential survival outcome.

Prof Knauer: Yeah. I absolutely agree. And I do the genetic counselling also myself because we also have such a regulation in Switzerland where you can do this yourself. But from the law, you have to do a genetic consultation even with a surgeon before you do a test. And this takes me, normally, it takes me an hour, a genetic counselling, it takes me 45 to 60 minutes normally. And if we go for all these patients, this will increase the workload. That is just what I wanted to say. And we have to organise this in our workflow, in our daily workflow.

Dr Criscitiello: Yeah, actually, as oncologists, we can perform a sort of mini counselling. So, when we see patients we should ask them about the family history, not only breasts and variant but all cancers. Of course, we need to consider the biology of the disease age, but irrespectively of these characteristics. So, we should test, or we should try to test all patients potentially candidates to olaparib. Of course, if I have a patient over 60 with no family history at all, with an HR+ HER2-negative disease, it's very unlikely that she will carry a BRCA mutation. So, maybe, if I have to spare someone to do the test, that could be an ideal candidate to be spared because, of course, I mean, the work will be huge. We'll be extremely busy with these patients and with these procedures, of course. But it's something that we cannot deny to patients.

Prof Knauer: Yeah. Okay. I think we are at the end of our session.

Dr Criscitiello: Yeah, exactly. It's 7:00 PM. We have to say thanks to everybody who attended the meeting. Thank you, Michael, for this very interesting lecture. And thank you all for being with us. This is the next e-ESO session that you can attend if you wish. Thank you everybody and have a nice evening.

Prof Knauer: Thank you so much and have a nice evening from my side as well. Bye-bye.