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Highlights of the 5th ESO-ESMO Breast Cancer in Young Women International Symposium

Dr Paluch-Shimon: Good morning, good evening, good afternoon to everybody. It's a real honor to be hosting this session, I'm looking at the highlights from BCY this year, together with Dr Olivia Pagani and I hope I'll be able to give you a good overview of what happened at this year's conference. This conference this year was virtual, so it presented with it several challenges. And that included that we had to have our Consensus panel on Zoom as well. So, that was challenging including our voting, but it was manageable. So, I'm just gonna start off with what is probably the most important general recommendations from BCY and this didn't really change with BCY5. And that is, the young age by itself should not be the reason to prescribe more aggressive therapy than in other age-groups. Factors influencing the choice of treatment should include, but not be limited to the complete biological characteristics of the tumor; hormone receptor status, HER2; proliferation markers; histologic grade; gene expression; stage; genetic status when available; and, of course, the patients' co-morbidities and preferences. And this is the key guiding line that should really guide our treatment when we look at young women with breast cancer. They do not need to be treated more aggressively than older patients. They need to be treated according to the breast cancer that they have. So, one of the focuses this year at BCY was breast cancer in young women on a global scale. So, what we can see is that in Asia, for example, approximately half of the breast cancer patients are in fact pre-menopausal. If we look at this table here, presented by my colleague Sung-Bae Kim, we can see that in across many of the Asian countries around 50% of the women who are diagnosed with breast cancer are premenopausal. So, that actually distinguishes breast cancer as opposed to in many Western countries. When we looked at some of the information from India, we could see that there was also an increasing incidence of breast cancer in younger women. And there are many reasons for this. Part of it is an increasing population, a decreasing mortality from competing causes, such as infectious diseases, which have always led the high mortality rates or elevated mortality rates in some lower income countries and changes from cancer transition. So, rather than just HPV-related cancers, many are being replaced with lifestyle cancers, such as breast cancer. There's changing social and cultural practices and practice in people's general behavior with a rural to urban divide. So, it's very dynamic what's happening in some of the Asian countries, particularly, those that are less westernized. And what is unique, at least in a country like India, is that many of the patients are diagnosed with very locally advanced or metastatic disease. The disease is often socially stigmatized. Again, 50 to 60% of these women are premenopausal, they do not have access to Oncofertility or to genetic testing. And the access to anti-HER 2 therapy is limited and the mastectomy rates are high. And this probably has to do also with lower availability of irradiation, and the reconstruction rates are low. And these are very significant for young women, and these are areas that need more research and work on access to care. When we looked at young breast cancer in the Middle East, we can see that in Saudi Arabia 18% of new cases are in women under 40 years of age. In

Western countries the number is more along the lines of 67%. And again, the disease is characterized by later stage at diagnosis than in some of the Western countries. In Israel, the situation is more aligned with some Western countries however, what's interesting and this is in line with what's seen in many of the Arab Middle Eastern countries is that there are more younger women amongst the Arab population. And this is one of the features that characterizes breast cancer in the Middle East, is that it appears a bit earlier amongst women of Arab origin. And this is often in the absence of hereditary causes. And similar features were seen also in Lebanon and other Arab countries with around 50% of cases being diagnosed in young women. In terms of health disparities and the global health burden it is important to realize that almost all the information that we have about young women, both in terms of the breast cancer management and also survivorship is based on what we know from Western countries. So, predominantly Caucasian countries, and we have very little information about the experience of breast cancer in young women in other countries. The US is a very prominent example of the price of health disparities. And what we can see, this has proved for all age-groups, is that in terms of mortality among non-Hispanic black women, the mortality rates are significantly higher than in non-Hispanic white women. And we can see also here in terms of trends in breast cancer death rates, they are much higher in black women even though mortality rates are coming down, they're still much higher in black women. And this has to do with health disparities, and we can see these health disparities across many countries, but this is just one illustration of that point. We also know that socio-economic status is important in terms of healthcare and survival, specifically, there is data in young women. Until we can see that in women who come from lower income or lower educational groups the outcome and survival is significantly lower. So, if a woman has low levels of education and lower income her survival is much lower than a woman who has higher levels of education and higher income. What we can also see here as in terms of constant access to care, women who are younger so, under 40, and compared to women who are very young, are less likely to have insurance coverage in the US and they are more likely to pass up on receiving care because of cost. So, these are really important issues to address and this was also addressed in the statements in this year's BCY5, specifically stating that in countries with universal health care improvements are significantly lower for women with low socio-economic status compared to those with high socio-economic status, and this is certainly the case in countries without universal healthcare. And that we emphasize that every young woman with breast cancer should have access to optimal care, supportive care and the highest standards of patient-centered care, irrespective of her social status. So, this was a real priority emphasized at BCY5. I'm just gonna remind everyone that you can ask questions and send comments at any time during the lecture. In terms of the biology of breast cancer in young women, we saw information that we are familiar with before, is that there is a high preponderance of luminal A tumors in women under 40, as compared to some of the older age-groups. And this is something to keep in mind when we think about their care. And one of the hot topics in recent years is how we apply multi-gene test for women who have hormone-receptor positive disease, particularly in lot of the result of the TAILORx and the MINDACT, and now the RxPONDER study. And there was interesting subset analysis, these were post-hoc analyses that found, at least in the TAILORx, which was a node-negative population, that women under 50 who had a recurrence score in the upper end of the intermediate range, so, 21 to 25, seem to have had a greater benefit from the addition of chemotherapy. The question here is though, is it really from the chemotherapy directly, or is it because of chemotherapy-related induced endocrine changes. So, we need to be careful with this information. This is from a study published also last year, looking at young women who either have no-nodal involvement or some nodal involvement and we can see that the blue line is women with a recurrent score of under 11, and the red line is an intermediate-risk. And in the node-negative population, we can see that in the women who are low- to intermediate-risk there is a similar outcome based on the TAILORx but in those who had a higher recurrence score, we can see the outcome is less favorable. And then, if we look at women who are node-positive, these graphs open up even more, and that seems to be in keeping with some of the data we saw in the RxPONDER study. But this is an enigma whether it is specifically from the chemotherapy or whether or not it's from the endocrine-induce changes. Although, there are some old studies that indicate that it may very well be from the endocrine changes from the chemotherapy. In terms of adjuvant systemic

treatment, a statement was made that many factors including the patient and tumor characteristics and genomic signatures should be considered, and that more research is needed on this topic in young women, particularly, the node-positive patients. And that commercially available gene expression tests have not been widely studied in young women. And most young women enrolled in these studies were not treated with modern risk-adapted endocrine therapy. And that is something that needs to be considered when interpreting available data. Available data in premenopausal women supports the role for gene expression tests in predicting additional benefit of chemotherapy over endocrine therapy alone. But we do need further data for guiding clinical practice. In terms of HER2+ patients, there is data from the HERA study that indicates that age is not a prognostic, nor predictive for an early recurrence in HER2+ disease. So, in general, treating principles are the same for women who are young compared to women who are older in HER2+ disease. A big focus of our treatments are neoadjuvant therapies. Today, in general, if we think that we're gonna be giving chemotherapy, we often will give it in a neoadjuvant setting. My colleague, Nadia Harbeck, did a review of new issues in neoadjuvant therapy, particularly, the question of immunotherapy in early breast cancer. One of the studies she looked at was the KEYNOTE study which looked at neoadjuvant chemotherapy with or without pembrolizumab. In this study, we could see that there was an improved pathologic complete response-rate. We know the pathologic complete response can be a surrogate for overall survival. However, it's unclear if an increasing delta or increasing improvement with PCR will continue to translate into a survival benefit. So, we can see that the addition to pembrolizumab improved PCR, particularly, notable in the PD-L1+ patients. However, it is important to note that there can be very serious long-term immune mediated adverse effects. And some of these would be something that we really need to take seriously, particularly, in a young woman who has a long life ahead of her to live. And in particular, we're looking at the endocrine-related toxicities. So, adrenal insufficiency or hypophysitis, which occurred in 1.5 to nearly 3% of patients, these could be irreversible and this is important to think about. So, before we run and provide additional treatment with an immunotherapy, we really need to see outcome data to ensure that any potential risks are justified. There was also the IMpassion data which incorporate atezolizumab in the neoadjuvant setting in triple negative breast cancer. Once again, there was a benefit seen in pathologic complete response. And it appeared that the benefit was seen both in women under 40 and over 40. However, as I've mentioned, there can be serious side effects from immunotherapy. We do not yet have outcome data from the KEYNOTE study or from the IMpassion study. These are early results; these results are not yet meeting the statistical requirements of the study. And so, we need to be cautious before we adopt this as part of the standard of care. As such, the statement at BCY is that in patients with triple negative breast cancer and an indication for neoadjuvant therapy, the addition of a checkpoint inhibitor should be very carefully considered and should not become yet standard of care, and should be considered in very specific settings because we don't have outcome data and because of the concern about the safety profile. Once again, if there are questions, Dr Pagani, I don't know if there are any questions yet that you wanna ask before I continue.

Dr Pagani: Well, that is a question on endocrine therapy. So, I think we can make it later on.

Dr Paluch-Shimon: Okay. So, we'll keep going. In terms of endocrine therapies, important data presented by Dr Pagani was building on the information that we have from the SOFT and TEXT studies. And so, what can help us make decisions which patients will get extra benefit from ovarian function suppression looks at this STEPP analysis, where we have a composite risk of relapse and it helps us decide which patients are gonna really gain the benefit. So, for example, if we look at a woman with favorable features so, she might be node-negative, a small tumor, AIPS are strongly positive, low grade, low proliferation score, this woman is not gonna have a significant benefit of incorporating ovarian function suppression using this model, I'm looking at the composite risk. However, if we look at a woman who is node-positive, grade 2 to 3, high Ki-67, we can start to see significant differences in the sorts of benefit these women might see. And in this sort of case, a woman might have a 6% benefit from the incorporation of exemestane with ovarian function suppression compared to tamoxifen and ovarian function suppression and also a significant benefit compared to tamoxifen alone of 5%. So, we need to look at the entire clinical risk of the patient in order to optimize and

pair up the best endocrine therapy for the patient. Just to remind everybody that aromatase inhibitor without ovarian function suppression is contra-indicated in a pre-menopausal woman and that the combination of an aromatase inhibitor with a GnRH agonist confers a significant absolute benefit in terms of freedom from distant recurrence and is the preferred option in high-risk patients, but not in all women. In addition, there was discussion about the optimal method for ovarian function suppression, and the optimal method for ovarian function suppression is a GnRH analog, or agonist. It should be given monthly, preferably, not three-monthly, and radiation is discouraged in the early breast cancer setting. The issue that came up in the setting of patients with hormone-positive disease was the question about adjuvant use of CDK4/6 inhibitors. Just to remind everybody that we have two studies looking at incorporating palbociclib that were negative studies, and then, we have one study with abemaciclib looked at a more high-risk group. And there seemed to be some benefit in the invasive disease-free survival of 3.5%. However, the follow-up time is short. The high-risk features for this study include multiple lymph node involvement or limited lymph node involvement with high-risk features. It might be considered in a high-risk group when it is approved. So, that's something to think about it but it needs further follow-up because the follow-up data here is quite short. And the other issue that we addressed is the ongoing question of bisphosphonates. Well, bisphosphonates are often used in women who are clearly post-menopausal, the question of using it in women who are pre-menopausal and rendered post-menopausal by the use of a GnRH analog has remained open. So, the ABCSG trial, just to remind everybody the ABCSG is a 12 study. Looked at tamoxifen, tamoxifen with zoledronic, anastrozole or anastrozole with zoledronic and all the women received a GnRH analog. And what we can see in the study was that this was 3.4% absolute risk-reduction with the use of zoledronic in terms of disease-free survival and this benefit was maintained in the long-term. In addition, there is data from the HOBOE study which also found an improvement in five-year disease-free survival with the incorporation of zoledronic. Subsequently a statement on adjuvant bisphosphonates is that there is accumulating data to support a benefit in disease free survival, even among pre-menopausal women who are rendered perimenopausal with the use of a ovarian function suppression and as such it might be considered on a case by case basis with six-monthly use. In terms of advanced breast cancer in young women, as a general rule, BCY5 endorses all ABC and ESO as most statements for the care of advanced breast cancer including in young women. And I think this is important to remind everybody that the treatment choice, like in early breast cancer needs to take into consideration the biological features of the woman's tumor, any need for disease or symptom control, other issues about availability and, of course, bear in mind, patient status. We reminded everybody that many trials in the past did not include pre-menopausal women. However, in recent years that has changed and more and more women are allowed to participate in clinical trials if they undergo ovarian function suppression, so, this is really a step forward. And future trials exploring new endocrine based strategies need to continue to allow for the inclusion of pre-menopausal women who can be rendered post-menopausal with GnRH analog and of course, should allow for the inclusion of men. In the lecture on advanced breast cancer, I just wanted to highlight that even in women with advanced breast cancer sexuality is an important issue. It's an important issue for all age groups. It's a particularly important issue for young women with breast cancer and so, it remains important across the spectrum of disease. Once again, if there are any questions Dr Pagani?

Dr Pagani: Yes, I think we have a few questions so, maybe we can start. Someone is asking why radiation therapy to ovaries is to be discouraged.

Dr Paluch-Shimon: Firstly, giving radiation if it's not needed for a curative purpose can give unnecessary toxicity, firstly to the pelvic region. But also, it may actually would potentially be irreversible and some women do not need to remain post-menopausal forever. So, ovarian function suppression is indicated for several years, according to SOFT and TEXT study for five years. And ovarian function suppression could be irreversible with radiation therapy, but additionally, radiation induced ovarian ablation, is not always reliable. So, sometimes, women have been given radiation doses it may induce amenorrhea but they won't necessarily be post-menopausal.

Dr Pagani: And then, the next: what is the optimal time-interval between starting an LH agonist and the aromatase inhibitor in terms of sufficient suppression of the ovaries? This is a very practical question, very important.

Dr Paluch-Shimon: So, my general rule of thumb is I start the aromatase inhibitor once the patient has already received her second-monthly dose of an LHRH agonist. I don't know, Olivia, what's your practice.

Dr Pagani: Yes, it's more or less the same. I think I gave at least two injections and then, I start and I check the ovarian function afterwards.

Dr Paluch-Shimon: Yeah, so, in my patients I check of their hormonal profile and ovarian function at least six-monthly so, at least twice a year.

Dr Pagani: Then, there are a lot of other questions. I think that one, according toward the chemotherapy because I think, now, we move on, is four cycles of AC alone recommended for patients with T1, 2, N0, N0 luminal-A in order to omit the Taxanes, instead of going through genomic evaluation, like Oncotype Dx because of costs and availability. So, this is a very complex question.

Dr Paluch-Shimon: I think cost and availability is always gonna really dictate treatment at the end of the day. So, people can only do what's cost-effective and available. So, we're gonna put that aside for a moment and think about what's the optimal medical approach. Just to remind everybody that there was a study that TC by-four, which is docetaxel and cyclophosphamide, is actually slightly superior to AC times-four, that's one important point. We don't have a study that looks at TC by-four compared to ACT, but we do have studies looking at TC by-six compared to ACT and we can see that in lower risk disease the anthracycline can be omitted, such as in the case that was presented here which is a T1-2 and 0 luminal tumor where chemotherapy was indicated. There's also excellent data from Nadia Harbeck's group in the ADAPT study, showing that anthracyclines can be omitted in certain cases where the disease requires chemotherapy, but there's no large burden of disease or it's not a very high-risk tumor.

Dr Pagani: I think the issue with him is that maybe, we can de-escalate according to stage and luminal characteristic, even if we do not have genomic testing available. So, I think that the clinical stage and all these characteristics, it can be enough to de-escalate chemotherapy so, we don't need to have genomic testing to do that.

Dr Paluch-Shimon: Yeah, I would agree. I mean, if there's no genomic testing available, then that's where the grade and the Ki-67 can be very helpful in trying to determine which patients would benefit from chemotherapy and which patients don't need chemotherapy.

Dr Pagani: Okay, so, there are other questions but maybe we can move on and ask them at the end.

Dr Paluch-Shimon: Okay, we'll keep going. In terms of breast cancer during pregnancy there was an excellent overview by Hatem Azim and I'm just gonna touch on the very important highlights. Which is to remind people that tamoxifen is teratogenic and that women who were exposed to tamoxifen during pregnancy there were congenital malformation rates that were quite high. So, tamoxifen cannot be given as treatment for a woman who is pregnant and has breast cancer and should be avoided during gestation, there are multiple studies that show that. The other issue is for women who have breast cancer during pregnancy is that trastuzumab should not be given either, not early on and not later on, so, when the exposure is after the first trimester there have been multiple reports of anhydramnios and that is definitely problematic, and can see that in some of these cases the outcome was respiratory failure and death of the baby. So, this again, trastuzumab should be avoided during gestation. We do have information that anthracyclines can be safely administered. Taxanes can also be safely administered. Platinum agents should be avoided when possible but there's a higher risk from cisplatinum, hormonal therapy and anti-HER2 therapies are contraindicated, as are bisphosphonates. In terms of using GCS, the effect, there was very limited data, should only be considered

if clinically indicated. Often, there is a discussion about when there's optimal timing of delivery when a woman has breast cancer and is pregnant. And there is a misconception that people often say, well let's try and deliver the woman as quickly as possible, but we need to remember, that fetal development and long-term wellbeing of children really can be very severely impacted by prematurity. So, today, we know that we can give a lot of optimized treatment during pregnancy. Safely do so, and it's safe for the mother and it is safe for these babies and there is long-term follow-up of these children that supported that this is relatively safe. And we also know that premature birth is not in the interest of the baby or the fetus and so, we try and promote these women having their babies as close to full term as is possible. So, in summary, in principle standard chemotherapy can be offered to most patients based on gestational age, tumor stage and biology. And just to reinforce that exposure to endocrine therapies and anti-HER2 therapies are contra-indicated for the most part. Moving on to hereditary breast cancer. So, this overview was given by Judy Garber and in young women the predominant breast cancer risk genes remain BRCA1, BRCA2 and in very young women we might see a P53 mutations. The rest of these mutations are not particularly common at all and they are less common in women under 40. When we look at these data, we can see that when germline panel testing was performed on a large group of women at one institution, but most common genes were BRCA1 and BRCA2. When looking at the issue of genetic counseling and testing, we did come back to the issue of health disparities and in BCY5 and reminded everyone that from women who are from minority or disadvantaged ethnic or racial backgrounds, utilizing and seeking genetic counseling services is problematic and we have limited literature on this. In addition to this, we also know that risk reducing measures are also underutilized in minority groups who have a BRCA 1 or 2 mutations. So, this is a really important issue that needs to be addressed and further research is needed into it. In terms of young women with a BRCA mutation, there is no difference in overall survival between BRCA patients who have a BRCA germline mutation and those who do not. And this was also true for patients with triple negative breast cancer. So, this is something that's important to remember, and BRCA studies should not be viewed as an independent poor prognostic factor. And now, the issue that was raised and has been demonstrated before also by some of my colleagues in Israel, is if we look at the distribution of Oncotype Dx risk categorization, it is different amongst women who do not have a BRCA mutation and those who do have a BRCA mutation. So, a woman with a BRCA mutation is more likely to have an intermediate or high risk. And it really just illustrates that often BRCA mutation carriers are more likely to need chemotherapy incorporated into their care and their biology is different. This is not to say that an Oncotype Dx risk is not an appropriate tool, it is an appropriate tool, but to keep in mind that the distribution will be different amongst BRCA carriers. There is an ongoing perception that there is a preference for platinum-based therapies in patients with germline BRCA mutations, this is well-established in advanced breast cancer. However, in early breast cancer the data is limited. So, Judy Garber presented this study that was presented at San Antonio in 2019 and in this study, there was neoadjuvant treatment for patients with the germline BRCA mutation and they were randomized to receive four cycles of platinum compared to four cycles of AC. And what we can see here is that the AC was actually superior than cisplatinum. And we need to remember that what works in advanced breast cancer is not always the case in early breast cancer and a BRCA mutation in early breast cancer is not an indication in and of itself for incorporating a platinum agent. Once again, please feel free to ask questions, I can say there are more questions coming in in the Q&A. Olivia, is there any questions.

Dr Pagani: Yes, I think that maybe, there are a couple of questions on why we discourage the three-monthly LHRH agonist as adjuvant therapy.

Dr Paluch-Shimon: Okay. So, what we know is that women are more likely to not be fully suppressed under three-monthly regimens. Obviously, there are problems or geographical or demographic issues and a woman cannot come in every month, that would be a reason to consider but then, the hormonal profile really needs to be monitored very closely. And the younger the woman is, the more likely is that she may not be fully suppressed. And particularly, if she's receiving an aromatase inhibitor, that's a real problem. As a woman is closer to 50, sometimes, then the three-monthly regimen is more reliable but when we are relying on the

ovarian function suppression for the administration of an aromatase inhibitor, I would strongly encourage to use a monthly formulation.

Dr Pagani: And then, if estradiol enough to monitor ovarian suppression.

Dr Paluch-Shimon: So, when I do the monitoring, I look at estradiol and I look at LH and FSH and there's a particular range that LH and FSH will be in, if the woman is properly suppressed with an LHRH analog. So, I would look at all three factors.

Dr Pagani: And then, there is a question which I think it's still open. If there is any news about the approval of abemaciclib in high-risk early breast cancer.

Dr Paluch-Shimon: There's no approval yet.

Dr Pagani: And so, I think the others are more or less on the survivorship. So, I think we will answer at the end.

Dr Paluch-Shimon: Okay, so, in terms of lifestyle factors and just before we get into survivorship, there was excellent data presented by Ellen Copson from the POSH group, which is a very large cohort prospective study, on women under the age of 40 based in the UK. And what it showed was that if women had an elevated BMI diagnosis, they had a poorer overall survival and poorer distance disease free survival. In terms of the BMI and pathological features there were some differences. So, ER- tumors were actually more common amongst women who were obese, and in terms of triple negative tumors, they were also slightly more common in women that were obese. Obesity in and of itself in this study group was not a risk-factor for being diagnosed with breast cancer. However, once there was breast cancer the features were different and the outcome was different. On a multi-variate analysis, they demonstrated that for estrogen receptor positive disease, obesity was a significant risk-factor for recurrence and for worse overall survival. Interestingly though, obesity was not a significant independent influence on distant disease-free survival or overall survival in women who were hormone negative in a multi-variate analysis. The other interesting data that was also presented there was that women who are obese are more likely to have a significant difference in dose-delays. So, there's another reason why healthy body weight is also important. In summary, obesity diagnosis is associated with a reduced breast cancer specific and overall survival in young women and young breast cancer patients are at significant risk of weight gain during the treatment. And this has a negative impact for quality of life as well as long-term outcomes. Physical activity post-diagnosis is associated with an improved long-term outcome and reduce comorbidity, and physical activity during treatment has been shown in several studies to be associated with improved treatment tolerance. So, along with my recommendations for anti-emetic therapy and any other pre-medication or GCSF or supportive care, all my patients go out with a written recommendation to try be physically active during their active period of treatment, as well as in their survivorship care. Weight management and encouragement of physical activity should be part of routine care and it's not nice to have, but should actually be prescribed by us for our young patients. And so, just to remember that obesity is a risk factor for many other diseases beyond cancer and we know that obesity is gonna be the most significant risk-factor for any cancer diagnosis in 2030 in most Western countries. And obesity is a risk-factor for heart disease, diabetes and diabetes is associated also with an increased risk of breast cancer. So, we need to encourage women to find a healthy body weight. In terms of specific survivorship issues. Important data was presented by Matteo Lambertini that pregnancy amongst BRCA mutated carriers is safe. So, in terms of disease-free survival and overall survival, we've known for a while based on a lot of retrospective data the pregnancy after breast cancer is safe in an overall population of women with breast cancer, but now we have this data as well for women who have a germline BRCA mutation. Just to point out, that there are new ESMO guidelines about fertility preservation for cancer patients, lead author on this was Matteo. And I strongly recommend for all of you to have a look at these guidelines that can be very helpful and are a must when you're taking care of patients of a reproductive age. So, this is just in support of use of guidelines. Fertility preservation needs to be offered to all women at all

stages of disease. And just to remind everybody, that women diagnosed with breast cancer during pregnancy need multidisciplinary care. And fertility preservation has to be discussed with all women and it's actually in part of the informed consent process. And often specialists do not always discuss this with women and who has advanced breast cancer but there was a step in in ABC5 endorsing that these issues need to be discussed with women who have advanced breast cancer before they start treatment. And obviously, this needs to be contextualized for their prognosis and the potential for a subsequent pregnancy which obviously in advanced breast cancer is usually discouraged, but it is a woman's right, for these issues to be discouraged with them, and we need to be careful not to be patronizing and paternalistic and not to discuss it with women. Another interesting important issue in survivorship care is looking at the impact of extensive surgery. So, often people are inclined to treat young women more aggressively, also surgically but there is actually no justification for this and this will have a negative impact on women's care. So, in this study presented by Shoshana Rosenberg's and Ann Partridge's group, we can say that firstly, amongst young women, 45% are having a bilateral mastectomy, I can assure you that 45% of women do not need a bilateral mastectomy. There are meta-analyses that demonstrate no-survival benefit in the use of mastectomies in women under 40 and more extensive surgery is associated with worse anxiety, worse body image and also, over here, worse sexual health, and we can see that this worst outcome is ongoing and does not really improve over time. So, the more aggressive or extensive the surgery is the worst the woman's quality of life is going to be and it will not improve their outcome, if it is not medically indicated. Another important issue in survivorship is adherence, typically, to endocrine care. Now we know that there are a few factors associated with non-adherence. One is the younger woman is the more likely there is to be non-adherence issues. A key factor is concern about fertility. So, women who are worried about their fertility are less likely to be adherent to their endocrine therapy, which another very important reason to address their fertility concerns. And another important issue is that women who have low levels of education, less social support are more likely to be non-adherent. So, these are groups of women that need more research and more support and follow-up care to ensure that they're adherent to their treatment. Another really important issue for all women with breast cancer, but especially young women is sexual functioning. And what we can see is that women who have poor symptoms, so, they've got very severe symptoms, these are not generally improving over time, whereas women who are asymptomatic remain asymptomatic. What's interesting there is a significant group of women who have worsening moderate symptoms over time. And what we know about sexual health is, first of all, if we don't ask about it the patients will usually not volunteer this information. There are studies that show that if interventions are performed a woman's sexual functioning and sexual health can improve dramatically. So, we have a responsibility to address this issue for our patients. The next issue on survivorship is employment. We know that employment outcomes after a breast cancer diagnosis are worse. This is data in a group of young women. Again, this is a predominantly high-income cohort and predominantly white cohort. So, we need this sort of information also for different cohorts, but a year after diagnosis, only 80% of women are employed and there is higher unemployment in the women post-diagnosis and half of those who were unemployed reported they were unemployed because of health reasons. Amongst the employed women, 7% reported treatment affected their ability to perform a job. So, employment is an important issue; it, obviously, has financial impact and we need to give more attention to this issue in our young women. In terms of supportive and follow-up care, psychosocial distress, pertaining to body image, sexuality and sexual dysfunction resulting from premature menopause, treatment related amenorrhea, weight gain, hair loss and breast surgery has to be routinely addressed by the healthcare team to make sure there's adequate support. Again, we need to make sure that issues of job, employment and insurance related issues are addressed because there's obviously financial toxicity after breast cancer diagnosis. And we need much more research into these issues particularly, in women who have lower insurance. So, most of this data is coming out of North America and from well-to-do cohorts. So, we need more information particularly, because there is certainly health disparities on these issues. And before I wrap up, I just wanna illustrate that a lot of this information, a lot of this ongoing data that's being generated about young women with breast cancer and survivorship has been generated by many of the faculty who participated at BCY and we owe them a great

thanks for the work that they've done. And hopefully, we will be able to have live meetings for the next advanced breast cancer conference and also for the next BCY conference and now, we're happy to answer some more questions.

Dr Pagani: Yes, I think two questions about survivorship. One is about oral contraceptives in breast cancer patients and the second one is the optimal timing between diagnosis and pregnancy, especially in ER+ disease.

Dr Paluch-Shimon: So, I think I'll start off with the oral contraceptive question. A, physicians often forget to talk about contraception and that issue actually has to be addressed with young women. The recommended contraceptive, best contraceptive options are non-hormonal, so, a copper IUD, not a Mirena, or condom use are the best options. And this is also true for women with triple negative breast cancer. The hormonal access and breast cancer is a complex access that we don't know everything about. So, even in women who have triple negative breast cancer we need to avoid any exogenous endocrine exposures. The oral contraceptive pill is contra-indicated in a woman who's had a breast cancer diagnosis. I think that the question about pregnancy particularly in hormone + breast cancer, I'll let Dr Pagani address because she is the PI on the very important study which is the Positive study, looking at this issue.

Dr Pagani: I think we are waiting for the results; the accrual has been finished last year. So, while waiting for the results, I think that we, usually, in clinical practice and so, I think you'll also do like that, we encourage women to wait at least two years before trying to get pregnant, especially, in ER+ women so, that they can complete at least two years of endocrine therapy. But this is true also for triple negative breast cancer patients, in order to be sure that they are free of disease and so, this is a reasonable time to wait. So, and then, if one patient cannot wait the end of the 5 or 10-years treatment, because she's approaching 40 and so, she will see her fertility vain over time, two years of endocrine therapy is the minimum duration before she stops and try to get pregnant. And then, the most important thing is that, after pregnancy, she needs to resume treatment and to finish the planned duration. So, I don't know if you want to add something Shani.

Dr Paluch-Shimon: I fully agree with you.

Dr Pagani: Yeah, and then, there is a question which is in your field of expertise about PARP inhibitors in metastatic breast cancer.

Dr Paluch-Shimon: Okay. So, in terms of PARP inhibitors and because of the time limitations we actually took that slide out, but we endorsed the ABC statement, which is that for patients who have a BRCA germline mutation with triple negative breast cancer, a PARP inhibitor is probably a preferred option in the first-line setting. Amongst women who have endocrine positive advanced breast cancer and have a BRCA mutation, the preferred first-line regimen is still gonna be a CDK inhibitor and endocrine therapy, and then a PARP inhibitor can be used as a subsequent line of therapy. But PARP inhibitors are certainly a preferred regimen in women with a germline BRCA mutation, if it's available.

Dr Pagani: Then another very important question about, because it's a late effect, about cardiovascular disease in young women. So, this is something which is very important.

Dr Paluch-Shimon: So, this is a really important issue which is another very important reason to encourage these women to maintain a healthy body weight and exercise. There is quite a bit of data showing that women who undergo premature menopause have worse cardiovascular morbidity and mortality and an increased risk of death, so, in the long-term from cardiovascular causes. So, if we have to balance out risk/benefit for most of these women the risk of the breast cancer is going to be significant. So, we're not usually gonna change their recommended treatment because of that. However, in survivorship care, this is something that should be monitored ongoing. Then other issue is left-sided radiotherapy that can have an impact on cardiovascular care, Herceptin which is normally reversible on cardiac damage and obviously

anthracyclines can have long-term damage. So, what we need to do is first of all, make sure that these women maintain a healthy body weight, exercise, have optimal management of their lipids and optimal management if there's any diabetes, and they should be followed, and the family physician should be made aware that these are issues that need to be closely monitored in these women.

Dr Pagani: Yeah, we are close to the end, but maybe a comment on, because there are a few questions about local regional treatment, specifically after neoadjuvant chemotherapy and then, immediate reconstruction after mastectomy, if you just want to make a short comment, of course, it's very difficult, but maybe a couple statements.

Dr Paluch-Shimon: In general, there was a statement in BCY that all women who are undergoing a mastectomy should be offered or have the opportunity to have immediate reconstruction. It's true that radiation can impact the reconstruction and there might be fibrosis, but a good radiation oncologist will know how to deal with that and this will have an important impact on the woman's quality of life. There are situations where immediate reconstruction is discouraged. So, if there was inflammatory disease, or any skin involvement that would not be a patient who's a good candidate for immediate reconstruction, but most women can undergo immediate reconstruction. In terms of radiation therapy, in hypofractionation the data so far appears to support that this can also be used in younger women. We know that there is a boost, there's a benefit sorry for boosts in women who are younger but depending on what their disease features were and that in general, women who have had node-positive disease and are young, usually, benefit from radiation therapy including post-mastectomy radiation.

Dr Pagani: And I think another comment to close up is that in general the minimum management after neoadjuvant chemotherapy is not different from older women, so it's, there are still a matter of debate what to do with axilla which was positive before and negative afterwards, but this is not different from other age groups. And the second thing you mentioned, hypofractionation, which I think is very important in this COVID period because I think that shortening the radiation therapy duration, I think it's very important in these times. So, then, another reason to adopt more largely this kind of schedule, and then, I think we need close. I'm sorry if we had no time to address all the questions and I will really want to thank Shani because she did a very good job just trying to summarize such a big and huge field in a very nice and comprehensive lecture. Thank you, Shani.

Dr Paluch-Shimon: Thanks Olivia, always fun to be able to host with you.

Dr Pagani: Bye and thanks to everyone.

Dr Paluch-Shimon: Have a good evening.