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## Can we adapt the standard according to patient's health status?

**Prof Audisio:** I'm very grateful to the organizer of this event for asking me to say a few words on surgery, particularly, surgery for breast cancer in older women, which has been the area of my interest for many long years and has been the most successful treatment option for millennia. And, as you know, breast cancer surgery was already presented into the Egyptian papyrus. So, it's a well-known treatment. Let me start from here. This is the slide that I presented in Boston, some 15 years ago, for which I was heavily criticized. This slide I've picked from Twitter where young breast cancer patient survivors were kind of angry saying that I was perhaps lying or minimizing their drama. I do not want to minimize the drama of young women with breast cancer at all. But let me just remind you that, as you can see here, when you are 60, 70, 80, 85, it is very likely to face with breast cancer whilst it's very, very unusual at a much younger age. So, breast cancer is a disease of older women. And I want to prove this to you by showing some hard data besides stating that breast cancer affects older women. And that's in fact the reason why you are attending this event. I want to remind you that breast cancer, as every other solid tumours, in Europe, is poorly treated. The outcome is heavily hampered by the patient's aging. Wherever you are, North, South, East, West, there is large evidence that past ages 60, 65, the cancer-specific survival, this is actually people not dying because of diabetes, a stroke, a fall, whatever. They die of cancer because we treat them miserably. And I find it difficult to blame my medical oncologist and radiation oncologist friends. This is by far a surgical failure. Breast cancer is rather easy to cure these days, and despite this, the outcome of older women is worse than expected. And that's mainly a surgical failure. Let me explain to you why. Here we go. This is the treatment-plan for all women, in Europe, and for different cancer sites. And as you can see, with the progression of the patient's age, past, again, 60, 65, 70, the surgical option, the surgical treatment is deranged and minimized. And that's a shame because we end up denying the state-of-the-art treatment, which is surgery. Medical oncology, radiation is very interesting, all advancement that you might fall in love with. But remember that breast cancer is cured by surgery. So, the strong point I wanna share with you is that there is no whatsoever contraindication to a surgical treatment. Mortality is un-existing, zero mortality, and there is no patient that cannot be treated with the removal. I know that people find this disturbing, but some juicy surgical images might help you to remember how patients, even in the worst condition, can receive general anaesthetics, local anaesthetics, or spinal blocks. And with the help of a brilliant anaesthesiologist, patients are sedated, are treated. The pain is completely controlled, completely treated, and you can spend half an hour, one hour with severely damaged, severely hampered patients, receiving surgery, including a full mastectomy, without the patient feeling anything, pulling jokes, telling stories, and ending up with a nice wound, and sending home the patient on the same evening. There is no drain. There is no need for keeping the patient in. So, patients should go out the same day, and this is how I recommend all your surgeons to deal with. Different thing is, when should I give surgery? Please remember that apart exceptional cases, breast cancer surgery is not an emergency, maybe, once in a lifetime. I very much recommend considering the combined use of endocrine treatment, like a pre-operative treatment, neoadjuvant treatment, to shrink the cancer, controlling most neoplasm,

given that elderly patients are more frequently luminal A, luminal B. And this is the advantage in reconditioning the patient, offering pre-habilitation. There is also some advance in the treatment of neoadjuvant, on the administration of adjuvant chemotherapy. This is a population-based investigation on triple-negative elderly women, where we assessed the SEER database in the States with Christopher Pezzi, and the whole Swedish registry. And we've discovered that it is indeed advantageous to offer chemotherapy as a treatment option for triple-negative breast cancer following surgery. Please be aware that the most important part, most crucial part is patient's preference, communication with patients, allowing information, informed choice. And be aware that misinformation, fear, misconception is a horrendous limitation to treatment option. This really hampers the outcome of the treatment. Most patients come to you and say, "I don't want surgery. I'm too old for surgery. I really don't feel I should be undergoing any surgical treatment." And you can reassure them that it's a day case. It's one shot. It's pain-free. And still, they will say, "Oh no, no, I don't want it. I don't want it. I don't want it." Then, you need to spend 10 minutes with this patient and really ask, why do you not want it? What is it that drags you away from the surgical option? You should discuss all available options including nonsurgical ones, assess for frailty, optimize patients, and engage with patients in the decision-making. It would not be a surprise to realize that patients, actually, have very strong reasons not to receive surgery. And I just want you to remember you that elderly patients have a different mindset which we should embrace and respect. One in two suffers from cognitive impairment. One in two suffers from incontinence. And again, some 50% is about undernourished and lacks mobility. So, when the decision-making process takes place, be aware that this might be a reason. I also want to remind you that the patient's perception and decision sometime is irrational to you. In the UK, we set up a deal with Age UK, the charity that sponsors older patients, and we discovered that most elderly people would not go breast cancer surgery because they had to walk their dogs, that no one to walk the dog. We set up with the charity a walk-dog team, and patients were very much reassured, and the pickup rate for surgery was tremendously increased. There are indeed special cases where we could derange the treatment plan. I want to remind you, for example, frail, elderly lady with a small luminal A with no palpable and no ultrasound-visible lymph nodes, maybe, you don't really want to offer sentinel node biopsy, given that even if the node is positive, you would end up with some endocrine treatment. So, you would not consider for chemotherapy. Maybe, sometimes, mastectomy is an option. Let me just give you the example of Greek colleagues, where you have a constellation of 3,000 islands. And the old lady is not able to travel in and through to Athens for radiotherapy once a day. So, a wide local excision plus radiation might not be the best option. And I also want to remind you of the increasing number of patients, elderly patients, requiring reconstruction, remodelling, and skin-sparing mastectomies and so on. So, be prepared to personalize treatment at all times. In order to do so, I very much congratulate Linda Wyld and the all Sheffield team where they produced this algorithm, which is available for free on the net. Here is an example of an 87-year-old lady with a grade-III tumour, 50 millimetres in maximum diameter, no lymph nodes, suffering from diabetes, and ADL stage 1. And you can tell her that surgery would offer her this number of opportunities and to be alive at two years whilst primary endocrine is shrinking her life expectancy, cancer life expectancy. Therefore, this is a visual straightforward method to offer a patient a better understanding. Here is the website, which I say it's for free. And it's for you to use at your convenience whilst you are negotiating, and, breaking news, and discussing treatment options. I think this is crucial because it allows you precise information and accurate data. Now, if we go back to the original question that my lecture was referring to, can we adapt standard treatment according to the patient's status? Well, my strong points are, please, do engage with patients. Try to appreciate their expectations, their fears, and help them in understanding which are the options and you to understand which is their target. Never forget appreciating or scoring for frailty and life expectancy. Be very flexible on personalization of the treatment option. There is definitely no need for downsizing surgery. Under-treatment is really a catastrophic option, the worst option you can pick, also, being aware that over-treatment can be avoided. And let me just show you this beautiful piece of information showing how the surgical community should be trained, and the medical community as well, in avoiding re-excision when the margins are considered not enough. No ink on

the tumour is the golden standard. I thank you for your attention and for your interest in breast cancer surgery. Thank you.

**Prof Kunkler:** I'd like to thank the organizing committee for their invitation. Because of constraints of time, I'm going to concentrate my comments on irradiation after breast conserving surgery, and I'm going to be highly selective. I have no financial disclosures or conflicts of interest. Health status can be defined as a range of manifestations of disease affecting the patient which include symptoms, functional limitations, and quality of life. And I'm going to focus initially on cardiac disease, which is common in older patients, and then talk about adaptations in terms of technique to reduce toxicity, the strategy of omitting adjuvant radiotherapy, the shortening of dose-fractionation regimes, which we call hypofractionation, the techniques of partial breast irradiation, and future directions and work in progress. One of the major barriers to the assessment of patients for radiotherapy is the lack of integration of comprehensive geriatric assessment into breast MDT teams. We know that geriatric assessment improves prognostication, risk-stratification, and indeed, there are two validated prediction models of severe toxicity with chemotherapy in older adults which are superior to performance status. But in present, we don't have any similar validated risk stratification tool in radiation oncology. In terms of risks of cardiotoxicity, there is the data from Darby and colleagues published in The New England Journal in 2013 showing the relationship between cardiac exposure and the risk of coronary events. So, there's a 7.4% increase in major coronary events per Gray. And, importantly, there is no threshold-dose for effect. There are techniques for reducing the dose to the heart, here in this slide showing in the left-hand panel, the situation in expiration and that in the right-hand panel, the impact of deep inspiration breath-hold in which the heart moves out of the field. There are also other techniques for reducing the dose to the heart in terms of prone radiotherapy position, shown in the left-hand panel, and in the right-hand panel, the reduction in dose to the heart as the heart is moved out of the field in the prone position. One might surmise that post-operative radiotherapy would impair the quality of life of patients, but here is data from the PRIME 1 quality-of-life trial in T1 to T2, node negative patients treated by breast-conserving surgery, randomized to radiotherapy or no radiotherapy with their quality of life measured by the EORTC QLQ-C30 scale. And you can see that there is no difference up to 15 months in the no-radiotherapy group in blue and the irradiated group in red. And that is also true at five years. Although, I have not shown the data. The other strategy is of omitting radiotherapy, and there are two randomized trials which have addressed this in older patients, the CLGB 9343 trial and the PRIME trial, which I'm showing you here. And these are the 10-year local control data of the PRIME 2 trial. So, these were patients 65-years or older, T1, T2, up three centimetres, node-negative, ER-positive, randomized to radiotherapy or not. And you can see at 10 years that radiotherapy reduces the risk of recurrence from 9.8% to 0.9%. And importantly, there's no difference in overall survival. The incidents of distant metastases and most of the deaths are not due to breast cancer. There are a number of guidelines on the omission of radiotherapy, the NICE guidance, which allows it in women 65-years or older with T1, ER-positive, HER2-negative, and grade-I and II-tumours if they're willing to take adjuvant endocrine therapy for at least five years. EUSOMA suggests older patients with small tumours over the age of 70 who receive adjuvant endocrine therapy can be treated without radiotherapy without a compromising in their overall survival. But they are concerned about extending this to a broader group until there are published studies with longer-term follow-up comparing the benefits and side-effects of post-operative radiotherapy and adjuvant endocrine therapy. And, finally, the NCCN guidelines where breast irradiation may be omitted in patients 70-years or older with ER-positive, T1 tumours who receive adjuvant endocrine therapy. The 5-year results of the PRIME 2 study were also considered, and the panel believed the data needed further maturation before extending the omission of radiotherapy to patients aged 65 or older. There are a number of trials of shortened fractionation, what we call hypofractionation, the START A, the START B, and the Canadian trial of Tim Whelan and colleagues. And these show no difference in terms of local recurrence but a reduction in breast toxicity in the hypofractionated arm. And more recently, the FAST-Forward trial looking at an even shorter duration of treatment comparing 40 Gray in the three arms, but given in the experimental arms, 5 fractions either of 27 Gray or 26 Gray and showing similar local recurrence rates but with less breast

toxicity in the 26-Gray in 5-fraction arm, suggesting that would be the preferred regime. If we look at the representation of older patients in randomized trials, we can see in the START A and START B trials, the proportion of patients between 70 and 79 is 11.6% in START A, 10.6% in START B. But in the more recent FAST and FAST-Forward trials, the representation is slightly higher, 40.6% in FAST and 12.9% in FAST-Forward. There are a number of techniques of partial breast irradiation based on the rationale that 85% of patients will have a recurrence, if they do have one, either in the primary tumour site or close to it. There are a number of techniques, interstitial brachytherapy, giving 32 Gray in 8 fractions, intraoperative radiotherapy, giving between 20 and 21 Gray in a single fraction, intracavitary brachytherapy with MammoSite, giving 34 Gray in 10 fractions or external-beam irradiation, giving typically 38 Gray in 10 fractions. The largest of the external beam trials is the IMPORT-Low trial from Charlotte Coles and colleagues published in the Lancet comparing, in the left-hand panel, whole breast irradiation in 15 fractions, 40 Gray, 2.76 Gray per fraction, and then, two partial breast irradiation groups, giving 2.7 Gray to the area closest to the primary site and 2.4 Gray to the peripheral of the breast, and then group two, concentrating the 40 Gray in 15 fractions at 2.7 Gray, 2.7 Gray in the primary tumour-bearing area. And here the results of partial breast irradiation. You can see in the left-hand part of the slide, the IMPORT-Low trial showing very little difference in local recurrence varying between 1.1% and 0.8% at 5 years. And then, three lines along the GEC-ESTRO trial of brachytherapy with the longest follow-up of 5 years and the most important evidence for the basis of brachytherapy in partial breast irradiation, again, showing no differences in local recurrence. There are a number of recommendations for accelerated partial breast irradiation. And one should be aware that the evidence-base for these is relatively weak. There are recommendations from ASTRO, GEC-ESTRO, and the American Brachytherapy Society, but there are differences. So, for example, the ASTRO recommends a threshold at 60-years, GEC-ESTRO at 50. In terms of tumour size, ASTRO recommends 2 centimetres or less, GEC-ESTRO and ABS, 3 centimetres or less. There's also a difference in terms of estrogen-receptor status, being positive for estrogen-receptor status being a requirement for ASTRO and GEC-ESTRO, but for ABS could be positive or negative. In terms of histology, partial breast irradiation is confined to invasive ductal carcinoma for ASTRO and GEC-ESTRO, but for the ABS, invasive cancer or ductal carcinoma, ductal carcinoma in situ, are allowable. So, in terms of future directions, there is the development of MRI-guided radiotherapy, which is in development and evaluation. And there is limited access to this at present, but it does allow much better resolution of the soft tissue, which may be relevant to the application of neoadjuvant accelerated partial breast irradiation. And I show in the upper panel in a primary intact tumour, in the central panel, the better soft tissue resolution on MRI compared to the left on the planning CT or on the right, the cone beam CT. And then, the lower panel following excision, where the black zone in the central part of the central illustration represents the excision cavity. Proton therapy is also under evaluation, very expensive and with limited access. But the Bragg peak reduces the dose to the heart from protons compared to conventional photons. And we can see this in the next slide from Stick and colleagues, where in the left-hand panel, you can see the coverage of the heart with photons, and with protons on the right, the heart out of the field. So, what can we conclude? There is a need for geriatric assessment to be incorporated into MDTs for older patients to assess their suitability for radiotherapy. At present, we really don't have any validated tools for predicting radiation toxicity. There are breath-holding techniques to reduce the dose to the heart. Omission of post-operative radiotherapy is an option for ER-positive patients 65-years old or older, pT1 or pT2 up to 3 centimetres, node-negative, as long as they are receiving at least 5 years of adjuvant endocrine therapy. Hypofractionation, more convenient for patients in 15 to 16 fractions. And now, in 5 fractions are well-validated in clinical trials, Partial breast irradiation by a variety of techniques can maintain good local control with less normal toxicity. And under development, protons as well as MRI-based neoadjuvant accelerated partial breast irradiation. I'd like to thank you for your attention.

**Dr Biganzoli:** Good morning. It's my pleasure now to discuss the systemic adjuvant treatment in elderly breast cancer patients that will try to address the question on whether we can adapt the standard according to the patient health status. One of the major challenges we have to face while defining the adjuvant strategy in an

older patient is related to the extremely heterogeneity of the population in terms of health status that translates in different life expectancies also, within the same age group. The health status of the patient is also extremely important in defying the risk of competing cause of deaths. Namely, the patient is dying for reasons that are not related to the breast cancer. Derks and colleagues, looking at patients entered in an adjuvant endocrine trial focused on post-menopausal patients, have clearly shown that there is a correlation between the risk of other cause of mortality and age and comorbidities. As you can see, if you focus on this square in which we have represented patients 70-plus presenting with more than two comorbidities, the risk of these patients to die from other causes than breast cancer is definitely higher than the risk of dying for breast cancer. Conversely, if we look at fit elderly patients, so, patients without comorbidity, we can observe that the risk of dying for breast cancer in these patients is higher than the risk are facing younger counterparts. And investigators offer as explanation for this finding, the fact that a dramatically smaller number of elderly patients, less than 1%, received before study-entry chemotherapy versus 50% of the younger counterparts. So, clearly when we are planning our adjuvant strategy in elderly patients, we have to be conscious that we have the risk of either over-treat or under-treat this population. And so, how we can try to tailor as much as possible our strategy? Of course, we have to consider information related to the tumour in order to be able to detect the risk of tumour relapse. But it's extremely important that we target the patient. We definitely need to have a clear idea of the health status of our patient. We need to have information on the physiological age, on the estimated life expectancy, and also, on treatment tolerance. And we can easily address this question nowadays by the meaning of instruments that you can see listed on the right part of this slide. So, what we have to define at the very end is to define, develop, and integrate it, an individualized plan for patients that can be informative for the treatment. And in this context, use of geriatric tools is extremely important because, for example, can allow us to identify non-oncologic problems that may be actionable, improving in this way the efficacy and compliance of our treatment. I will focus my presentation, adjuvant chemotherapy, on adjuvant strategies in patient with HER2-positive tumour, and on neoadjuvant therapy. Starting with chemotherapy, I'm not going to tell you who should or shouldn't receive adjuvant chemotherapy. My goal is to define which is the standard of treatment for elderly breast cancer patients and to discuss the different treatment options. So, based on the results of two prospective trials focused on elderly patients, the CALGB 49907 and the ELDA trial, we can state that the standard treatment for elderly patients is polychemotherapy. And since the comparators, the standard comparators that were AC or CMF, have been prospectively evaluated in these two trials, we can say that these two regimens are validated for their use in elderly breast cancer patients. Speaking about validated treatment, we can state that TC is a validated treatment in elderly patients based on this group analysis conducted within the US oncology research trial 9735 that shows that TC is superior to AC irrespective of age. But what about the sequential administration of anthracyclines and taxane? We cannot say that this regimen is validated in the elderly patients because it's never been evaluated prospectively in this population. We have a retrospective per-age, subgroup analysis data from fit patients, included in randomized clinical trials that are telling us that elderly patients are exposed to a higher risk of haematological toxicity and treatment deaths, reduced treatment compliance, higher incidents of hospitalization than younger patients when treated with the sequential regimen. And I would like to draw your attention on these two plots in which are described the risk of being hospitalized for severe adverse events in patients younger or older than 65 when a sequential AC weekly paclitaxel is prescribed. You see the numbers are 9% in the younger population, 23% in the older one. So, we clearly can state that the sequential administration is to be considered only for selected high-risk elderly patients. So, what we are going to do in patients who are unfit for polychemotherapy? There is a new way to personalize the treatment. My personal view is that if the patient is unfit for chemotherapy because of comorbidities, these comorbidities are going to reduce the life expectancy of the patient. And so, if the tumour is at low risk, I wouldn't treat this patient. Conversely, if the patient has a high-risk of tumour relapse, I would consider a personalized treatment. And my option is weekly paclitaxel based on the results of the Alliance trial, here described, even if failed to show non-inferiority of paclitaxel over AC, clearly showed that we lost not so much with a difference in terms of absolute benefit, in terms of overall survival, just 1%. And

clearly less toxicity for our patients. So, let us move on to management of HER2-positive tumours despite the under-representation of elderly patients in the registrational trials, the benefit that adjuvant trastuzumab has brought when inserted in the adjuvant systemic treatment is so huge that today, one-year trastuzumab plus chemotherapy are representing the standard treatment in older patients with breast cancer who do not present cardiac contraindication for the use of trastuzumab. In fact, the main concern using trastuzumab, especially, when used in combination with anthracyclines, namely not a combination putting the two agents together, but in a sequential strategy, has the risk of a cardiotoxicity that we know is particularly high in the elderly patients, has been nicely shown in this report published in 2016. So, with the blue line, the blue curve, represents the risk of severe cardiac events in respectively, the group A, younger patients, and patients 65-plus. So, our goal in treating elderly patients will be the de-escalation of the chemotherapy backbone. And recent recommendations from SIOG and EUSOMA recognize four cycles of TC or weekly paclitaxel times-12 as the preferred chemotherapy backbone for a trastuzumab-based regimen. In these contexts, the sequential administration of anthracycline, taxane, or more intensive regimens like, for example, the TCH regimen, can be considered only in very selective groups of fit patients, while in frail older patients, we consider as the standard regimen weekly paclitaxel in combination with trastuzumab. What about increasing the level of HER2 blockade in the adjuvant setting? So, new strategies like the double blockade with trastuzumab, pertuzumab is considered only in high-risk and fit patients, while extended adjuvant therapy with neratinib is possibly not an appropriate option in elderly patients, even the fit, because of the probability of high-grade diarrhoea. The use of single agent trastuzumab, without chemotherapy and associated with endocrine therapy in HR-positive tumours can be appropriate in frail, unfit patients. And we have data now to support the statement that was till recently, and I would say more an expert opinion. And these data are coming from the RESPECT trial in which patient aged 70 to 80 had been randomized to receive trastuzumab plus or minus chemotherapy. While this trial failed to show that trastuzumab monotherapy is not inferior to trastuzumab plus chemotherapy, but you can see that the loss in survival without chemotherapy at 3 years is very, very small and that chemotherapy had a negative impact on the quality of life. So, this study offers support, evidence-based data for our statement. And another strategy that we can consider in unfit patients or those are at risk to develop cardiac problems is the shortening of the duration of HER2 therapy. And nowadays, we have also data presented recently at ESMO that confirmed, that support this statement, this recommendation, because a meta-analysis, individual patient-based meta-analysis of the five non-inferiority randomized clinical trials on the duration, or reduced duration, of trastuzumab has clearly shown that when we have treated the patients for six months with trastuzumab, the additional benefit to go to 12 months is really narrow. And now, I would like to conclude with this slight focused on adjuvant systemic therapy for patients with triple-negative and HER2-positive disease. So, this strategy is becoming more and more common in the global breast cancer population. And EUSOMA and SIOG recommend that this strategy can be considered for carefully-selected fit older patients in which, if a PCR is not achieved, we can personalize the adjuvant treatment with either capecitabine or adjuvant T-DM1 based on the biology of the tumour, while, up to today, in less fit older patients, the standard of care is considered to be upfront surgery. Thank you for your attention.

**Dr Brain:** Hello, I'm Etienne Brain. I am a medical oncologist working at Institut Curie, in Paris area, in France. And I'm going to cover the topic of older patients with advanced breast cancer from the medical oncology perspective. These are my conflicts of interest. And the first question which comes to me in my mind is what makes the difference between metastatic and early-stage setting for older ones? The first answer is that very often, these patients have a past medical history with comorbidities but also, with potentially long-term toxicity of previous cancer treatments, including cognition impairment, cardiac issues, depression, neurological symptoms, and so on, osteoporosis, for example, also, metabolic syndrome, et cetera. The second answer is that very often, they take other co-medications. Polypharmacy is a very common situation. 1/3 of these patients take more than seven drugs, including non-inflammatory drugs, pain medication, and others. The third aspect is that reaching the end of life, reaching old age, create a fear for pain and

dependence and all these end-of-life aspects. So, these are specific considerations. The second point I would like to make is that, of course, the distribution of potential endocrine treatment sensitivity according to age makes endocrine treatments very important in older ones. You see that the majority of the older ones, above 60 have a phenotype, a breast cancer phenotype, including luminal expression with expression of endocrine luminal receptors compared with type triple-negative tumours and HER2-E disease, which are much rarer. So, actually we have two situations in metastatic setting for these cases. One is in favour of chemotherapy when we face a triple-negative breast tumour or when we face an ER, oestrogen-receptor, negative, HER2-positive disease and one which is very in favour of endocrine treatment either as a monotherapy or in combinations when there is an expression of oestrogen receptors in the tumour following the standard times that we just mentioned. And so, that is a strong basis for all the recommendations which are set or established every two years by the ABC program. Next session will be next October. So, do we have high-quality data for our older patients when we treat them with metastatic breast cancer? It covers chemotherapy, endocrine therapy, as I said, I just said, very important, and, of course, the era of targeted therapies. And actually, we do not have that many good high-quality data. Few older adults have been included or enrolled in registration studies. That is very clear for breast, like with eribulin, like with a lapatinib, like with targeted treatments or more recent chemotherapy. Hardly, the rate or the percentage of older patients enrolled in these programs have hit more than 10%. And that's very worrying because we keep on applying these registration-trial results to our older patients, who are quite common in our daily practice, while they've been quite absent of these investigations. And that's very important, that those trials, moreover, these trials have included older patients, very selected, highly selected, often younger, often with less comorbidities, with less organ dysfunction, and much fitter. So, the applications of how we implement these results in our daily practice is sometimes debatable. Having said that, we need to adjust. We need to adjust most of our systemic treatment. And how can we do that? Can we follow the general recommendations set almost two decades ago by Lodovico Balducci with splitting the population of older ones between fit and frail, with, in the middle, the vulnerable ones, with some reducibility of functional dependence or geriatric issues and choosing the standard treatments, the adjusted one, or the best supportive care for the frail one? So, that's a main question. Is it realistic? Is it a model that we can apply and use, implement easily in our daily life? And I must say that it requires some insights. And the first one is certainly how many patients can be classified as fit with breast cancer in the metastatic setting? Actually, fit, what does it mean? What does it mean? How do we proceed to discuss classification? So, potentially fit are those, what we can say as a shortcut, as potentially fit are those with a screening tool which is correct, with a score, for example, on G8 derived after ENCORE-DASH which is above 14. And for metastatic setting and early-stage breast cancer, what does it mean? It means in large cohorts or in large trials, almost 60 to 70% of all patients. So, depending on these assessments, we can proceed to a specific treatment. Chemotherapy is certainly the component of treatment which is the more difficult to handle because the therapeutic ratio is lower compared with endocrine treatment or even targeted treatments. If we look at the two main cytotoxic agents, which are doxorubicin, anthracyclines, and taxanes, for example, with anthracyclines, the risk of congestive heart failure occurs at 400-milligram per meter squared of cumulative dose of doxorubicin compared with 500 if we look at younger adults, above 65, 400, below 65, 500, 520, or, yeah, almost 50. So, the functional reserves in the heart is not the same depending on age. And the risk of cardiac issues and toxicities is higher. That's the same for taxanes, for bone marrow and for also neurotoxicity. The neurotoxicity grade 3-4 doubles from 15 to 30% almost whether you consider patients below or above 65. And that doesn't come with very different pharmacokinetics. That means that the drugs can give the same distribution in the body, but that reflects mostly the functional reserve in the bone marrow, which is different. And you have differences in terms of occurrence, of febrile neutropenia or grade 3-4 neutropenia whether you consider a person above or below 65. And that leads to different attitudes in terms of doses and certainly not below 100-milligram per meter square for docetaxel that we use sometimes very widely in younger adults. So, we need to adjust, and that opens also room for alternatives like nab-paclitaxel with efficacy comparable with solvent-based taxanes and no need for steroid pre-medication and other to be added to the polypharmacy

when it's used with more standard taxanes. Another aspect for chemotherapy is that you can try to anticipate the risk of toxicity through the use of algorithms which have been developed to anticipate or to predict the risk of serious side-effects, grade 3 to 5 toxicity. And two models exist not specific of breast cancer, but which, in 10 to 12 items, can give you an assessment of this risk quite accurately. So, there is a model of the CARG published by Arti Hurria, and the other one is the model of CRASH published by the team of Tampa with Lodovico Balducci and Martine Extermann. And both are ways to anticipate the toxicity and to adjust potentially upfront the doses of chemotherapy that you want to use. For endocrine treatment, it's less... it's easier, let's say. It's easier because the therapeutic ratio is easier compared with chemotherapy. However, within the era of targeted treatments and combinations with CDK4/6 inhibitors or mTOR inhibitors, we are facing also similar issues of potentially adjustments in terms of dose. In this pooled data analysis by FDA, we see that the use of CDK4/6 inhibitors, which have transformed prognosis of endocrine, estrogen receptors, luminal receptor-positive disease with metastasis, we see that despite a similar efficacy across age, there are greater serious side-effects and discontinuations in patients above 75. And that again reflects the functional reserve in terms of bone marrow for some CDK4/6 inhibitors, which is impacted with aging and which differs according to age. So, given that, it can impact quality of life, we need to potentially adjust. We may have to adjust that, and real-world data or large cohorts show that, very often, you have an adaptation in one patient out of four with a lower dosage upfront even and the same for all the anti-HER2 treatments, like pertuzumab. You know that the results of CLEOPATRA, the big trial in metastatic setting which has shown a very large impact on outcome and overall survival when you use two antibodies, pertuzumab and trastuzumab combined with docetaxel. There is a subgroup analysis in 65-plus and 75-plus patients, not a large number, but which shows that we have more frequent side-effects, grade 3 diarrhoea, peripheral neuropathy, and that you lose also dose-intensity in those patients. So, all that stresses very well that you may have to adapt, adjust to a certain level of geriatric assessments that you introduce upfront. And that's why you create also room for alternatives, and instead of combining these two antibodies, pertuzumab and trastuzumab, systematically with taxane, with risk of side-effects, you may look or seek milder regimen, like the metronomic therapy with cyclophosphamide. And in these trials, randomized phase II, we compare two antibodies alone with no chemotherapy and with two antibodies and metronomic chemotherapy. What was shown is that the combination with chemotherapy was better and with a more acceptable safety profile certainly compared with indirect comparison, but with what has been the rationale for the approval of the dual combination with taxanes. So, that's typically the alternative treatments or strategies that we can use in older ones and with very acceptable safety profile and a good reserve for T-DM1 at progression after this trial's done. So, all that stresses the need to develop specific recommendations for the management of older patients with cancer and with breast, and that's what has been very recently updated by EUSOMA and SIOG. And I recommend you to follow the Lancet oncology publication just from 2021. Last point I would like to make is regarding the fourth component which needs to be stressed when you manage older ones. It's the patient preference and acceptability. And I referred to a very old study, almost 20 years ago, which looked at older patients not that old, 60 plus, but with attitude at the accessibility of treatment according to the burden of the treatment and especially, when there was some severe or functional or cognitive impairment triggered by the treatment. And it shows that there is a very important decline, almost 90% decline, when there is a high-risk of severe functional and cognitive outcomes of treatment. And so, that requires explicit consideration in older ones. To conclude, I hope I showed you that it was very important to adjust treatments and using probably very often lower doses of chemotherapy, let's say. We shouldn't forget also that in society, we have... there was a very important shift in the way we appreciate old age. And if you look at these three photos, on the left side, you have Marie Curie in her fifties in 1920, '25. And she would be what we would label today as an old lady. And on the other side, you have Pierre Soulages, 101, last year, and Queen Elizabeth 95 or 94, I cannot tell you exactly. But they're iconic figures showing that the way we consider older ones have changed through communication, through the way media report on older age. But we should never forget that these are iconic figures, and the common situation that we face with our patients is not really the same. And when we look at the impact of the use of geriatric assessment on treatment decision

and interventions, we see that after an MDT, the decision taken before or after integration of some kind of geriatric assessment can revolutionize or change completely the initial treatment plan in almost 50% of cases with 2/3 less intensive treatment, stressing that we need to have these considerations specifically for older ones. And that comes only through collaborations between oncology and geriatrics. And that's the purpose of SIOG conference, which will be held very soon in November, virtual, unfortunately, in this period, but where we stress that optimizing treatments in older ones is precision medicine too. And that's true for breast and especially for metastatic breast cancer. Thank you very much.