[MUSIC PLAYING]

SHIPRA GANDHI: So I'll be discussing the neoadjuvant and adjuvant updates first, so let's start with a question. We have a 55-year-old female diagnosed with clinical T3N1 breast cancer, ER/PR negative HER2 positive, treated with docetaxel, carboplatin, pertuzumab and trastuzumab in the neoadjuvant setting. Status post lumpectomy and sentinel lymph node biopsy, there is residual breast cancer. At the time of surgery, she is in excellent performance status. What would be the recommendations?

[MUSIC PLAYING]

OK. All right, so this brings us to discuss the KATHERINE study. So the KATHERINE study included HER2 positive breast cancer patients who had been treated with neoadjuvant chemotherapy and had residual invasive tumors in the breast or axillary lymph nodes. They were randomized 1:1 to receive T-DM1 for 14 cycles or trastuzumab for 14 cycles, which was currently the standard of care at the time of the study. So in the two cohorts, trastuzumab and T-DM1, we see the baseline characteristics were similar. About 80% of patients had received previous anthracyclines in the neoadjuvant setting, and about 20% had received dual anti-HER2 targeted agents in the neoadjuvant setting.

So if you look, the primary endpoint was three-year invasive disease-free survival, and we actually see that T-DM1 did better than trastuzumab. The three-year invasive disease-free survival was 88.3% vs. 77% with trastuzumab, with a hazard ratio of 0.5, and the results were statistically significant. Also, in terms of freedom from distant recurrence, T-DM1 did better than trastuzumab. An overall survival rate is immature at this time. So clearly, the T-DM1 was better than trastuzumab in residual cancer. So this is a forest plot looking at the different subgroups, and we see that all the subgroups have benefited from T-DM1. No matter what the hormone receptor status was, whether they were ER/PR negative or ER/PR positive, what the preoperative HER2 directed therapy was, what the pathological nodal status was. No matter what the amount of residual disease was, even if it was at T1a, they happened to benefit from T-DM1 in the adjuvant setting.

So the KATHERINE study concluded that there is a statistically significant and clinically meaningful improvement in invasive disease-free survival with T-DM1 compared to trastuzumab, and all the key subgroups happen to benefit from T-DM1. No matter what the hormone receptor status is, what the extent of residual invasive disease is, or whether the patients got single or dual HER2 targeted agents in the neoadjuvant therapy. In terms of safety, T-DM1 did have more toxicities than trastuzumab. Especially there was more thrombocytopenia, more LFT abnormalities, but they were all manageable with dose interruptions or dose reductions, and no greater toxicities than what we see with T-DM1 in the metastatic setting. So KATHERINE does form the foundation of a new standard of care in the population, and it will increase the use of neoadjuvant therapy in the HER2 positive setting.

So some questions, some clinically relevant questions. What if a patient does not attain path CR with neoadjuvant therapy? Do we continue pertuzumab with T-DM1? So we do not. T-DM1 by itself is sufficient, as this trial showed. Was radiation allowed with T-DM1? Yes. The protocol would allow for radiation to be given concurrently with T-DM1 in the adjuvant setting. If a patient has bad CR and receives trastuzumab and pertuzumab in the neoadjuvant setting, what do we do in the adjuvant setting? We would continue both of them, because the hypothesis is that you attain the bad CR because of dual HER2 directed agents. So if the patient has started eating well, we should continue both of them in the adjuvant setting. And if the patient is experiencing toxicities with T-DM1, then we should go for those interruptions, dose reductions, and if not validated, then we should switch to trastuzumab and pertuzumab. No matter what the amount of disease is in the breast or axillary lymph nodes, T-DM1 is the standard of care now in the adjuvant setting. And the big question is, where does neratinib stand here? So that's currently a data free zone. The ExteNET trial looked at neratinib after trastuzumab, since now we have T-DM1, we will currently not be giving neratinib after completion of T-DM1 in this situation.

So shifting gears to de-escalation of therapy in the adjuvant setting, we have had two trials, the PHARE and the PERSEPHONE trial, that looked at 6 versus 12 months of trastuzumab in adjuvant settings. The final analysis of PHARE's trial were presented at San Antonio last year. And it shows that-- so this was a non-inferiority trial of 6 versus 12 months, and as we can see here, the confidence interval actually crosses the non-inferiority boundary, which shows that 6 months is inferior, so 12 months still remains the standard of care.

The other trial, the PERSEPHONE study, conducted in the UK, also looked at 6 versus 12 months, and actually showed that in terms of disease-free survival, and overall survival, there was no difference between 6 or 12 months of treatment. And actually, if you look at the upper limit of the confidence interval, it was lower than the non-inferiority margin, saying that probably 6 months-- we could do 6 months versus 12 months. However, when we look at the forest plot here, in the ER negative population, those treated with taxane-based chemotherapy, neoadjuvant chemotherapy, and concurrent trastuzumab with chemotherapy, we see that 12 months does better than 6 months.

And in our current standard, current practice, we are mostly doing neoadjuvant treatment for our HER2 positive patients. We are doing concurrent treatment, we are giving trastuzumab with chemotherapy, and especially with the APT clinical trial, we are going for a de-escalation of treatment and not giving anthracyclines any more. So even though PERSEPHONE did meet its primary endpoint, you would still say 12 months remains the standard of care. So definitely if a patient is having toxicities in the adjuvant setting, not able to tolerate treatment very well, we can go for 6 months, but we should try to push for a year of adjuvant trastuzumab.

Now, moving on to hormone receptor-positive breast cancer, let's begin with a question here. So a 45-year-old premenopausal female with 1.6 centimeter, grade 1, ER/PR positive, HER2 negative, invasive ductal carcinoma with an oncotype Dx of 23, what is the best management plan after lumpectomy? Would it be adjuvant hormonal therapy with ovarian suppression, adjuvant chemotherapy, or would we go for shared decision making with the patient?

[MUSIC PLAYING]

OK, so it's hormonal therapy with ovarian suppression or shared decision making. OK, let's talk about the updates. So TAILORx, as we all know, included hormone receptor-positive pre or postmenopausal patients, lymph node negative, and based on the oncotype recurrence score, they were divided into low recurrence score, which got endocrine therapy, from 0 to 10. 26 or higher got chemotherapy, and intermediate, score 11 to 25, was randomized to receive endocrine therapy or endocrine therapy with chemotherapy. This was a non-inferiority study, and it did show in the intention to treat population that the two were the same and we could go for de-escalation with endocrine therapy. However, in premenopausal females below 50 years, there was a benefit with chemotherapy.

So at this year's ASCO, an important aspect was looked at, which is the clinical risk, which depends on the size of the tumor and the grade of the tumor. And they wanted to see if, in addition to the recurrence score, does it have any prognostic value. So we see in females above 50 years and below 50 years the different recurrence scores. If they had high clinical risk, they tend to have a worse invasive disease-free survival and a worse distant recurrence-free interval. So that means, yes, clinical risk does have a prognostic role in addition to the recurrence score.

The second question was, what is the influence of clinical risk on predicting benefit from chemotherapy? We know that the oncotype score does predict benefit from chemotherapy, but does clinical risk add on to that? So if we see a low clinical risk-- so all the figures to the right mean that chemotherapy is better, so all patients, low clinical risk, high clinical risk, we see that there is no predictive benefit of chemotherapy. Sorry, there's no predictive benefit of clinical risk on chemotherapy, because low and high clinical risk have almost the same hazard ratio. Females above 50 years, again, we see that whether they are low or whether they're high clinical risk, they are not deriving benefit from chemotherapy. But premenopausal females, below 50 years, we see whether they are low or whether they are high clinical risk, they both seem to derive benefit from chemotherapy. So basically, the first thing is that clinical risk does not predict benefit from chemotherapy. The second point is that the premenopausal females are deriving this benefit from chemotherapy. So an important thing to think here is, is this benefit from chemotherapy or is this benefit from the castration effect of chemotherapy? So since this was an exploratory study, we can't say that with certainty that this was the castration effect, but yes, definitely something to think about.

So now we know that a recurrence score of 16 to 25 in premenopausal females, we have seen, does benefit from chemotherapy from the TAILORx data. So 16 to 20, if you don't stratify them by clinical risk, the absolute chemotherapy benefit is about 2%, whereas in recurrence score 21 to 25, it is about 6.5%. Now, when we stratify them by clinical risk, we actually see that low clinical risks do not derive any benefit from chemotherapy, whereas high clinical risks, we actually see a pretty significant benefit from chemotherapy, 6.5%, and the same in recurrence score 21 to 25, no matter what the clinical risk is.

So the TAILORx concluded that this population of patients, in recurrence score 16 to 25, premenopausal females below 50 years who have a recurrence score of 16 to 20, but low clinical risk, may not actually need chemotherapy. So it is recommended that we start using the integrated score in our clinical practice now, which is the combination of clinical risk with the oncotype, with a genomic risk oncotype Dx, and recurrence score. So a recurrence score 0 to 10, tamoxifen is sufficient. 11 to 15, again, tamoxifen is sufficient. But 16 to 20, with low clinical risk, as we saw, they do not derive much benefit from chemotherapy. Tamoxifen may be sufficient in this group. The high integrated risk, which has a recurrence score of 16 to 25, with high clinical risk, and 21 to 25, with low clinical risk, we continue to see them benefit from chemotherapy. So definitely something to consider is, can we just do ovarian function suppression with an AI as an alternative to chemotherapy. And recurrence score 26 to 100, it is chemotherapy.

So we should be using the integrated risk, combination of clinical risk and genomic risk, in our clinical practice. Premenopausal females below 50 years, recurrence score 16 to 20 with low clinical risk, probably do not need chemotherapy and tamoxifen is sufficient. And below 50 years, recurrence scores 16 to 20 with clinical high risk, and recurrence scores 21 to 25 with any clinical risk, ovarian function suppression with AI could be considered as an alternative to chemotherapy.

So now moving us to triple negative breast cancer. We know in the neoadjuvant setting, we used doxorubicin, cyclophosphamide, and paclitaxel. A lot of clinical trials are looking at the addition of immunotherapeutic agents. One clinical trial had added durvalumab and showed an improvement in path CR, but this was not clinically significant. Another clinical trial had looked at the addition of pembrolizumab and the path CR was clinically significant. So still, immunotherapy agents are investigational and not FDA-approved yet. Another question that we often encounter in our clinical practice is the carboplatin data in the neoadjuvant setting, so two clinical trials had looked at the addition of carboplatin to neoadjuvant ACP chemotherapy, and the CALGB 40603 did show an improvement in pathological complete response. However, the three-year remain free survival was not statistically significant. And the GeparSixto trial also showed an improvement in pathological complete response, especially in the homologous recombination deficient population. There, there was a statistically significant increase in path CR. So carboplatin is not recommended for all patients, it is on a case-by-case basis right now.

So in my opinion if a patient has a BRCA associated breast cancer, inflammatory breast cancer, locally advanced disease, and is healthy and clinically fit, and we are really trying to get a higher pathological complete response, we can consider adding carboplatin to neoadjuvant chemotherapy. Checkpoint inhibitors in the neoadjuvant setting are still investigational. They are associated with immune-related adverse events, as we all know. And this is an area where clinical trials are needed. We actually have a clinical trial open here at Roswell Park which would be opening, actually, in the next few weeks. In early stage triple negative breast cancer patients, we are adding chemokine modulation, which is a combination of an NSAID, celecoxib, with interferon and a TLR3 agonist. And the hypothesis is that this chemokine modulation will cause more immune cells to come and infiltrate into the tumor and make the tumors more responsive to chemotherapy, and we can have a better path CR.

So now moving to metastatic breast cancer, updates in triple negative breast cancer. So let's begin with the question. So we have a 56-year-old postmenopausal female with germline BRCA1 mutation, newly diagnosed with metastatic triple negative breast cancer with PD-L1 5% on tumor infiltrating immune cells. What is the treatment of choice? Is it talozaparib, paclitaxel, atezolizumab and Abraxane, or capecitabine?

[MUSIC PLAYING]

OK, so that is good, so we all know the status of quick updates on this. So this is the IMPassion 130. So IMPassion 130 was a randomized study in metastatic triple negative breast cancer patients who had completed adjuvant chemotherapy about more than a year back, and they were randomized 1:1 to get atezolizumab with nab-paclitaxel. By the standard of care, which is nab-paclitaxel, with the primary endpoint in the intention to treat in the PD-L1 positive population of progression-free survival and overall survival. So as we can see, in the intention to treat population, the progression-free survival improved from 5.5 to 7.2 months, with a hazard ratio of 0.8. This was statistically significant. And in the PD-L1 positive subgroup, we see the PFS increased from 5 to 7.5 months, with a hazard ratio of 0.62. So PFS was statistically significant. Overall survival, however, in the intention to treat population increased from 17.6 to 21.3 months. This was not statistically significant. And when we look back in the PD-L1 positive subgroup, we see the improvement in overall survival from 15.5 to 25 months. Because this was a hierarchical study, design p-value could not be calculated.

So at this year's ASCO, updated overall survival results were presented. So this was the second interim overall survival analysis, and we see that the overall survival in the PD-L1 positive population continues to be higher in the atezo Abraxane arm compared to the Abraxane arm. It's 18 to 25.0 months, with a hazard ratio of 0.71. Now, when you look at the PD-L1 negative cohort, we do not see any benefit of adding atezolizumab to Abraxane. As we can see the lines here, it's only the PD-L1 positive group where we have actually seen this improvement in overall survival. So basically the IMPassion 130 is the first and only Phase 3 study that has shown a clinically meaningful benefit of first line immunotherapy in metastatic triple negative breast cancer. Of note, atezolizumab and nab-paclitaxel has been FDA-approved for metastatic triple negative breast cancer. With PD-L1, more than 1% on the immune cells and the companion diagnostic assay approved with it is the Ventana SB 142 assay.

Another question that comes is where do we test the PD-L1. So in this trial, 40% of the PD-L1 testing was from the primary archival specimen, and in 60% of cases a new biopsy was updated. This could be a metastatic site, or this could be the primary site also. This trial definitely sets a new benchmark, because this is the first therapy that has crossed the two year line marking overall survival benefit in first line therapy for PD-L1 positive metastatic TNBC. And there is a current ongoing clinical trial, which is looking at the combination of atezolizumab with paclitaxel. So now we all know that a lot of studies that have shown that if you do checkpoint inhibitors early on, the overall response rate is actually higher than if checkpoint inhibitors are done as the second or third line of treatment. So checkpoint inhibitors by themselves as monotherapy have limited efficacy, and we have to generally look at combination approaches to improve efficacy.

The big question here is that we have seen this data in combination with nab-paclitaxel. Can we extrapolate this data to other chemotherapy combinations? We do not know this, and there are current ongoing trials addressing this question. The other thing is IMPassion 130 took patients who had completed adjuvant chemotherapy more than 12 months before, so if a patient has recurred sooner than 12 months, again, we do not have any data there, and there are current ongoing trials addressing that question. So clearly, this is an area where we need some more clinical trials, because we know checkpoint inhibitors by themselves do not work, and metastatic triple negative breast cancer has a poor prognosis. So we have another clinical trial in the metastatic triple negative breast cancer patients, where we are combining chemokine modulation with pembrolizumab. We would give chemokine modulation pre-treatment, make the tumors more immune responsive and then give pembromizulab, so there is no chemotherapy in this trial. So if you have any patients you think would be eligible, please do refer those.

Now, moving on to hormone receptor-positive breast cancer, some quick updates from the MONALEESA-7 study. So the MONALEESA-7 study was a study in pre/perimenopausal women with hormone-receptor positive breast cancer who had received less than one or one line of chemotherapy in the advanced setting. They were randomized 1:1 to ribociclib with an aromatase inhibitor or tamoxifen with ovarian suppression, or placebo with AI tamoxifen and ovarian suppression, so basically trying to see if ribociclib addition would improve progression-free survival or overall survival. So progression-free survival, we already know that the PFS increased from 13 months to 23.8 months in the ribociclib arm. And this year, the second [INAUDIBLE] point, which is the overall survival results, were presented. And as we can see here, ribociclib with endocrine therapy continues to have a better overall survival than placebo endocrine therapy. So this is the first study that has actually shown a benefit of CDK4/6 inhibitors on overall survival in the first line setting.

At the 42 months line map analysis, 46% of patients are alive in the placebo arm versus 70.2% in the ribociclib arm. And then, looking specifically in the AI subgroup, we again continue to see the benefit of ribociclib on overall survival. All the subgroups, there was a consistent overall survival benefit seen within all these subgroups. So MONALEESA-7 is the only study that has evaluated CDK4/6 inhibitors exclusively in premenopausal women, and we see a statistically significant longer overall survival compared with endocrine therapy alone. So the question here is, can we generalize these results to postmenopausal patients? I think yes, because the premenopausal patients were made postmenopausal by ovarian suppression, and there is data coming from other studies, now MONALEESA-3, which has actually shown that CDK4/6 inhibitors' first-line setting in postmenopausal patients do have an overall survival benefit.

OK, then, moving on from first-line treatment to second-line treatment, we'll begin with the question here. A 57-year-old female diagnosed with metastatic breast cancer, ER/PR positive, HER2 negative, to the bones has progressed on CDK4/6 inhibitors and letrozole. There's PIK3CA mutation identified on tumor genomic testing. What is the next best management plan? Is it everolimus and exemestane, alpelisib and fulvestrant, capivasertib and fulvestrant, or fulvestrant alone?

[MUSIC PLAYING]

OK, so that is good. So I'll be discussing the SOLAR-1 trial, which actually led to the approval of alpelisib for the PIK3CA-mutant cohort. So we know PIK3CA has four isoforms, alpha, beta, gamma, and delta, and the previous clinical trials that have studied PIK3CA mutation in breast cancer have been targeting pan-PI3-kinase or the beta-sparing inhibitors. These are associated with a lot of toxicities with a very narrow therapeutic index. So as we can see here, there were studies, BELLE-2 and SANDPIPER, which have looked at other PIK3C inhibitors, they have seen an improvement in progression-free survival. However, it has been a modest improvement and there have been a lot of toxicities. So until now, the standard of care for patients who have progressed on CDK4/6 inhibitors in the second-line setting remain exemestane and everolimus, based on the BOLERO-2 study that showed a median PFS improvement from 4 to 10.6 months. This was irrespective of PIK3CA mutation.

The current clinical trial, which was presented at San Antonio last year, is the SOLAR-1 trial. This is a Phase III randomized trial which looked at postmenopausal women with hormone receptor-positive breast cancer. They were stratified into two cohorts, the PIK3CA-mutant cohort and the PIK3CA-non-mutant cohort, and then randomized to receive alpelisib with fulvestrant or fulvestrant alone. Alpelisib only targets the PIK3C-alpha isoform, so it has a vital therapeutic index and less toxicities than the previous PIK3CA inhibitors. So the primary endpoint here was progression-free survival in this cohort, the PIK3CA-mutant cohort, and the secondary endpoints include an overall survival in this cohort, progression-free survival in the PIK3CA-non-mutant cohort.

Another secondary endpoint was actually looking at PIK3CA mutation in ctDNA in the peripheral blood and try to see that, can we expect a PFS improvement based on that. So this is the primary endpoint. We see that locally-assessed progression-free survival in PIK3CA-mutant cohort with alpelisib improved from 5.7 to 11 months with a hazard ratio of 0.65, and the results were statistically significant. So their trial did meet its primary endpoint. Now, when we look at patients, whether they had received prior CDK4/6 inhibitors or not, so we have a very small population here, we have only 5.9% of patients, but we do see that alpelisib continues to show a PFS improvement of 5.5 vs. 1.8 months with just fulvestrant alone. And patients who have not received prior CDK4/6 inhibitors, we see an improvement with alpelisib in median PFS of 11 months versus 6.8 months.

So this was the secondary end point. So liquid biopsy was done, PIK3CA-mutation was analyzed in ctDNA from the peripheral blood, and it was seen better these results would correlate with the results from tissue biopsy. And as we see here, so this is patients with PIK3CA-mutation identified from tissue, so we see the median PFS improved from 5.7 to 11 months. And this is in the plasma, we continue to see that the PFS did improve from 3.7 to 10.9 months, with a hazard ratio of 0.55. Patients who did not have PIK3CA-mutation in that tissue or in the plasma, we saw very modest improvement, but the hazard ratio was only 0.85.

So the SOLAR-1 did meet its primary endpoint. There is a statistically significant and clinically meaningful prolongation of median PFS seen with the addition of alpelisib to fulvestrant in patients with PIK3CA-mutant disease. We did see benefit in patients who had received prior CDK4/6 inhibitors, however, of note, it was a very small population, 5.9%. The overall survival data at this time are immature. The thing that we should be aware of is alpelisib does cause toxicities, mostly hypoglycemia, rash, and diarrhea. For hypoglycemia, it is recommended that these patients should have a blood glucose under [INAUDIBLE] so we can identify the patients who are developing hypoglycemia earlier and start them on oral anti-diabetic agents. For rash, it is recommended that we should do prophylaxis with antihistamines when we are starting a patient on alpelisib, and diarrhea is managed by oral antidiarrheals.

So what is the take home point? So if we see a patient with ER positive metastatic breast cancer in our clinic who's progressed on CDK4/6 inhibitors, if they have the PIK3CA-mutation, we should give them alpelisib and fulvestrant based on this data, and, if absent, everolimus and exemestane based on BOLERO-2. The PIK3CA-mutation can be checked on the archival tissue, or we can get a new metastatic biopsy. Our patients who have just bone disease, we can go for peripheral blood also, the ctDNA from peripheral blood. There is a current study, the BYLieve study, going on, which is addressing the issue of alpelisib post-CDK4/6 inhibitor progression. And preliminary results were presented at ASCO, and it shows that alpelisib does retain its efficacy post progression on CDK4/6 inhibitors.

Now moving on to HER2 positive metastatic breast cancer. So just to recapitulate here, so first line is the CLEOPATRA. First line we would give taxanes, pertuzumab and trastuzumab is the current standard of care. And second line, based on EMILIA, after progression on taxanes, pertuzumab and trastuzumab you do T-DM1. Third line and beyond is a little gray area, and a lot of clinical trials are actually addressing this question as to what should be, ideally, the third line of treatment in HER2 positive metastatic breast cancer.

So I'll briefly mention the NALA study that was presented this year at ASCO. It took metastatic breast cancer patients, HER2 positive, who had progressed on two lines of HER2-directed therapy to be and randomized them to neratinib and capecitabine, with loperamide as antidiarrheal prophylaxis, against lapatinib and capecitabine, which is currently the standard of care. So the primary endpoint here was progression-free survival and overall survival. So we see here that neratinib and capecitabine-- the mean PFS was 8.8 versus 6.6 months with lapatinib and capecitabine, so this was statistically significant. The overall response rate was 33% in the neratinib arm vs. 27% in the lapatinib arm. And in terms of patients who required CNS intervention, who required some intervention for CNS metastases, it was lower in the neratinib group compared to the lapatinib group.

However, definitely neratinib and capecitabine has more toxicities than lapatinib and capecitabine, especially grade 3 diarrhea was 30% with neratinib and capecitabine. So the NALA study concluded that neratinib and capecitabine were superior to lapatinib and capecitabine in terms of progression-free survival, especially with fewer patients needing intervention for symptomatic CNS metastases. However, I would just like to point out that neratinib and capecitabine is not yet FDA-approved, and it is recommended as a Category 2B for treating HER2 positive metastatic CNS-- HER2 positive metastatic breast cancer with CNS met in the NCCN guidelines.

And then just a quick mention about the SOPHIA study. I briefly wanted to discuss it here because the SOPHIA study brings home the point that we could probably be using a predictive biomarker to treat HER2 positive metastatic breast cancer. So this looked at HER2 positive advanced breast cancer who had received 1 to 3 prior lines of treatment and randomized them to margetuximab with chemotherapy or trastuzumab with chemotherapy. So margetuximab is like trastuzumab, but it has a different Fc component that has a higher binding to the F allele, so the F allele, trastuzumab has a lower binding to the F allele. So if you look at the results, this was PFS analysis by the CD16A genotype in the FF or the FV allele, margetuximab had a better median PFS of 6.9 months vs. 5.5 months with trastuzumab, whereas in the VV allele we did not see any difference. So again, margetuximab is not FDA-approved, there's no overall survival data that we have right now, but this is something that clinical trials are ongoing.

So just take home points are standard of care in the first line setting in HER2 positive metastatic breast cancer remains taxane, pertuzumab and trastuzumab, and second line is T-DM1. Third line and beyond, we have some interesting data with the NALA trial showing that neratinib and capecitabine has activity in CNS disease, but also comes with 30% grade 3 diarrhea, so not yet FDA-approved. And the SOPHIA trial brings an interesting point of a predictive biomarker for selecting patients for treatment. So the third line is an upcoming [INAUDIBLE] a lot of clinical trials addressing this phase.

So just as a quick recap, HER2 positive breast cancer, CLEOPATRA as a first line, T-DM1 second line, and then more treatments upcoming. The big thing in hormone receptor-positive breast cancer is CDK4/6 inhibitors have shown overall survival benefit in the frontline setting, and if patients have PIK3CA-mutation they should get alpelisib and fulvestrant. If not, then everolimus and exemestane remains the standard of care. And in triple negative breast cancer, now we have had the first checkpoint inhibitor approved in breast cancer, so if PD-L1 positive, they should get PD-L1 inhibitor with chemotherapy. And we should be seeing data from sacituzumab, which is an antibody-drug conjugate, there could be inhibitors and more checkpoint inhibitors coming soon.

So I just wanted to do these post test questions quickly. So this is a 55-year-old female who had HER2 positive breast cancer and residual disease after neoadjuvant chemo. So what would be the recommendation now?

[MUSIC PLAYING]

Yes. OK. It is radiation and T-DM1 based on the KATHERINE study. Any amount of residual disease benefits from T-DM1, and radiation can be combined with T-DM1 at the same time. So the second question is, this is a postmenopausal female with germline BRCA mutation, newly diagnosed with metastatic triple negative breast cancer, PD-L1 5% on tumor infiltrating immune cells. What is the treatment of choice?

[MUSIC PLAYING]

Yes, so it is atezolizumab and Abraxane, so it's not a BRCA inhibitor because checkpoint inhibitors have shown more efficacy in the front line setting, and also there is overall survival data now we have in the front line setting, so the earlier we can push the checkpoint inhibitors in treatment, the better outcomes. So this is the next one, this is a 45-year-old premenopausal female with 1.6 centimeter, grade 1, ER/PR positive tumor with an oncotype of 23. What would be the management plan?

[MUSIC PLAYING]

OK. So yes, there is no correct answer here, because this was definitely a non-inferiority study. We cannot make a lot out of it, but I think it should be shared decision making with the patient, giving them this data and telling them that this is not what the study was supposed to see, but yes, we are looking at some signals that all the benefit is coming from ovarian suppression. And then, this is the last question, so this is metastatic breast cancer ER/PR positive, progressed on CDK4/6 inhibitors and letrozole with a PIK3CA mutation.

[MUSIC PLAYING]

Yes, so this is the SOLAR-1 data showing superior efficacy compared to fulvestrant in the PIK3CA-mutant cohort. All right, thank you so much.

[MUSIC PLAYING]