SPEAKER: Today, we have the pleasure of hearing about some of the work being done in Dubin Breast Center, including some of the latest treatment options the talk will be moderated by Dr. Elisa Port, the assistant chief for breast surgery and the director of the Dubin Breast Center. Our speakers will be Dr. Amy Tiersten, Dr. Anya Romanoff, and Dr. Hank Schmidt. Please join me in welcoming our speakers.

[APPLAUSE]

ELISA PORT: Well, first of all, thank you so much for having us. We look forward to giving a bit of an update from the Dubin Breast Center every year to our colleagues in medicine who we view as our partners in the care of all of our patients. We're so, first of all, grateful for your collaboration on our mutual patients, and really feel like we're here to serve you, in terms of our mutual patients and their overall well-being.

There is a lot that is going on in the Dubin Breast Center, and just-- I want to give you a two minute update before we go to our speakers. We have a really ambitious agenda with three speakers, but we have a lot to share with you. So as you know, the Dubin Breast Center opened in 2011, and we've experienced extraordinary growth from that time. We started out in 2011 with 13,000 new visits a year, and we're up to over 30,000 projected for 2019.

And this includes surgery, medical oncology, radiology visits, and all kinds of other services we provide. We have expanded our physical footprint. We have four more infusion suites to accommodate our growing volume, and those are opening in the next month. It's interesting to know we started out with a very modest group of nine physicians. We're now at 24, including five surgeons, six oncologists, seven radiologists, and one psychiatrist.

And I want you to keep in mind that all of these physicians, surgeons, oncologists, radiologists, are breast-specific, breast-specialized, and breast only. We really, I feel, run a true multidisciplinary care environment in a very patient-centered environment. We provide a wealth of other services for the benefit of our patient beyond just basic medical treatment.

So for example, we've developed a cold cap program. I see our dear manager Rayna [INAUDIBLE] in the back, who was instrumental in getting that going. And this allows for hair preservation in our patients who undergo chemotherapy. We have a full-time nutritionist for patients to manage weight gain and weight loss during their treatment.

We have complete social work services and support programs, including yoga, that are free, that we run in our waiting rooms. And these are available to patients, regardless of their ability to pay. We have a full service genetic testing and counseling service embedded in our center. We have full service imaging. I always brag that we were the first in New York City to offer 3D mammography. And it's now offered in all our system sites, and really has become the standard of care.

And we have a very robust research program. We offer between 20 and 30 clinical trials. I use that number loosely, because at any given time, one trial is opening and another is closing, and you'll hear about some of those exciting trials from Dr. Tiersten. And it's important to know that these trials span the range of stages in breast cancer.

We offer a trial for observation only in DCIS-- very controversial area-- stage-zero breast cancer, all the way up to options for treatment metastatic disease, for those who have failed conventional therapy. Today, who you'll hear from is my dear colleagues and friends, first, Dr. Hank Schmidt, M.D., PhD, who's an associate professor of breast surgery and director of our CARE high-risk program.

He's going to talk to you about a new program we have called IORT, or intra-operative radiation therapy. And what that does is offers patients some new cutting-edge treatments, as they relate to radiation. Dr. Any Romanoff, who is an assistant professor of breast surgery and global health as well-- and she's going to speak to us about the rising de-escalation of chemotherapy, meaning the decrease use of chemotherapy in our patient populations.

I think this is really important for all of you to know, as we share patients. They come back to you and say, guess what-- I didn't need chemotherapy, even though my tumor was large or lymph nodes were involved. And I think that's important for primary care providers and internists to understand why there's a trend in that direction.

And lastly, you'll hear from Amy Tiersten, professor of medicine and clinical director of breast medical oncology, regarding the newest options and treatment and clinical trials. So without further delay, Dr. Schmidt--

HANK SCHMIDT: Good morning, everyone. I'm Hank Schmidt, and thank you very much for the opportunity to talk to you about one of the exciting options for patients being treated for breast cancer at Mt. Sinai. We started a IORT team program at Mt. Sinai-- have been adding patients in a registry format now for about a year. I have no disclosures.

So the standard of care for treatment of patients with early-stage breast cancer, as you are aware, is either mastectomy for some patients or breast-conserving surgery-- namely, lumpectomy with clear margins followed by radiotherapy. This figure, as well as the next one, are collections of data from the early breast cancer trialist collaborative group that document or demonstrate a very significant effect of radiotherapy in preventing local recurrence, both in node negative and in node-positive patients.

In some groups, these studies-- the effect is significant-- perhaps 30% to 40% reduction. These are a similar, somewhat overlapping group of studies stretching back to the early 1980s that, again, show for most patients that radiotherapy does have an important effect for those patients who choose to save the breast. When we look over a longer period of time, we can see a small, but consistent and measurably significant increase or advantage in survival as well for patients treated with radiotherapy.

So the standard external beam radiation treatment typically happens about three to four weeks after surgery. The total dose is 50 Gray. This is typically administered Monday through Friday in a daily treatment with 25 fraction-- so over five weeks. More recently, we've been able to embrace a more abbreviated schedule called hypofractionated radiation treatments.

This is 16 fractions. Patients can typically be treated with a slightly different schedule over three weeks. The trials that have explored this against standard external being treatment show equivalent control and cosmetic outcome. So the advantage of this is this treatment is very well-tolerated. In general, patients are able to receive optimal local disease control, use CT planning to allow very precise field definition to treat a specific region.

The downside of this, however, is that there is skin reaction that, as I'm sure you've seen, typically involves a majority of one side of the chest. This is an inconvenient process for patients who are required to be close to a radiation treatment center daily for a period of three to five weeks. Patients experience fatigue while they're on treatment.

And even though our technology is much better over the last few years, there's still dose and exposure radiation to surrounding anatomy-- most notably heart and lungs, which is an issue for patients with underlying heart and lung disease. So because of those downsides, people have developed partial breast or radiation therapy, or APBI. APBI is sort of an umbrella term that encompasses a variety of techniques.

The one we're going to focus on today is IORT, interoperative radio therapy. It is also defined by IMRT, or intensity modulated radiotherapy; interstitial brachytherapy, which most recently has been done in the form of a mammosite balloon catheter; and then 3D conformal external radiotherapy as well. All of these techniques take advantage of the concept that we can treat a very small, focused area-- namely, the lumpectomy bed or lumpectomy cavity-- while sparing the remainder the organ and minimizing radiation exposure to the aggressive the patient, as well as their immediate environment.

So the system that's most widely-used in the United States is Intrabeam. This is produced by Zeiss, and this is a photo of the device. It has a large floor stand with an arm with a number of articulating joints attached to a source, and an applicator. We'll take a closer look at this. These are the applicators, which come in a variety of sizes. Obviously, different patients and different tumors have various-sized lumpectomy cavities, and so the surgeon chooses the right size applicator, once the lumpectomy is completed.

The applicator is attached to the arm. You can see the tip of the applicator is a glass sphere which goes into the lumpectomy cavity. This is the applicator attached to the HDR, or high dose rate source, which generates X-rays. So this is essentially what the source looks like inside that applicator.

This probe, essentially at the end of it, produces a very discrete sphere of radiation treatment in the form of high-dose, low-energy X-rays. The unique thing about this system is it can be used in any operating room. It does not require shielding, as more traditional IORT devices in the past. The way that is accomplished is a very rapid dose fall off, as you move away from the sphere of the applicator. And that's shown in this figure here.

You can see along the X-axis is increasing distance from the applicator surface, and dose along the y-axis. We intend to provide 20-Gray dose rate at the lumpectomy cavity bed, or the margin of our tumor resection. You can see here that, as you move away 1 centimeter, your dose is already down to 5 Gray. By the time you get to 2 centimeters, your dose is less than 1.

So essentially, we can do this anywhere in the operating room without concern for people in the hallway or people in the adjacent room. This is very convenient for us to move the device around the operating room. This is what it looks like with a patient. You can see the applicator extending through the incision of the lumpectomy cavity. And the source is inside the breast there.

This is another photo that shows our old format of external shielding we used to minimize room scatter. You can see at the foot of the bed, there's a lead shield. Behind that in some environments is a radiation control console. The next photo shows it-- in some operating rooms, the anesthesiologist can stay inside the room, also behind a lead shield. In other formats, they'll step outside and look through a window, where the patient can be monitored.

This picture shows a surgeon securing a purse string suture. We placed that in the breast above the applicator to secure the breast tissue flat against the surface of the applicator so we get even-dose delivery right along the edge of the lumpectomy cavity. Sometimes the radiation oncologist will also be scrubbed in, or at least in the operating room, to ensure correct placement of the probe. We want to minimize any toxicity to the skin above the lumpectomy cavity.

So what are the results from this device? The major study that was reported in *the Lancet* was a target trial. This is targeted intra-operative radiotherapy. This was an international study across 33 centers in Europe and the United States that explored in a randomized fashion IORT, using this Intrabeam device against traditional external beam radiotherapy.

3,451 patients, randomized, received either standard treatment or a single intraop dose. Important to know that patients who, on their pathology results that came back a few days later-- if they had positive margins, if they had positive nodes or extensive amount of DCIS, they went on to also get external beam radiotherapy after their intraop dose.

The outcome showed essentially similar local control. This was a non-inferiority design, and so the results showed that, in fact, there was no significant difference between these two approaches. When we limit the analysis to patients who had IORT dose at the time of tumor resection, the difference is only about 1% in local recurrence. The trial also reported similar complication rate, similar cosmetic outcomes, and similar mortality. This trial is still in the follow-up phase, and subsequent reports are expected.

This is the first five years of follow-up. You can see events of local recurrence are spread pretty evenly over five years-- 10 in the intraop group, six in the external beam group. ASTRO, or the American Society of Radiation Oncology, evaluates all this APBI data from a number of devices and studies, and produces guidelines. We've used these guidelines to develop a registry trial for our use here at Mt. Sinai over the last year.

Our criteria are approximately what are recommended by ASTRO in 2016. We want to target relatively low-risk patients, typically over the age of 50 with somewhat smaller tumors, primarily limiting it to invasive disease at this point-- although there is growing data in DCIS. We want to make sure patients have widely negative margins, and we're focused right now on patients with ER positive breast cancers. Thank you very much.

[APPLAUSE]

ELISA PORT: Thank you Dr. Schmidt. And we just wanted to present this to you to show you some of the newer offerings that we have at the Dubin Breast Center. It's really been quite remarkable to have appropriately-selected patients come in and to be able to say to them-- especially if they're in geographic areas, where radiation isn't readily available, that we can deliver your radiation at the time of surgery.

It's really actually quite novel, and Dr. Schmidt has spearheaded bringing this incredibly exciting treatment option to our patient population. So I'm really happy to have about that. Our next speaker, Dr. Anya Romanoff, is going to speak to you today about trends in de-escalating chemotherapy in our estrogen receptor positive patients.

ANYA ROMANOFF: Good morning. Thank you for the opportunity to present today. As Dr. Port said, I will be talking about assessing the need for chemotherapy in this age of personalized breast cancer care. I have no disclosures. So by way of background, overall, chemotherapy and hormonal therapy to reduce breast cancer mortality by about 1/3.

Historically, chemotherapy was given to all patients with large tumors or positive lymph nodes. However, in the last several decades, this has really begun to change, as we learn more and more about breast cancer. So in 1985, the National Institutes of Health put out a consensus statement that chemotherapy does not improve survival for women with a negative lymph nodes.

About three years later, the National Cancer Institute said essentially the opposite-- that chemotherapy does have a potential benefit for women with negative lymph nodes. In the year 2000, the NIH essentially said chemotherapy can potentially benefit everyone-- that it improves survival, and should be recommended to the majority of women with breast cancer, regardless of their nodal menopausal or hormone receptor status.

So how did we get from this blanket statement of chemotherapy for all to where we are today in an era of really individualized care? Well, we've learned a lot about the biology of disease and the ability to use that to predict someone's risk of recurrence, as well as their response to chemotherapy. So a quick case presentation, and we'll come back to this patient at the end of the talk as well-- a 57-year-old woman presents with hormone receptor positive HER2 negative breast cancer-- undergoes a lumpectomy and a sentinel lymph node biopsy, and on final pathology, is found to have a 2.3-centimeter tumor and negative lymph nodes.

About 10 years ago, this woman would have received chemotherapy, and we'll talk about why today, maybe she would not. So a lot of this development in hormone receptor positive disease has come out of a recurrence score, which was initially described in 2004 in the *New England Journal of Medicine.* And this was a multi-gene assay that was used to predict recurrence of tamoxifen-treated node-negative breast cancer.

This group used a 21-gene analysis to calculate a recurrence score and stratify women with each positive breast cancer into low, intermediate, and high-risk groups. They then found that women who fell into this low-risk group, on a score of 0 to 100, had a distant recurrence rate at 10 years of 6.8%. The intermediate risk group had about a 14% risk of recurrence at 10 years, and the high-risk group had over a 30% risk of recurrence at 10 years.

And subsequently, these different groups have been studied to display how they would potentially respond to chemotherapy. So also in the *New England Journal of Medicine,* there was a large prospective trial looking at how these people respond to chemo. So women with a low-risk score of 0 to 10, whether they received chemotherapy or chemotherapy-- excuse me-- or endocrine therapy alone had no difference in their recurrence free survival or overall survival from breast cancer at five years-- namely, that these people did not benefit from the receipt of chemotherapy. And their overall survival is 99%.

Women with a high-risk score, greater than or equal to 31, did benefit from chemotherapy. So those who received tamoxifen and chemotherapy in the blue line had significantly better distant disease-free recurrence than those who received tamoxifen alone. The question was what to do with the women who fell in this intermediate risk group. And for a while, these people were receiving chemotherapy on the whole.

And a large study was published last year in June called the TAILORx trial that looked at adjuvant chemotherapy for this intermediate risk group. They stratified women who had an intermediate risk score that, in this study, was defined as between 11 and 25, and they randomized them to either endocrine therapy alone or chemo endocrine therapy.

And what they found was that overall, women who fell into this intermediate category had no benefit from chemotherapy-- that they had similar disease-free recurrence and overall survival whether they received endocrine therapy alone or chemotherapy and adequate therapy together. The one subset of patients who did potentially have a benefit from chemotherapy in this study were women who are under the age of 50 with an intermediate risk score of above 15.

And so what they concluded from this trial was that the 21-gene assay may identify up to 85% of women with early-stage breast cancer who can be spared adjuvant chemotherapy. And the groups of patients who could potentially be spared chemotherapy are those who are greater than 50 years of age with a recurrence score of 25 or less, or those who are under 50 years of age with a recurrence score of under 15.

And so we've really now implemented these guidelines at the Dubin Breast Center to potentially spare many women the side effects of chemotherapy. Our group subsequently published results of the National Cancer Database study that was aimed to determine the practice-changing potential of this TAILORx trial that came out last year.

We looked at over 37,000 patients who had an intermediate risk score, and looked at trends over time from 2010 to 2015. The use of chemotherapy in all patients decreased. These patients were then broken down into several groups. Groups A and C, in the blue and green lines toward the bottom of the screen, would not, following the publication of TAILORx, be recommended to have chemotherapy.

So these are women under the age of 50 with a lower intermediate risk score, or over the age of 50 with any intermediate score. The group B, in the yellow, as we said, are patients who are 50 or younger with a recurrence score of 16 to 25, who actually would be recommended to have chemotherapy following the results of TAILORx.

So this is one group where potentially, overall, TAILORx could change management, as we see these people received less chemotherapy over the last five years, when in fact, perhaps, they should be considered for more. And so to come back to our case presentation of this 57-year-old woman with a 2.3-centimeter ER positive tumor and negative lymph nodes, who 10 years ago, would have received chemotherapy, today would have had a recurrence score sent.

And if this returned a lower-intermediate score-- for example, 15, which this patient did have-- she now can be spared chemotherapy-- spared the side effects. And we can assure her that her overall survival and her distant disease-free survival are excellent, regardless. Thank you.

[APPLAUSE]

ELISA PORT: Thank you, Dr. Romanoff. I really felt like this was an important topic to cover because, as you see more of these patients circling back to you with recommendations for no chemotherapy, it's important to understand the rationale for this. And we're thrilled that we're able to do that in this age of no one-size-fits-all.

On the other end of the spectrum, while we're de-escalating chemotherapy use inappropriate patients, it is important to know that, again, breast cancer is not one disease. It's a lot of different diseases with a lot of different biologic potentials. And while the cure rate for breast cancer is extremely high overall, there are subsets of patients with breast cancer who do not enjoy those high cure rates and who have biologically aggressive disease.

And so again, in the age of personalized care, it's important that we can pick and choose who can benefit from which treatments. And you just learned a bit about which patients we don't think need chemotherapy, and more importantly, are going to enjoy an excellent overall prognosis, even without it. But what do we do for those patients with biologically aggressive breast cancers or those patients who fail first line therapy and recur or have metastatic disease?

So one of our commitments, of course, at the Dubin Breast Center is to provide a multitude of treatment options for second and third line treatment so that we can give our patients the best chances for survival and quality of life. And Amy Tiersen has been sort of our secret weapon at the Dubin Breast Center developing and bringing online these clinical trials so that we have so much to offer for patients who failed these treatments. And I'd like for her to speak to you about some of these incredible trials that she has spearheaded.

AMY TIERSTEN: I'm very excited to be able to share with you all some of the very exciting advances. It's a very exciting time for the treatment of breast cancer. These are my disclosures. The objectives of my talk today are to review some of the latest advances in breast cancer and to familiarize you all with a few of the clinical trials available at the Dubin Breath Center.

As Dr. Port mentioned, we have a very large menu of clinical trials to address-- every specific subtype of breast cancer and every stage of breast cancer. In the interest of time, I'll only be able to share a smattering, but here we go. So there's really been a revolution in all of oncology, and it really is the age of targeted therapy or precision medicine.

So traditional prognostic factors, such as size of the cancer, number of positive axillary lymph nodes, while they're still important, there's been a tremendous shift in understanding now that actually, the biological subtype-- and for example, estrogen receptor, progesterone receptor expression, as well as the protein HER2/neu-- actually dictate prognosis more so than arbitrary cut-offs, in terms of size of the cancer.

And we really gear our treatment based on these specific biological subtypes, which have very different behaviors. So in addition, there have been tremendous advances based on understanding molecular and genomic pathways that make cancer cells preferentially grow abnormally, and developing extremely intelligent targeted therapies to inhibit these pathways.

If you think about it, chemotherapy's pretty crude. We're killing all rapidly-dividing cells. It's not very targeted. And targeted therapies are-- offer the opportunity to potentially improve outcome with less toxicity, as they're more precise. So in terms of some of the new drugs that have been changing the face of breast cancer, one of the most important category of medications over the last number of years are category of drugs which are called CDK4/6 inhibitors, or cyclin-dependent kinase 4 and 6 inhibitors.

So these kinases and cycling D play a very important role in the regulation of cell cycle progression. And in cancer, these pathways are upregulated, and that upregulation of this cell cycle progression pathway causes abnormal tumor proliferation and resistance to our anti-estrogen therapies. Palbociclib is the first in its class to be FDA approved. It is one of the CDK4/6 inhibitors.

These are oral medications which block the pathway, and thereby result in cell cycle arrest. And they have been proven clinically to delay the time to endocrine resistance. So the Paloma 2 is a trial that was published from the *New England Journal of Medicine* in 2016. This was a randomized trial in metastatic breast cancer patients who were hormone receptor positive and HER2/neu negative, and had not previously received any therapy for their newly-diagnosed metastatic disease.

They were randomly assigned to either receive the standard of care of anti-estrogen therapy alone-- in this case, an aromatase inhibitor-- versus an aromatase inhibitors plus the CDK4/6 inhibitor. And this study showed essentially a doubling of the progression-free survival or the amount of time that that disease was responding to that therapy.

There have been later studies with one of the three available CDK4/6 inhibitors that are now not just showing progression-free survival benefit, but overall survival benefit as well. At the current time, anti-estrogen therapy plus CDK4/6 inhibitor therapy is now the standard of care for hormone receptor positive HER2/neu new negative breast cancer.

So when we have these new drugs, we always want to-- there's tons of unanswered questions and what other role can we use them, et cetera. And here are some of our studies-- a couple of our studies that look at, where else can we go with the CDK4/6 inhibitors? So research question number 1 here is, can we extend the benefit that we see with the CDK4/6 inhibitors in a hormone receptor positive HER2 negative patient population to a hormone receptor positive HER2 positive population-- so patients who are estrogen, progesterone, and HER2/neu positive, which are about 15% of all breast cancers.

Currently, the standard of care, regardless of hormone receptor status, for HER2 positive metastatic breast cancer is traditional cytotoxic chemotherapy in combination with two antibodies to the HER2 protein-- trastuzumab and pertuzumab, otherwise known as Herceptin and Perjeta. But at this point in time, no studies have looked at the role of CDK4/6 inhibitors in HER2 positive breast cancer patients.

So at the Dubin Breast Center, we have a multi-center trial of an anastrozole-- one of the aromatase inhibitors-- palbociclib-- CDK4/6 inhibitor-- in combination with trastuzumab and pertuzumab as first line therapy for hormone receptor positive HER2/neu positive metastatic breast cancer. This is an investigator-initiated trial that we have at Sinai, and it's soon to open at NYU, Columbia, and Cornell. It's accruing well.

This study really represents a novel fully-targeted approach to allow patients with HER2 hormone receptor positive, HER2 positive breast cancer to potentially avoid or delay traditional cytotoxic chemotherapy, as we are currently able to do in hormone receptor positive HER2/neu new negative patients, who can do well with sequential endocrine therapy sometimes for years.

In all of oncology, the question always is we find new drugs that improve survival in metastatic disease, improve progression-free survival-- but the real important question here is, if we introduce them into the earlier stage setting, will we be able to cure more patients to never have a recurrence? So at the Dubin Breast Center, we're participating in the PALLAS trial-- the Palbociclib Collaborative Adjuvant Study-- which is a randomized study for stage 2 or 3 hormone receptor positive, HER2 negative breast cancer patients.

And everyone in the trial receives the standard anti-estrogen medication that would be appropriate for them. The experimental arm receives CDK4/6 inhibitor for two of the years of the standard anti-estrogen medication. And it's a 4,600-patient trial. The primary endpoint is disease-free survival, and it recently closed to accrual.

So over the next number of years, we may be able to offer these drugs, which are currently only used in metastatic disease, to cure more of our early-stage patients-- very exciting. Next major advance I'm going to speak about his immunotherapy. So immunotherapy is kind of the hot buzzword that all the patients come in and ask about. And in fact, immunotherapy has been extremely effective in a variety of cancers-- most effective in cancers that are highly mutated, which are more immunogenic, which are easily recognizable as other than a patient's normal cells.

And again, these drugs are widely-used in many different types of breast cancer, but this past year has been the first time that these immunotherapies have shown any benefit in breast cancer. So PD-L1 is receptor on the surface of immune cells, and cancer-mediated upregulation of this receptor inhibits T cells that might otherwise attack cancer cells.

So this effectively puts what we call a checkpoint on the immune system, and allows cancer cells to evade the immune system. Antibodies, which are called checkpoint inhibitors, bind to this PD-L1 receptor, thereby allowing T cells to attack cancer cells-- so basically, restoring immune function or unleashing a patient's own immune system to be able to fight the cancer cells and recognize them as other.

So triple-negative breast cancer-- again, breast cancer that does not express estrogen, progesterone, or the HER2 receptors, referred to as triple-negative breast cancer-- it's the most aggressive form of breast cancer-- highly mutated more than other subtypes, suggesting a potential role for immunotherapy. It's also been shown, when the pathologist describes extensive lymphocytic infiltration in a triple-negative breast cancer pathology specimen, that that has been associated with a better prognosis in patients with triple-negative breast cancer, suggesting a role in this type of breast cancer for immunotherapy.

This past fall, the Impassion 130 trial was published in the*New England Journal of Medicine.* It's a randomized trial for newly-diagnosed metastatic triple-negative breast cancer patients who were randomly assigned to either receive chemotherapy-- in this case, with a microtubule inhibitor called abraxane-- plus or minus a checkpoint inhibitor-- in this case, atezolizumab. There are multiple checkpoint inhibitors.

And this was the first study to really show any role for immunotherapy in breast cancer with a median overall survival of 25 versus 15 months for the patients who received the immunotherapy in addition to the chemotherapy. So what are some of our studies addressing ongoing questions for the use of checkpoint inhibitors?

Research question number 1 here-- will other chemotherapy agents, in combination with other checkpoint inhibitors. Have activity in breast cancer, and is their efficacy in the hormone receptor positive population as well? So the study that we have addressing this is a phase I study evaluating the safety and tolerability of durvalumab-- which is a checkpoint inhibitor-- in combination with eribulin in patients with HER2 negative breast cancer patients. They can be hormone receptor positive or negative.

The rationale-- eribulin is a very active chemotherapy agent. It's actually derived from the marine sponge, and has been shown to have a survival benefit compared to other chemotherapies that we use in metastatic breast cancer, with some less toxicities. Eribulin has been shown to increase tumor perfusion, which may allow tumor-infiltrating lymphocytes to penetrate tumor better, and thereby increase the effectiveness of immunotherapy.

The objective of this trial is determine the safe dose of this combination, describe toxicities, and obtain preliminary evidence of efficacy. The trial's fully accrued, and now close to a cruel, and we're going to be looking at analyzing the results soon. Again, the important question is, as we-- can we move immunotherapy into the treatment of earlier stage disease and cure more patients-- prevent metastatic disease?

So patients with triple-negative breast cancer are frequently treated with preoperative chemotherapy, and those that are found to have residual invasive cancer in the surgical specimen are at significantly higher risk for recurrence or metastasis than patients who have no residual cancer found at the time of surgery. We are participating in a randomized trial to evaluate the efficacy and safety of pembrolizumab-- which is one of the checkpoint inhibitors-- as adjuvant therapy for patients with triple-negative breast cancer with greater than 1 centimeter of residual invasive cancer found at the time of surgery, or positive lymph nodes.

Patients are randomized to observation versus every three-week checkpoint inhibitor for one year. The goal of the study is to see a difference in disease-free survival, hopefully overall survival, and describe toxicities. Going to finish off talking about another category of very exciting drugs in the treatment of breast cancer, which are called PARP inhibitors. Essentially, BRCA-mutated cancers-- BRCA-mutated cells in general are characterized as having difficulty repairing DNA damage.

And PARP is an enzyme that helps to repair DNA damage, thereby inhibiting PARP could be lethal to a BRCA-positive cell that already can't repair DNA damage. In a clinical trial published in the *New England Journal of Medicine* in August of 2017, 302 patients with germline BRCA mutations and metastatic breast cancer were randomized to receive one of the PARP inhibitors called olaparib, or treatment of physician's choice, which was one of three standard cytotoxic chemotherapies-- in this case, either capecitabine, eribulin, or vinorelbine.

The risk of death or disease progression was 42% lower with olaparib than treatment of physician's choice of standard chemotherapy. And tumor shrinkage rate was 60% versus 29%, with significantly less toxicity for the PARP inhibitor. So these are now standardly used in the treatment of metastatic breast cancer in BRCA-mutated patients.

Again, the recurring question-- can we move the PARP inhibitors into the earlier stage of disease, and hopefully cure more BRCA-positive breast cancer patients? So we participated in a pilot study evaluating the anti-tumor activity and safety of niraparib-- which is one of the PARP inhibitors-- as preoperative treatment in localized HER2 negative BRCA-mutated breast cancer.

This trial has also just close to accrual, and the objective's to evaluate the anti-tumor activity of the PARP inhibitor, when used as preoperative treatment, assessed by change in tumor volume and breast MRI and ultrasound, and also to evaluate the pathologic complete response rate or the chance of finding no residual disease at the time of surgery, as added to standard therapy-- going to stop there, and I guess Dr. Port will tie it up and take questions.

[APPLAUSE]

ELISA PORT: Thank you, Amy-- really exciting developments. So I hope what you've learned today with these three talks-- that there's a lot going on at our center, and that it really-- we really offer the full thickness of breast cancer treatment options and care, including the most cutting-edge options, to our mutual patients. We are so appreciative of the support of the Mt. Sinai community in sending us patients and honoring us with the care of your patients-- and look forward, obviously, to continuing many of these collaborations. I think right now, what I'll do is open it up for questions for our three speakers, if anybody has any questions regarding these three topics, or any other, as it relates to the Dubin Breast Center.

AUDIENCE: [INAUDIBLE]

AUDIENCE: So it seems recently there's been more interest in male breast cancer, but of course, the number of patients is very small. Have there been any suggestions that the treatment of the male should be different from the female?

ELISA PORT: Sure. I'll take that. You're right. Male breast cancer is a very rare disease. Of the approximately 300,000 cases of breast cancer diagnosed in this country each year, less than 1% are in men. So it's about 2,500 to 3,000 cases. We do see our fair share of those, in part because with the connection at Mt. Sinai what's very interesting is because of the preponderance of BRCA mutations in Ashkenazi Jews.

And the BRCA2 mutation is associated with a higher risk of male breast cancer. We do get these patients a lot. And the issue is, because of the rarity, though, of the disease nationally, there's no ability to really conduct clinical trials looking at men alone. The cases are too few-- too small in number and too few and far between.

But we do extrapolate the treatment from female breast cancer to male, and obviously, hope to translate the benefits that we've seen in female breast cancer to men-- so for example, things like sentinel node biopsy, which was a huge advance in female breast cancer approximately 20 years ago now to stage lymph nodes under the arm.

I was at Sloan Kettering for 10 years before coming here, and one of my biggest areas of research was, is sentinel lymph node biopsy a valid way to assess nodes in men? It would seem intuitively obvious, but no one had really shown that. So I think along the way, what we've done is tried to validate the advances in treatment in women for men, and we definitely take care of our share.

Another example of this is for example the Oncotype. This is something that really isn't validated among men. These large trials have few to any men involved in them, so we don't know for sure that the data is absolutely applicable to men. But we use it nevertheless. So I hope that answers your question.

AUDIENCE: [INAUDIBLE] age of patience seems to be very strong corollary for breast cancer. And cellular aging, which is a different phenomenon-- it seems to me, by logic, to be important. Do your studies look at age [INAUDIBLE] at the cellular level or the patient level, with regard to giving us an insight into this disease?

ELISA PORT: I think it's a good question in the sense that what [INAUDIBLE] we are all very affected by some of these very dramatic stories of breast cancer [INAUDIBLE] the important thing to note is that, in general, breast cancer is still a disease of older women. The average age of a woman diagnosed with breast cancer in this country is still 60. And the vast majority of the cases are in post-menopausal women.

So I do think it is predominantly a disease of aging. In terms of measuring cell age, I don't know that there's any objective measure of doing that. I don't think there's ever been shown to be any kind of research tool where you can determine age of a cell or health of a cell in that way on any kind of microscopic level.

AUDIENCE: [INAUDIBLE]

AUDIENCE: Great presentation. Thank you. Nobody mentioned proton therapy.

ELISA PORT: Proton therapy-- it's really an exciting area in the news. We just opened up-- in combination or in collaboration, I would say-- the Proton Center. And proton therapy, as it relates to breast cancer, is a very exciting area because it's-- the goal of proton therapy is obviously targeted treatment with minimal damage to healthy surrounding tissue.

It is still an area of research, as it relates to breast cancer. One of the things that it's being looked at is-- and I'll invite Dr. Schmidt up to make some additional comments-- is, as I'm sure all of you know, one of the biggest limitations of radiation, when you do a lumpectomy and radiation, is that treatment can only be done once. And so if someone recurs, the standard of care in that breast is to do a mastectomy, because you can't give them radiation again.

So that's one very active area of interest in protons, as to whether or not you actually can give a second round of radiation perhaps in a different way. Hank, do you want to address that further at all, as it relates to IRT? Any comments about your time?

HANK SCHMIDT: Yeah, just that I think it's still definitely a research question, in terms of breast cancer. Because as you know, the resources are so scarce to study proton radiotherapy, I think that breast cancer is not quite high enough on the priority list to have a lot of data generated. And so far, people are really looking to that modality to look at CNS tumors and so forth. But hopefully, as we have greater availability-- hopefully, through this new center, we'll be able to explore in recurrent breast cancer, I think, would be our target certainly.

AUDIENCE: [INAUDIBLE]

AUDIENCE: For the second presenter-- in your study, you assign this recurrence score to prior patients. I guess the gene data was available for those patients and you could retrospectively do that?

ANYA ROMANOFF: It's an excellent question. I talked about a few different studies. The first wave of studies use tissue blocks from large randomized controlled trials from the past. And then some of the later studies that I talked about were prospective-- so used ongoing accrual of patients, and used their tissue. Does that answer your question?

AUDIENCE: So then you just quantify how those-- whether those different risk groups would-- were receiving chemotherapy?

ANYA ROMANOFF: So in the prospective study-- the last one that I talked about, the TAILORx trial-- they did this recurrence score and then randomized patients based on the recurrence score to either receive endocrine therapy alone or chemotherapy with endocrine therapy, and compare those two groups. The initial retrospective studies used tissue blocks, looked at the scores, categorized people into different groups. And then a subsequent study looked at whether those groups were also prognostic-- so whether chemotherapy affected each of those different groups differently.

AUDIENCE: Great, thanks. Let's thank our speakers for their talks today.

ELISA PORT: [INAUDIBLE]

[APPLAUSE]