Assessing the Clinical Potential for Immunotherapies in the Treatment of Breast Cancer

Dates of certification: *February 22, 2016, to February 22, 2017*
Medium: *Print with online posttest, evaluation, and request for credit*

Disclosure: *No relevant financial relationships with commercial interests to disclose.*

Faculty

Elizabeth Mittendorf, MD, PhD
Associate Professor
Department of Breast Surgical Oncology
The University of Texas MD Anderson Cancer Center
Disclosure: *Grant/research support: Galena Biopharma and Antigen Express (institution receives funding)*

Staff/Planner Disclosures and Conflict of Interest Resolution

The staff of Physicians' Education Resource®, LLC, (PER®) and the editorial staff of *The American Journal of Hematology/Oncology®* have no relevant financial relationships with commercial interests to disclose.

It is the policy of PER® to ensure the fair balance, independence, objectivity, and scientific objectivity in all of our CME activities. In accordance with ACCME guidelines, PER® requires everyone who is in a position to control the content of an educational activity, including spouses/partners, to disclose all relevant financial relationships with any commercial interest to participants as part of the activity planning process. PER® has implemented mechanisms to identify and resolve all conflicts of interest prior to release of this activity.

Overview

This activity is designed to inform physicians about the latest treatment advances in early-stage and metastatic breast cancer, including approved and investigational management strategies.

Target Audience

This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat patients with breast cancer. Surgical oncologists, radiation oncologists, pathologists, gynecologists, fellows, physician assistants, and other healthcare providers interested in the management of breast cancer are also invited to participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

- Explain the rationale and appropriate place for vaccines in the treatment of breast cancer
- Discuss the role of checkpoint blockade in the treatment of breast cancer
- Summarize data from recent trials of vaccines and immunotherapies in breast cancer
- Describe some of the combination therapies currently being studied in breast cancer
- Discuss issues involved in matching patients with appropriate treatments for breast cancer

Accreditation/Credit Designation

Physicians' Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Physicians' Education Resource®, LLC, designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physicians' Education Resource®, LLC is approved by the California Board of Registered Nursing, Provider #16669 for 1.0 Contact Hour.

This activity is funded by PER®.

Instructions for Participation/How to Receive *AMA PRA Category 1 Credit™*

1. Read the article in its entirety.
2. Use the QR code or type into your Web browser to access the posttest.
3. Complete and pass the posttest with a score of 70% or higher.
4. Complete the evaluation and request for credit.

Participants may immediately download a CME or CE certificate upon successful completion of these steps.

Off-Label Disclosure and Disclaimer

This continuing medical and nursing education activity may or may not discuss investigational, unapproved, or off-label uses of drugs. Participants are advised to consult prescribing information for any products discussed. The information provided in this CME/CE activity is for continuing medical and nursing education purposes only and is not meant to substitute for the independent medical judgment of a physician or nurse relative to diagnostic, treatment, and management options for a specific patient's medical condition.

Disclaimer

The opinions expressed in the content are solely those of the individual faculty members and do not reflect those of Physicians' Education Resource®, LLC. Contact information for questions about the activity:

Physicians' Education Resource®, LLC
666 Plainsboro Road, Suite 356
Plainsboro, NJ 08536
Phone: (888) 949-0045
E-mail: info@gotoper.com

Although the incidence of breast cancer in the United States remains high–an estimated 249,260 new cases are anticipated in 2016–the rate of death from breast cancer has been decreasing. Between 1989 and 2012, the mortality rate declined by 36%. In 2016, 40,890 deaths due to breast cancer are anticipated. The decline in mortality is caused in part by improvements in early detection rates, and also by advances in the treatment of breast cancer.[1]

The fact that current treatments for breast cancer are relatively effective does not reduce interest in finding even more specific and effective therapies, especially for advanced metastatic breast cancer, which remains incurable. The continued high level of interest is evidenced by the finding that more than 1000 abstracts on breast cancer were presented at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO).[2] Further, a brief search of the ClinicalTrials.gov website indicates that almost 60 clinical studies of novel therapies for breast cancer are currently, or soon to be, recruiting.[3]

Initially it was thought that breast cancer did not elicit an immune response and would not be affected by immunotherapies in the same way that other cancers were. It is now apparent that there is the potential for a host immune response in breast cancer, albeit not as robust as those in other cancers. These responses are seen particularly in more advanced subtypes of triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2-positive (HER2+) breast cancer.[4] Thus, much of the current research focus is on immunotherapies, specifically vaccines and checkpoint inhibitors.

The HER2 E75 peptide vaccine nelipepimut-S was evaluated in phase I/II trials enrolling node-positive and high-risk node-negative patients whose tumors expressed any degree of HER2. The 5-year disease-free survival (DFS) rate for the vaccinated group was 89.7% versus 80.2% seen among the unvaccinated controls in these nonrandomized studies. Among patients receiving the optimal dose of nelipepimut-S, the 5-year DFS rate was 94.6% versus 87.1% among those receiving less than the optimal dose. These results led to design of the randomized phase III PRESENT trial,[5] which is currently ongoing.[6] Additional peptide vaccine studies are under way or being planned, including the multicenter VADIS study of nelipepimut-S plus the granulocyte colony-stimulating factor (GM-CSF) sargramostim in patients with ductal carcinoma in situ (DCIS).[7] Although it is likely that vaccines are not appropriate for use alone in metastatic breast cancer, their potential in primary prevention has stimulated interest and study. For example, a HER2/*neu* dendritic cell vaccine was shown to reduce disease burden when given in the neoadjuvant setting to women with DCIS.[8]

Checkpoint blockade is also the subject of several clinical trials. The KEYNOTE trials evaluated the anti-programmed cell death 1 (PD-1) antibody pembrolizumab. Data from the KEYNOTE-012 trial showed an overall response rate (ORR) of 18.5% among patients with metastatic TNBC expressing programmed cell death receptor ligand 1 (PD-L1).[9] KEYNOTE-028 is a basket trial including a cohort of patients with PD-L1+, hormone receptor-positive, HER2-negative breast cancer. The ORR among 25 treated patients, of whom four had received three prior lines of therapy, was 12%.[10] The KEYNOTE-086 trial, evaluating pembrolizumab monotherapy in TNBC, is currently recruiting.[11]

The PD-L1 antibody atezolizumab showed activity in a Phase Ib trial, with an ORR of 19%.[12] In another study, the combination of atezolizumab and *nab*-paclitaxel yielded an ORR of 42%.[13] Another PD-L1 antibody, avelumab, has also shown activity in metastatic breast cancer, with an ORR of 4.8% among all receptor subtypes, and 8.6% in TNBC.[14]

Attention to combination therapy is increasing, based on the possibility for synergistic activity: An agent such as a vaccine could stimulate an immune response in a breast tumor, and a concomitantly or subsequently administered checkpoint inhibitor could then intensify that response.[4] Various combinations are currently under investigation. Some recent/ongoing studies include a completed trial evaluating a combination of a GM-CSF-secreting vaccine with cyclophosphamide and trastuzumab[15] and the PANACEA trial, which is designed to evaluate the ability of a checkpoint inhibitor (pembrolizumab) to enhance the efficacy of targeted therapy (trastuzumab) in HER2+ breast cancer refractory to trastuzumab.[16]

The discovery that there are numerous subtypes of breast cancer, as there are of other types of cancer, has opened the door for development of more targeted therapies. This discovery, along with abundant evidence that different therapies are effective in different types and at different stages of breast cancer, emphasizes the need for study of biomarkers in breast cancer and methods of matching each patient with the drugs, combinations, and/or sequences that will be of most benefit.[17-19]

Data on current and emerging treatment options for breast cancer were presented at the 2015 ASCO Annual Meeting and the 2015 San Antonio Breast Cancer Symposium. Elizabeth Mittendorf, MD, PhD, of the University of Texas MD Anderson Cancer Center in Houston, shared her insights on the significance of recent discoveries and the optimal application of emerging data to the planning and implementing of treatment for patients with both early- and advanced-stage breast cancer.

Moderator: Based on the initial studies with nelipepimut-S, what do you expect to see coming out of the PRESENT trial?

Dr. Mittendorf: The phase I-II studies of nelipepimut-S provided the data and rationale to support the design of the PRESENT study, a phase III registration trial. We know from the phase I-II data that the vaccine was effective in decreasing the risk of recurrence by about 50%, and it was a population of patients who, in general, had about a 20% risk of recurrence. In the unvaccinated controls, in fact, the DFS rate was 80% compared with 89.7% seen in those who were vaccinated.

Those were the phase I-II studies, so they began with a dose-escalation group, and not everyone who enrolled received the optimal dose, which turned out to be the highest dose. If we look at just those

patients, their disease-free survival rate at 5 years was 95%. There are other differences between those early-phase trials and the PRESENT study. The early-phase trials identified very robust immune responses in patients with HER2 1+ or 2+ breast cancer versus 3+, so the PRESENT trial has enrolled only patients with node-positive, HER2 1+ or 2+ tumors.

With that said, I think the PRESENT trial was designed in such a way that we've chosen the optimal patient population, the optimal dose, and an achievable hazard ratio. So do I think it will show a 70% reduction in recurrence, which is what we saw with the optimally dosed patients in the early phase trials? I think that is unlikely, but the study is not powered to show that. It's powered to show a lesser but still very clinically relevant benefit. We're hoping that that will be the case so that the vaccine would be offered to patients to whom it might be of benefit.

Moderator: It seems as if vaccines are most useful for patients with early-stage breast cancer. Do you think that they could become standard therapy in that setting?

Dr. Mittendorf: That's a specific question that actually can have a really broad response. With the nelipepimut-S vaccine strategy specifically, it's a single epitope. It stimulates CD8+T cells that recognize that epitope, but we've also shown that it causes something called epitope spreading. That means that it also stimulates T cells to recognize other epitopes. This response may be enough to prevent disease recurrence when administered in the adjuvant setting to patients who have been rendered disease-free with standard-of-care therapy; however, it's probably not enough of an immune response to fight big bulky tumors that may be seen in patients with metastatic disease.

We know from previous experience from the National Cancer Institute, not in breast cancer but in melanoma and ovarian cancer, that these peptide vaccines probably won't work in the metastatic setting. So as for the first part of my response to your question, if they are going to have a role, it will be in patients with early-stage breast cancer as secondary prevention.

Do I think they'll become standard therapy? I can only speak for the PRESENT trial that is enrolling patients who are HER2 1+, 2+ node positive, and they have the appropriate HLA haplotype. They have to be HLA-A2 or -A3 positive. If the results of this study were positive, then my hope is that it would lead to an application to the FDA for approval of nelipepimut-S in that clinical setting. I also think that it would open the door for investigation of other vaccines that can target the patients who don't meet those criteria that I just mentioned, which are the eligibility criteria for PRESENT (perhaps they have a different HLA type, or perhaps they are HER2 3+, or other considerations).

Moderator: Are there any other trials with vaccines currently under way that should be noted?

Dr. Mittendorf: Yes, there are multiple trials. There's a lot of interest now. Our group is conducting two trials evaluating vaccines in combination with trastuzumab, and that's based on some preclinical data generated by multiple investigators showing that there might be synergy between a vaccine that evokes a T-cell response and trastuzumab.

We also have colleagues throughout the country who are looking at vaccine strategies. The Johns Hopkins group has recently published data on a GM-CSF-secreting vaccine. One thing that's interesting about their strategy is that they're also combining it with trastuzumab, but they're additionally thinking about combining it with other drugs that could further augment the immune response. That leads to one of the things we've been discussing, and that is, if vaccines were going to work in a more advanced stage, in the metastatic setting, would they do so as monotherapy? I think the answer is no. But, if groups were to employ novel strategies to combine them with other agents, it may work in that setting. There are several groups interested in combining vaccines with checkpoint blockade, as an example.

There are other groups who have ongoing vaccine strategies. Mary Disis and her group in Seattle are working on a very nice vaccine strategy that combines multiple epitopes into a single vaccine that stimulates a Th1 immune response. A group from the Mayo clinic led by Keith Knutson is evaluating a vaccine targeting folate binding protein in TNBC.

Other groups are moving into a different direction, and that is, can we take the vaccine into earlier stages of disease or towards true immunoprevention? What we've been talking about today is using vaccines for secondary prevention. We've discussed the limitations of vaccines in the metastatic setting without additional combinations of therapy. But what is the likelihood that we can move them back into a truly preventive setting? Brian Czerniecki's group at the University of Pennsylvania has been very interested in a dendritic cell vaccine approach, administering it to patients with DCIS. And with that being an approach for stage 0 breast cancer, you could see that this could be a next step before we get to truly preventive vaccines. Our group at MD Anderson is about to launch a trial with collaborators at Memorial Sloan Kettering, Dana Farber, and Columbia looking at the simple nelipepimut-S peptide vaccine strategy in DCIS.

Moderator: Can you talk about the significance of KEYNOTE-012 and -086?

Dr. Mittendorf: The KEYNOTE trials are a series of studies that are being conducted by Merck for their anti-PD-1 compound, pembrolizumab. Data from the KEYNOTE-012 trial were initially presented at the San Antonio Breast Cancer Symposium in 2014. The study targeted patients with TNBC, enrolling individuals with recurrent or metastatic disease. They had to have PD-L1 staining on their tumors as determined using the Merck proprietary antibody. They found that about 58% of patients screened had PD-L1-positive tumors. The interesting thing that was presented at San Antonio, and I'm not aware of any further updates to this dataset, was that they had an ORR of 18.5%, which is pretty good and encouraging, because it looked not dissimilar to what we saw in initial trials in melanoma and lung cancer, where these agents have now gotten approval. It looks as if those who respond can have durable responses. Those are encouraging data, and they support the design of subsequent studies,

which is what the KEYNOTE-086 trial is. That is a phase II trial looking specifically at the role of pembrolizumab as monotherapy in metastatic TNBC. The trial is currently enrolling; we don't have any data yet.

There's another KEYNOTE trial that probably warrants some mention, because Hope Rugo presented data from the study at San Antonio 2015. This was a cohort from within the KEYNOTE-028 trial. Within that trial there was a group of hormone-receptor-positive (HR+) breast cancer patients, which is very interesting, because a lot of groups are exploring checkpoint blockade in TNBC and not as much work is being done in HR+ breast cancer. In KEYNOTE-028, they screened 261 patients. They were able to assess PD-L1 status in 248 patients, of whom 48 were PD-L1 positive. That's about a 20% rate of PD-L1 positivity. They ended up treating 25 patients, and among those 25 patients, there were three who responded. With respect to clinical benefit rate, which is complete response plus partial response plus stable disease, there were 5 patients, or 20%.

The interesting thing about these data was that the investigators concluded–and I think rightly so–that this does provide support or rationale for further investigation of these agents in breast tumor subtypes other than triple-negative, specifically in HR+ breast cancer.

Moderator: Going back to TNBC, do you think that immuno-oncology strategies could change treatment paradigms in that setting?
Dr. Mittendorf: I believe that there's a high likelihood that therapeutic strategies that augment the immune response will become a standard part of treatment for patients with TNBC. Now that these agents are being investigated in the metastatic setting, where they are being shown to be safe with some efficacy signal, there are several groups interested in moving them back either into the neoadjuvant setting or for patients with residual disease after treatment.

Our group here at MD Anderson has just initiated a trial where we are taking patients with TNBC and giving them doxorubicin and cyclophosphamide. For those who do not appear to be having a robust response–instead of just continuing on with the standard therapy, which would be paclitaxel followed by surgery–we're offering an opportunity to participate in a study where they would receive *nab*-paclitaxel in combination with atezolizumab before being taken to the operating room.

So can we augment the immune response in the pre-surgical setting to potentially increase the rate of achieving a pathologic complete response? I think that is possible, but perhaps it's more likely that we will generate an adaptive immune response that may help decrease their risk of recurrence even if they do not achieve a pathologic complete response.

There's a strong interest in taking these patients with TNBC, giving them standard-of-care adjuvant chemotherapy, which for most groups would be an anthracycline taxane-based regimen, and for those who at the time of surgery are found to have residual disease, give the immune therapy then. The SWOG Cooperative Group has a study in development, led by Dr. Pusztai from Yale, in which they are proposing to enroll patients with TNBC who receive chemotherapy and at the time of surgery are found to have at least 1 cm of residual disease or positive lymph nodes, and randomize them to checkpoint blockade with pembrolizumab versus observation, with observation being the standard-of-care arm. So this could be an example of immunotherapy having the potential to change treatment paradigms if it were administered to patients with residual disease identified after they have received standard-of-care chemotherapy regimens in the neoadjuvant setting.

Moderator: Staying with pembrolizumab, what do you expect to see from the PANACEA trial?
Dr. Mittendorf: The PANACEA trial is a nice study that's being led by our colleagues in Europe and Australia. They are looking at the combination of trastuzumab and pembrolizumab in HER2+ patients who have progressed in the metastatic setting on trastuzumab.

Based on preclinical data suggesting synergism, I think that it is likely that that combination will demonstrate clinical benefit. The trial is actually a fairly small study–fewer than 50 patients. They will need first to demonstrate safety of the combination. I don't anticipate any issues there. Hopefully they'll show some evidence of clinical benefit, which would inform the design of a larger trial to, perhaps, consider this combination as one option for patients with HER-2+ breast cancer.

Moderator: Are there other combination therapies that are being studied that are of interest, or ones that you think should be studied but aren't?
Dr. Mittendorf: A lot of investigators are looking at these combinations. There are combinations of chemotherapy with checkpoint blockade–the example I mentioned previously was the *nab*-paclitaxel plus atezolizumab–or combinations of immunotherapy with targeted therapy such as in the PANACEA trial. I anticipate that there will be significant interest in combining immunotherapy with other targeted agents besides trastuzumab. There's preclinical data in an ovarian cancer model that suggests potential benefit to combining checkpoint blockade with PARP inhibitors.

Breast cancer for a long time was thought not to be immunogenic. Published data now show that there is an immune infiltrate in many breast tumors, and that infiltrate has both prognostic and predictive significance. Data were published to suggest that it is, and that is the presence of T cells in these tumors. So when I lecture, I like to show a figure from a publication by Sherene Loi and her colleagues in the *Journal of Clinical Oncology* from 2013 that shows the extent of lymphocytic infiltrate in breast tumors broken down by subtype. Triple-negative tumors have the most robust infiltrate; hormone receptor positive tumors have the least robust infiltrate. With that said, even though triple-negative tumors have the most robust infiltrate when compared to other subtypes of breast cancer, TNBC does not have a robust infiltrate when compared to more immunogenic tumors to include melanoma and lung cancer. So I believe that could

impact how effective checkpoint blockade may be in breast cancer. If you consider checkpoint blockade as a therapy that takes the brakes off of T cells, if there is not a significant T cell infiltrate, there would be nothing to take the brakes off of. So this is where I think there is an opportunity to look at combinations to see if we can stimulate an immune response and then come in with checkpoint blockade.

Would there be a role for coming in with a vaccine first and then checkpoint blockade? Is there a role for stimulating an innate immune response with an intratumoral injection of a toll-like receptor agonist and then come in with checkpoint blockade? There's great interest in combining checkpoint blockade with radiation to take advantage of the abscopal effect. I anticipate in breast cancer that one direction will be to try to figure out an initial strategy to bring in an immune response to then be followed by checkpoint blockade to augment that response.

Moderator: Are there any issues with toxicity that need to be accounted for in combination trials?
Dr. Mittendorf: The toxicities could potentially be additive for any of these strategies, so that's a good point. We will of course have to evaluate toxicities in the conduct of clinical trials.

Moderator: Are there particular combinations where we'd have to look more carefully than others?
Dr. Mittendorf: We know already that the combination of the anti-CTLA-4 and anti-PD-1, or anti-PD-L1, is more toxic than either one alone. And then if we put these with our standard chemotherapies, there is a likelihood that that will add further toxicity.

Moderator: With all the targeted therapies being developed and tested, what progress has there been in identifying biomarkers to match patients with the specific therapies that are most likely to be effective for them?
Dr. Mittendorf: In breast cancer we have two of the absolute best targets, the estrogen receptor and HER2. I would contend that we actually had targeted therapy before anybody even thought about the term, because we knew that patients who underwent oophorectomy did better than patients who did not. This was the first endocrine therapy. And then clearly HER2 is an excellent example of a biomarker that predicts response to HER2-targeted therapies that include the antibodies trastuzumab and pertuzumab as well as T-DM1.

Within the field of immunotherapy, the analogous situation would be if PD-L1 expression identified patients who would respond to anti-PD-1 or anti-PD-L1 therapy. It does not appear that that will be the case. In fact, experts in the field, including individuals such as Dr. Jim Allison, who developed the first approved checkpoint inhibitor, ipilimumab, are now suggesting a little more caution–to take all comers onto clinical trials, regardless of PD-L1 expression in their tumors, and then see in a retrospective analysis what that PD-L1 expression is. It's not quite as straightforward as perhaps we had initially hoped it would be. This likely speaks to the multiple factors within the tumor microenvironment that can impact or alter PD-L1 expression.

So in the field of immunotherapy, I think it will be a challenge to identify single biomarkers that will predict response to therapy. Any immune response will result in release of cytokines and other factors that may recruit additional cells that will change the landscape of that microenvironment, which means that the potential biomarker expression will change. This will be a robust field of research in the coming years.

Moderator: In lung cancer, it seems as if every day there's a new subtype. Do you think it will become that extensive with breast cancer?
Dr. Mittendorf: I would argue that it already is. Broadly speaking, we have HR+, HER2+, and triple-negative tumors, but as Jennifer Pietenpol's group at Vanderbilt published, there are actually 7 subtypes of TNBC, and I suspect it's probably not even that simple.

Moderator: What else do you think is important for us to know?
Dr. Mittendorf: I think we should all have enthusiasm for the opportunities and the potential of immunotherapy in breast cancer. Our challenge in implementing immunotherapy for our breast cancer patients is very different from the challenges faced by our colleagues treating other disease types. For instance, in melanoma, when they first started having success with immunotherapy, I would argue that on some level it was a little "easier," because they didn't have effective systemic therapies. In breast cancer we do have highly effective therapies, so it's going to be a challenge to determine how best to incorporate immunotherapy into these therapeutic regimens that are already used effectively in clinical practice.

I also think it's going to be important to figure out what form of immunotherapy we can utilize in which disease setting. For a patient whom we've rendered disease-free with our standard-of-care therapy but who still has a risk of recurrence of about 20%, there probably is a role for something relatively nontoxic such as a vaccine, but that vaccine by itself is not likely to be effective in the metastatic setting. In that setting, you would likely be willing to accept more potential toxicity. Perhaps that's the setting in which we will employ these multiple combinations, or even something as aggressive as adoptive T-cell therapy.So I think that there is a lot of opportunity and we're going to have to be very thoughtful. Overall, one might suggest that we have made such significant improvements in caring for breast cancer patients that it is now more difficult to "move the bar." As an example, if somebody has a 98% 5-year DFS rate, do I want to make it 100%? I absolutely do. But, to move that bar 2 percentage points, it can't come with much toxicity. We have to realize that a 50% reduction in recurrence risk means something very different if your risk is 2% than if your risk is 20%, particularly as it relates to how much toxicity we, and our patients, would be willing to accept for novel therapies or therapeutic strategies. So if you were considering a novel agent that was known to cause diarrhea and it was something that impacted the lifestyle of the individual taking it so much that they actually knew

where every convenience store was between home and work, if they had a risk of recurrence of 2%, would you consider it to decrease that risk to 1%? Probably not. If their risk is 20% and you could cut if to 10%, would you consider it then? Perhaps. If the risk of progression was 60%, you probably would consider it. So we have to be thoughtful about how we go about incorporating immunotherapy into the care of our breast cancer patients.

REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2016. Available at http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf. Accessed January 21, 2016.
2. American Society of Clinical Oncology. ASCO Meeting Library. Available at http://meetinglibrary.asco.org/search/site/breast%20cancer?f[0]=fctDate%3A2015&f[1]=meetingId%3A156&f[2]=fctContentType%3AAbstract. Accessed January 26, 2016.
3. ClinicalTrials.gov. Open studies of "breast cancer" and (immunotherapy or checkpoint or vaccine). Available at https://www.clinicaltrials.gov/ct2/results?term=%22breast+cancer%22+AND+%28immunotherapy+OR+checkpoint+OR+vaccine%29&recr=Open&no_unk=Y. Accessed January 26, 2016.
4. Mittendorf EA, Hunt KK. Breast cancer immunotherapy: is it ready for prime time? *Am J Hematol Oncol*. 2015;11(9):6-9.
5. Mittendorf EA, Clifton GT, Holmes JP, et al. Final report of the phase I/II clinical trial of the E75 (nelipepimut-S) vaccine with booster inoculations to prevent disease recurrence in high-risk breast cancer patients. *Ann Oncol*. 2014;25:1735-1742.
6. ClinicalTrials.gov. Efficacy and Safety Study of NeuVax™ (Nelipepimut-S or E75) Vaccine to Prevent Breast Cancer Recurrence (PRESENT). Available at https://clinicaltrials.gov/ct2/show/record/NCT01479244. Accessed January 26, 2016.
7. ClinicalTrials.gov. Nelipepimut-S Plus GM-CSF Vaccine Therapy in Treating Patients With Breast Cancer (VADIS). Available at https://www.clinicaltrials.gov/ct2/show/NCT02636582?term=02636582&rank=1. Accessed January 28, 2016
8. Sharma A, Koldovsky U, Xu S, et al. HER-2 pulsed dendritic cell vaccine can eliminate HER-2 expression and impact ductal carcinoma in situ. *Cancer*. 2012;118(17):4354-4362. doi: 10.1002/cncr.26734.
9. Buisseret L, Specht J, Dees EC, et al. KEYNOTE-012: A phase Ib study of pembrolizumab (MK-3475) in patients (pts) with metastatic triple-negative breast cancer (mTNBC). *Ann Oncol*. 2015;26(suppl 3):iii6-iii9.
10. Broderick JM. Pembrolizumab continues to show promise in breast cancer. OncLive. 2015. Available at http://www.onclive.com/conference-coverage/sabcs-2015/pembrolizumab-continues-to-show-promise-in-breast-cancer. Accessed January 25, 2016.
11. ClinicalTrials.gov. Study of pembrolizumab (MK-3475) monotherapy for metastatic triple-negative breast cancer (MK-3475-086/KEYNOTE-086). Available at https://clinicaltrials.gov/ct2/show/record/NCT02447003. Accessed January 14, 2016.
12. American Association for Cancer Research. Investigational PD-L1–targeted immunotherapy safe for patients with triple-negative breast cancer, effective in some. Available at http://www.aacr.org/Newsroom/pages/News-Release-Detail.aspx?ItemID=707#.VrT5HjHSncs. Accessed February 5, 2016.
13. Adams S, Diamond J, Hamilton E, et al. Safety and clinical activity of atezolizumab (anti-PDL1) in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer. Available at http://www.abstracts2view.com/sabcs15/view.php?nu=SABCS15L_1208. Accessed February 5, 2016.
14. Dirix LY-Y, Takacs I, Nikolinakos P, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A phase Ib JAVELIN solid tumor trial. Available at http://www.abstracts2view.com/sabcs15/view.php?nu=SABCS15L_984. Accessed February 5, 2016.
15. Chen G, Gupta R, Petrik S, et al. A feasibility study of cyclophosphamide, trastuzumab, and an allogeneic GM-CSF–secreting breast tumor vaccine for HER2+ metastatic breast cancer. *Cancer Immunol Res*. 2014;2(10):949-961. doi: 10.1158/2326-6066.CIR-14-0058.
16. ClinicalTrials.gov. Anti-PD-1 monoclonal antibody in advanced, trastuzumab-resistant, HER2-positive breast cancer (PANACEA). Available at https://www.clinicaltrials.gov/ct2/show/record/NCT02129556?term=%22breast+cancer%22+AND+immunotherapy&recr=Open&no_unk=Y&rank=18. Accessed January 14, 2016.
17. Lehmann BD, Pietenpol JA, Tan AR. Triple-negative breast cancer: molecular subtypes and new targets for therapy. *Am Soc Clin Oncol Educ Book*. 2015:e31-e39. doi: 10.14694/EdBook_AM.2015.35.e31.
18. Arnedos M, Vicier C, Loi S, et al. Precision medicine for metastatic breast cancer—limitations and solutions. *Nat Rev Clin Oncol*. 2015;12(12):693-704. doi: 10.1038/nrclinonc.2015.123.
19. Loi S, Savas P. Looking deep into the heterogeneity of human epidermal growth factor receptor 2-positive breast cancer: can we understand it better? *J Clin Oncol*. 2016. Epub ahead of print.