Recent Developments in the Treatment of HER2-Positive Breast Cancer

Dates of certification: *June 30, 2016, to June 30, 2017*
Medium: *Print with online posttest, evaluation, and request for credit*

The American Journal of Hematology/Oncology Editorial Board

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Disclosure: *Grant/research support from Genentech/Roche, Pfizer, Puma Biotechnology Inc, and Novartis (clinical trial support contracted to the University of Southern California and MD Anderson Cancer Center); consultant for Eisai, OncoPlex Diagnostics, Merck, and Novartis.*

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Overview
This activity is designed to inform physicians about the recent developments, as well as anticipated advances, in the treatment of patients with HER2-positive breast cancer.

Target Audience
This activity is directed toward medical oncologists, nurses, and nurse practitioners who manage and treat patients with HER2-positive breast cancer. Breast surgeons, surgical oncologists, radiation oncologists, pathologists, fellows, physician assistants, and other healthcare providers interested in the treatment of HER2-positive breast cancer are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Describe the unmet needs in the treatment of patients with HER2-positive breast cancer
- Review recent developments in the treatment of patients with HER2-positive breast cancer
- Review current and emerging clinical trial information concerning the use of investigational therapeutic approaches to care for patients with HER2-positive breast cancer

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Human epidermal growth factor receptor 2 (HER2) is prevalent in about 20% of breast cancer patients and is known to have a particularly aggressive natural history.[1] This discovery paved the path for the development and approval of the first HER2-targeted therapy, ie, trastuzumab.[2] Following the approval of trastuzumab, several other HER2-targeted therapies have been successfully designed and approved for HER2-positive breast cancer treatment.[2] Advances have occurred since then, in both metastatic, as well as neo/adjuvant settings. Significant improvement in pathologic complete response rates have been observed in neoadjuvant setting with the combination of chemotherapy, trastuzumab, and pertuzumab (in patients with tumors >2cm or positive lymph nodes).[3] In the metastatic setting, availability of several effective HER2-directed therapies including trastuzumab, pertuzumab, lapatinib, and T-DM1 have led to significant improvement in patient outcomes, including in some cases, improvements in overall survival.[4] Indeed, median survival times for patients with HER2-positive metastatic breast cancer was in the range of just a couple of years prior to the launch of trastuzumab versus nearly 5 years currently.[5] Unfortunately, despite these improvements and availability of neo/adjuvant therapies, HER2-positive local regional breast cancer can still relapse, with a frequency of approximately 15%-20% in the case of stage II disease. Moreover, metastatic HER2-positive breast cancer continues to remain incurable (apart from rare exceptional responders) despite these advances.[5]

HER2 amplification or overexpression is also associated with a high risk of brain metastasis, and a significant proportion of patients with HER2-positive metastatic breast cancer will experience brain metastases at some point in time. Increased incidence of brain metastasis seen in the recent years may be attributed to more efficient treatments that have led to improved survival and the availability of better imaging techniques that have led to increased detection of brain metastases. Radiation is still considered the mainstay therapy in these patients. Although, neurosurgical resection of the brain metastasis (followed by radiation) is an important treatment option in patients with single or few (≤3) lesions, especially in instances where systemic disease is well controlled and when the brain metastases are symptomatic.

Stereotactic radiosurgery (SRS) is another option that may be considered for patients with limited brain metastases who are considered poor candidates for surgical resection or those with lesions that are located in difficult anatomic locations.[4] In patients with multiple brain lesions, whole brain radiation therapy (WBRT) is an important option. However, its role in patients with ≤4 lesions remains less well defined. In this setting, published data shows that patients treated with SRS alone had similar survival compared with patients who received both SRS and WBRT, however intracranial relapse occurred considerably more frequently in those who did not receive WBRT.[4,6] On the one hand, WBRT is also associated with significant toxicities that include worse neurocognitive outcomes and quality of life. On the other, withholding WBRT can lead to progressive disease in the brain, which in turn, could also negatively impact cognition. In a study conducted by the North Central Cancer Treatment Group (NCCTG) N0574 where patients with 1 to 3 brain metastases were randomized to SRS or SRS plus WBRT, frequent decline in cognitive function was noted in patients as a result of WBRT even though better brain control was noted. At this point, it appears that delaying or avoiding the administration of WBRT in metastatic breast cancer, after surgical resection or SRS by considering careful use of effective systemic therapies may provide substantial benefits in terms of improvements in the quality of life of the patients.[4]

In patients with metastatic breast cancer, including those with brain metastases, improved control has been observed with systemic therapy. Trastuzumab combination with chemotherapy has been shown to improve survival despite development of brain metastases. In heavily-pretreated patients, treatment with lapatinib has shown objective response rates ranging from 2.6% to 6.0%, and addition of capecitabine further increased the response rates ranging from 20% to 33%.[4] Trastuzumab emtansine (T-DM1), a novel antibody–drug conjugate, has been shown to improve overall survival versus lapatinib and capecitabine combination in patients with previously treated HER2-positive metastatic breast cancer in the landmark EMILIA trial.[4,7] T-DM1 treatment has also demonstrated to be active in HER2-positive patients with brain metastases. Results from a study that retrospectively assessed the response rates for T-DM1 in patients with central nervous system (CNS) metastases from HER2-positive metastatic breast cancer were presented at the 2016 ASCO annual conference and showed durable responses with T-DM1 in this subset of patients; an objective response rate of 40% was noted in this study.[8] Additional combinations and therapies continue to be evaluated in this setting.

Among the several novel therapies that are currently being evaluated in HER2-positive patients are the CDK4/6 inhibitors. Given that most resistance mechanisms identified for HER2-targeted therapies are caused due to alterations to the receptor or intracellular signaling cascades, and as several of these events occur upstream of the cell cycle machinery, targeting CDK4/6, which is downstream of multiple resistance mechanisms appears a rational approach. CDK4/6 action influencing cell cycle progression occurs downstream of HER2, and inhibition of these CDK4/6 kinases by CDK4/6 inhibitors may represent an important therapeutic approach to augment the effectiveness of standard therapies.[9] Currently, these inhibitors are in preclinical and early clinical stages of development in combination with HER2-directed therapy (NCT02657343) for future patients with HER2-positive disease.[10,11] Research efforts continue in the field of breast cancer including HER2-positive breast cancer with the efforts to further improve survival rates and quality of life of patients.

Dr. Mark Pegram, MD, director of the Breast Cancer Oncology Program at Stanford Women's Cancer Center, and co-director of Stanford's Molecular Therapeutics Program at Stanford, CA, provided his insights and point on view on recent developments in the treatment of HER2-positive breast cancer.

Moderator: What are some of the unmet needs in the treatment of patients with HER2-positive breast cancer?

Dr. Pegram: There remain issues with HER2 diagnostics. Despite best efforts, the ASCO/CAP, in my view, has not completely succeeded in the mission to make clear interpretation of HER2 diagnostics a reality for practicing clinicians. In particular, in cases with deletion of chromosome 17 centromere, sequence must not be confused with true HER2 gene amplification simply because of a ratio of >2. Deletion of chromosome 17 centromere would not be expected to render a cell line responsive to trastuzumab. It is critical for clinicians to know the HER2 copy number per tumor cell nucleus and the number of CEP17 signals per nucleus. Also it is critical to know the number of nuclei actually counted. Areas of focal amplification (and the fraction of the total number of cells) should also be clearly articulated in pathology reports in order for the clinicians to accurately interpret the molecular phenotype for consideration of HER2-targeted therapies. Moreover, I am, at times, troubled by template language utilized in some pathology reports stating that "HER2-targeted therapy should be considered." This should be left for face-to-face discussion between patients and their oncologist (after all, there remain gray areas, such as the case of chromosome 17 ploidy — let's say with copy number of 4 — without HER2 amplification or protein overexpression). Many patients (rightly) obsess over pathology report language, and so clinical therapeutic recommendations should not be rendered by template language, especially in complex cases where efficacy of HER2-targeted therapy may not have (yet) been established.

Sadly, except for rare exceptional responders, all HER2-positive metastatic breast cancer patients eventually succumb to their disease despite the major inroads that have been made with antibodies, antibody drug conjugate-based therapeutics, and tyrosine kinase inhibitors (TKIs) in the metastatic setting. But, despite this progress, patients continue to die of their disease, in particular, they continue to die from brain metastasis. Between a third and a half of all metastatic HER2-positive breast cancer patients get brain metastasis. The majority of patients who get HER2-positive brain metastasis die from them, so this remains a really critical need — a big issue.

Next, for the early stages, we're awaiting results from the ongoing adjuvant APHINITY trial (NCT01358877) [12] adding pertuzumab to chemotherapy plus trastuzumab. Results from this trial will help define the ideal care for early stage HER2-positive breast cancer. New data from the KRISTINE trial at ASCO 2016 were disappointing for T-DM1 in the neoadjuvant setting, where T-DM1 plus pertuzumab yielded significantly lower pathologic complete response rates as compared to chemotherapy plus pertuzumab plus trastuzumab. Moreover, the breast conservation rate in the T-DM1 arm was numerically less than chemotherapy plus the 2 HER2 antibodies.

There are new naked antibodies and antibody drug conjugates in development in the HER2-positive space, and they show great promise. For example, MGAH22 (margetuximab) is a HER2 targeted monoclonal antibody with enhanced ADCC activity that has moved into phase III development in HER2-positive advanced breast cancer (NCT02492711).[13] And Medimmune has a phase I study of a new HER2 antibody drug conjugate, which looks very interesting. MEDI4276, a biparatopic antibody that targets subdomain 2 and subdomain 4 of the HER2 extracellular domains simultaneously, which results in cross linking of adjacent receptors and is a more potent stimulus for internalization (by receptor-mediated endocytosis) of the ADC.[14] This is potentially another path forward to address unmet needs in terms of therapeutic efficacy.

Moderator: What, in your opinion, are some of the most promising strategies/options on the horizon for the treatment of HER2+ breast cancer?

Dr. Pegram: At Stanford we are very interested in augmenting antibody-dependent cell-mediated cellular cytotoxicity (ADCC) using agonistic antibodies directed to CD137. Published work in Dr. Ronald Levy's laboratory has demonstrated synergistic interactions between CD137 agonist antibody and trastuzumab. Also at Stanford, Irv Weissman and Ravi Majeti have pioneered work on CD47 blocking antibodies, which break the macrophage phagocytic checkpoint. CD47 is upregulated in most breast cancers which blocks recognition and phagocytosis by macrophages. By blocking CD47, macrophage phagocytosis of tumor targets is potentiated. A humanized CD47 antibody (Hu5F9-G4) is now in human phase I studies at Stanford (in solid tumor neoplasms), and at Oxford, UK (in myelogenous leukemia). Unpublished preclinical data from Dr. Weissman's laboratory indicate synergism between CD47 antibody and trastuzumab *in vivo* against HER2-positive xenografts. We are optimistic that this could be a future novel combination for clinical development.

Another promise are the forthcoming results awaited from the NSABP B50, which is a trial for patients who failed to achieve a pathologic complete response from neoadjuvant chemo plus HER2 targeted antibodies. Those patients were then randomized to standard adjuvant trastuzumab for the rest of the year or T-DM1 every three weeks for the rest of the year. So that will be a very interesting protocol to follow. The trial has completed accrual and is in follow-up. The results are anxiously awaited, and (if positive) could provide a therapeutic niche for T-DM1 in the (post) neoadjuvant setting.

Moderator: Is there a potential role of CDK4/6 inhibitors in the

treatment of HER2+ breast cancer?

Dr. Pegram: There are recently published elegant preclinical data from the group at Dana-Farber directly addressing this issue.[15] The preclinical data looks intriguing. Using transgenic mouse models, cell line-based functional studies, and clinical specimens, they have shown that cyclin D1/CDK4 mediates resistance to targeted therapy for HER2-positive breast cancer. This is overcome using CDK4/6 inhibitors. Consequently, there is enthusiasm to move such combinations forward into the clinic in phase Ib and then phase II trials.

Moderator: Which CDK4/6 inhibitor?

Dr. Pegram: I don't have any insight into which one would pair best with a HER2-targeted treatment strategy, so I would be happy with any one of the three currently in clinical development, ie, palbociclib (PD0332991), ribociclib (LEE011), and abemaciclib (LY2835219) moving into that space in terms of future development of CDK4/6 in the HER2-positive space. So I think it could be interesting. It might also be interesting to look at CDK4/6 in the context of HER2-positive and ER-positive disease**.** This group of patients typically have lower pathologic complete response rates to HER2-targeted neoadjuvant regimens. Recall that about half of all HER2-positive breast cancer patients are also ER-positive so that would be a significant fraction that might benefit from this kind of a strategy.

Moderator: Phase 3 EMILIA trial also evaluated the role of tumor infiltrating lymphocytes (TILs) in HER2+ metastatic breast cancers (MBC) treated with trastuzumab emtansine (T-DM1) or lapatinib plus capecitabine (L+C).[16] The authors concluded that TILs impact may vary based on HER2+ targeted therapy. Would you able to help understand the implications of this study in a clinical setting?

Dr. Pegram: I think that's still investigational. I'm concerned that baseline pretreatment TILs may not reflect the potential infiltration of TILs at the time of metastatic relapse or even later. These cells can move around and are highly dynamic. Having an absence of TILs in a sample biopsy doesn't mean that they might not be able to be recruited into the metastatic tumor deposits if you have the right stimulus. The clinical utility of TILs as a predictive marker for response must be confirmed in large cohorts. Moreover, many have hypothesized that understanding the many and complex immunophenotypes of TILs may be far more useful than simple enumeration of such cells.

Moderator: What are some of the strategies for the management of patients whose disease progresses after two lines of HER2-targeted therapy in metastatic setting?

Dr. Pegram: So the fist-line right now in 2016 would be a CLEOPATRA-like regimen with both chemotherapy, pertuzumab, and trastuzumab. Second-line would be T-DM1, and then third-line for patients who are not on studies would be a lapatinib-based regimen, either lapatinib/capecitabine or lapatinib/trastuzumab. If they are also ER-positive and have low volume and/or asymptomatic disease burden, you could consider lapatinib/letrozole. However, I will freely admit that we have no data on lapatinib-based regimens following pertuzumab (trastuzumab) and T-DM1. So I have no idea whether lapatinib will work well in that setting. It probably will have challenges, but it is the only HER-targeted therapy left on the formulary at the moment. And so that would be the logical next step for a HER2-positive patient in third line. A more logical strategy would perhaps be an investigational agent in the third line. That would be a fair discussion to have with a patient.

Moderator: Patient-reported outcomes from phase 3 MARIANNE study evaluating trastuzumab emtansine (T-DM1) +/- pertuzumab (P) versus trastuzumab plus taxane in HER2-positive advanced breast cancer were presented at ASCO this year.[17] Would you be able to share a few key takeaways from this study?

Dr. Pegram: The bottom line from the presentation at ASCO is that the T-DM1 arms had a lower incidence and longer time to clinically important differences in neurotoxicity as well as less alopecia versus the control arm which in this case taxane/trastuzumab. The T-DM1 arm obviously had less nausea and diarrhea and then the quality of life measures by FACT-B and TOI-PFB surveys was maintained longer in the T-DM1 treated versus the chemotherapy/trastuzumab patients. That said, as I mentioned at the top of this discussion, that's not going to rehabilitate T-DM1 in the first line because the efficacy simply doesn't support it. So, I think the presentation was valuable, providing insight into types of tools that are available for patient reported outcomes. I think the patient reported outcomes (PROs) need to be more involved in drug development as a whole, including as a consideration for regulatory approval by various authorities globally. I think that should become a routine component of future investigations, along with the investigator-reported outcomes.

Moderator: What progress have we witnessed in the recent years in the management of HER2-positive breast cancer with brain metastases? Are there any advantages of adding whole brain radiation therapy to localized therapy in this patient population?

Dr. Pegram: Off study, I'm typically staggering whole brain or stereotactic with follow-on systemic approaches, predominantly capecitabine/lapatinib. And now in the wake of the Zephir trial[18] presentation at ASCO two years ago and now updated data presented on T-DM1 in HER2-positive brain metastasis at this year's ASCO,[8] I've been using T-DM1 in some of my HER2-positive brain metastases. So I don't know an advantage of adding brain radiation (concomitantly) to other systemic therapies for HER2-positive brain metastases, and I would be concerned about added toxicity to surrounding normal brain tissue. That said, we're still miles away from important advances in treatment of

HER2-positive brain metastases.

Another approach that I should mention that is in development is a new TKI (ONT-380) that is specific for HER2 and doesn't have as many EGFR-like side effects, so less cutaneous rash and less diarrhea. ONT-380 is now being studied in HER2-positive brain metastases and hopefully will yield positive results. Yet another strategy is the PATRICIA study (NCT02536339)[19] which just started, and is giving high-dose trastuzumab in HER2-positive brain metastases, reasoning that by mass action (since there is no maximum tolerated dose [MTD] systemically for trastuzumab once all the HER2 sites are saturated) trastuzumab may achieve blood-brain barrier penetration. As there is no anticipated added toxicity by substantially increasing trastuzumab dose, hopefully it will afford greater CNS penetration and could (in theory) have an impact on HER2-positive brain metastases.

Moderator: KRISTINE trial is the first phase 3 data evaluating complete neoadjuvant regimen omitting standard chemotherapy. Results show that treatment with docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) yielded a significantly higher pCR rate; however, T-DM1/pertuzumab had a notably better safety profile, and HRQoL and physical functioning were maintained longer.[20] What likely impact can these findings have? What are the clinical implications of this data?

Dr. Pegram: I don't think it's going to have any impact because it's the efficacy that we're all concerned about, and having a higher pCR rate certainly could put a patient into a favorable prognostic category. It would be expected to have an excellent to outstanding long-term disease-free interval or hopefully no relapse in the future as we're seeing for many of these patients, frankly. And so I don't think we would risk that by compromising TCHP. That said, if there is somebody who you think can't tolerate TCHP or for some other reason, couldn't tolerate H- or P-based regimens, then there's nothing wrong with T-DM1/pertuzumab. It has respectable pCR rates but still not as high as TCHP, so I don't think simply having an easier quality of life is going to help. But I could imagine, perhaps, maybe an elderly patient or a patient with comorbidities where you think they simply couldn't tolerate full-on chemotherapy, two antibody regimen, then T-DM1/pertuzumab could be considered in that context. But I think that's probably going to be infrequent in most instances.

Moderator: Results from PHEREXA, a phase 3 study of trastuzumab plus capecitabine ± pertuzumab for patients (pts) who progressed during/after one line of trastuzumab-based therapy in the HER2+ metastatic breast cancer (MBC) were presented at ASCO 2016 annual meeting.[21] Would you be able to discuss a few key takeaways from this study?

Dr. Pegram: I think that this trial is irrelevant in the United States because we use first-line pertuzumab/trastuzumab and chemotherapy. So we're just not going to have patients coming off of one line of trastuzumab only in the metastatic setting. So the results, from my point of view, are largely irrelevant for practice as it exists in the US in 2016. Perhaps when this trial commenced, the control arm may have been relevant, but unfortunately this happens from time to time in the context of phase III drug development. Sometimes the control group simply changes based on new data, in this case CLEOPATRA. And so I don't see us using PHEREXA because there really should not be any patients who don't have consideration of pertuzumab-based regimens in the first-line metastatic setting.

I understand that there are market research data from this country showing that there are some patients who don't receive pertuzumab in the first line. I am extremely puzzled by this in light of the long-term overall survival benefit that has been proven in the CLEOPATRA trial.[22] Ethically, I don't see how pertuzumab could be denied in the first line. It certainly is covered by third-party payors for insured patients. If, for some reason, a patient did not receive pertuzumab in the first line, PHEREXA would be highly applicable, but that should be in a vast minority of patients, market research notwithstanding.

Moderator: How do you anticipate the treatment of early and advanced HER2-positive breast cancer evolving in the next couple of years?

Dr. Pegram: Well, there are a lot of trials out there that are still in the pipeline, and it will be very interesting. I mentioned that the MGAH22 Fc optimized chimeric anti-HER2 monoclonal antibody with enhanced ADCC activity is in phase III in the salvage setting against treatment of physician's choice. I mentioned NSABP 50, whether post neoadjuvant T-DM1 will be superior to trastuzumab in patients who failed to achieve a pathological CR with induction chemotherapy plus trastuzumab and pertuzumab regimens. That's very exciting. The AFFINITY trial as adjuvant therapy for HER2-positive early breast cancer will test whether a full year of adjuvant pertuzumab is beneficial in those patients who are HER2-positive with early disease (NCT01358877).[12] So that's extremely exciting, and that study also has completed its accrual.

I guess, finally, I should mention that there is an adjuvant T-DM1 trial that was initiated, came close to completing its accrual, but then was terminated early in the wake of the MARIANNE metastatic trial, hopefully, not too prematurely but we'll see. That trial looked at the substitution of taxane plus trastuzumab and pertuzumab following anthracycline with T-DM1 plus pertuzumab. So, we'll see whether that trial has enough patients to test the hypothesis that it might be possible to omit paclitaxel plus trastuzumab/pertuzumab in the adjuvant setting. So that remains to be seen, however, but the trial accrued a fair number of patients and hopefully, we'll report the data at some point in the future.

I should also mention ONT-380, the small molecule HER2-specific kinase inhibitor. As I mentioned, that's moving into phase III right now, also in the salvage setting in previously treated met-

astatic HER2-positive disease, and also the HER2-positive brain metastasis space. And both of those spaces could have potential for registration data sets. I guess lastly, I'll mention a couple of approaches that we're taking at my institution at Stanford. We're about to start a phase Ib/II trial looking at incorporation of CD137 antibodies with HER2 antibodies, CD137 antibodies that will activate CD137 can potentiate ADCC activity by immune effector cells, for example, NK cells. So NK cells that are treated with CD137 agonist antibodies will have more robust ADCC activity created by greater release of granzyme and perforin, which is a potent stimulus for cell killing of tumor target cells in ADCC reaction. So that looks like it may be very interesting.

And then, finally, I'll mention that we have preclinical data here at Stanford looking at combinations of CD47 antibody with HER2 antibody. CD47 in essence is a checkpoint for macrophage phagocytosis. And tumors that upregulate CD47 will block macrophage phagocytosis of tumor target cells. However, if you block CD47 with a blocking antibody, the one that's under study now in phase I at Stanford is called Hu5F9-G4. It's currently in a first-in-human, first-in-class phase I study that's investigator initiated at Stanford in solid tumors (NCT02216409).[23] And that same antibody is also in development in myeloid leukemia by the Octo Group in the UK, which is based in Oxford, to see if it has activity in liquid tumors. But, at any rate, preclinical data in Irv Weisman's lab at Stanford indicates synergism between CD47 antibodies and trastuzumab. So there's enthusiasm to study that when the humanized CD47 antibody completes its phase I stage of clinical investigation. There was a poster discussion at ASCO earlier this week on Hu5F9-G4 antibody presented by Brandy Sikik, so you could see from that data set that the dose escalation in the solid tumor trial is well underway and hopefully will be of great interest to the field if we can demonstrate efficacy in future studies.

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