Understanding the Educational Needs of Healthcare Providers on Emerging Treatments for HER2-Positive Advanced Breast Cancer

Supported by an educational grant from Seattle Genetics.

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EXECUTIVE SUMMARY

Background

The management of and the prognosis for patients with HER2-positive breast cancer (BC) drastically improved after the introduction of the HER2-targeted monoclonal antibody trastuzumab. More recently, the approvals of a second HER2-targeted monoclonal antibody, pertuzumab, and an antibody-drug conjugate, ado-trastuzumab emtansine (T-DM1), have further improved the prognosis of patients with HER2-positive breast cancer. However, many patients with HER2-positive metastatic breast cancer (MBC) continue to receive suboptimal care when compared with expert consensus recommendations. Moreover, the advent of new and next-generation HER2-targeted agents in late-stage clinical development such as the tyrosine kinase inhibitors (TKIs) tucatinib and neratinib, as well as the antibody–drug conjugates trastuzumab deruxtecan and trastuzumab duocarmazine, will likely increase the challenges faced by healthcare providers who care for patients with HER2-positive MBC.

Study Goal

The goal of this comprehensive needs assessment was to understand current practice patterns in managing patients with HER2-positive MBC as well as clinician knowledge of emerging therapeutic options for these patients in order to identify the current educational needs of healthcare providers across the United States. Clinical Care Options (CCO) and Thistle Editorial, LLC, strategically designed a multi-methods assessment involving an in-depth qualitative exploration and a quantitative survey of current approaches to practice, knowledge of emerging therapy options, and specific challenges faced by US healthcare providers responsible for treatment decisions for patients with HER2-positive MBC.

Design and Methodology

This two-phase, mixed-methods needs assessment study consisted of qualitative telephone interviews (Phase 1) and an online survey (Phase 2). Phase 1 of the study explored gaps in the knowledge, skills, and clinical confidence of US medical oncologists, radiation oncologists, and advanced practice providers responsible for the treatment decisions for patients with HER2-positive MBC. Phase 2 (quantitative) examined practice trends among clinicians within the United States.

Key Clinical Practice Gaps

Practice Gap #1: Disparities in Using a Multidisciplinary Approach to Decision-Making and Treatment Planning

A multidisciplinary approach to cancer care that relies on the expertise of all relevant disciplines to discuss optimal disease management is recommended by experts and clinical practice guidelines. Clinicians with access to tumor boards are more likely to describe treatment planning as a collaborative or multidisciplinary process. Clinicians without access to multidisciplinary planning or other clinical decision support resources are more likely to view themselves as primary decision-makers when it comes to treatment planning for patients with advanced HER2-positive BC.

Practice Gap #2: Deficits in Clinical Trial Referral

Participation in clinical trials is encouraged by clinical practice guidelines and experts in an effort to optimize outcomes for patients with cancer and to promote discovery of new therapies. Although clinicians say they discuss clinical trials with patients, they vary in the timing of such discussion and the estimated percentage of patients that clinicians said they were able to refer for clinical trials is low.

Practice Gap #3: Deficits in Selecting Optimal First-line Therapy for Patients With de novo HER2-Positive MBC

Many clinicians appropriately chose THP (docetaxel plus trastuzumab and pertuzumab) and HP (trastuzumab and pertuzumab) maintenance as initial therapy for de novo HER2-positive MBC; however, overtreatment in the de novo setting is evident, with approximately one half of clinicians reporting they would also add local therapy (surgery or radiation) to the treatment regimen.

Practice Gap #4: Challenges in Selecting First-line Therapy for Patients With Newly Diagnosed MBC Who Were Previously Treated for Early BC

Many clinicians are unsure which first-line therapy is appropriate for patients who received TCHP (docetaxel/carboplatin plus trastuzumab, and pertuzumab) and T-DM1 for early-stage BC. Clinicians also vary in how they define a treatment-free interval, which is an important factor in choosing subsequent therapy at the time of progression to metastatic disease. Clinician uncertainty about therapy selection is noticeably greater concerning treatment for metastatic disease following therapy with adjuvant T-DM1 or for patients whose disease recurs after a longer treatment-free interval, which some clinicians defined as after more than 6 months while others defined it as after more than 12 months.

Practice Gap #5: Challenges in Managing Patients With CNS Disease

A majority of clinicians would switch systemic therapy in a patient with brain-only progression in contrast to the expert recommendation to continue with the same systemic therapy and treat central nervous system (CNS) metastases with local therapy. Managing patients with leptomeningeal disease and identifying radiation necrosis after radiation therapy are significant challenges in the management of CNS disease for clinicians in all specialties, including radiation oncology. Most clinicians are imaging symptomatic patients when they present with metastatic disease vs at baseline. Few clinicians, even radiation oncologists, are aware of investigational therapies that have shown activity in patients with CNS metastases after treatment with available standard of care options.

Practice Gap #6: Challenges in Selecting Optimal Therapy for Patients With HER2-Positive MBC and Disease Progression Following Treatment With Current Standard of Care Therapies

Clinicians are challenged to identify optimal third-line therapy following progression after THP and T-DM1 for HER2-positive MBC and are unfamiliar with investigational agents/regimens that have shown clinical activity in heavily pretreated patients.

Practice Gap #7: Challenges in Treating Patients With Low HER2 Expression
There was broad consensus among interviewed clinicians that they would not treat patients with low or indeterminate HER2 expression with anti-HER2 therapies and low awareness that there are emerging therapeutic options for patients with low HER2 expression.

Practice Gap #8: Deficits in Familiarity With Novel Agents
Clinicians are largely unfamiliar with novel agents being developed for the treatment of HER2-positive MBC or their associated toxicity profiles, and in interviews, their mechanisms of action. A majority consider only FDA approval based on phase III clinical data as sufficient evidence to incorporate a new agent or regimen into their practice for patients with advanced HER2-positive BC.

Practice Gap #9: Inconsistencies in Defining Quality of Life and Palliative Care
Although quality of life factors into discussions about goal and expectation setting, there is little consensus among clinicians about how best to define quality of life. Similarly, clinicians view palliative care as an important component of addressing quality of life but vary in how they define palliative care and when they initiate discussions about palliative care with their patients.

Key Recommendations

This study highlights a global need for education and resource exposure across professional role, specialty, and practice setting in the following areas of clinical knowledge and practice in the treatment of patients with HER2-positive MBC:

Recommendation #1: Promote Use of a Multidisciplinary Approach to Decision-Making and Treatment Planning
Develop resources to support multidisciplinary pathways in HER2-positive MBC treatment planning that reinforce the importance of team-based approaches to patient care.

Recommendation #2: Enhance Clinical Trial Referral
Direct clinicians to resources that increase awareness of and ability to access available clinical trials as part of their routine approach to managing patients with HER2-positive MBC.

Recommendation #3: Optimize Therapy Selection for Patients With de novo HER2-Positive MBC
Clinicians need access to expert perspectives on the appropriate therapeutic strategy for patients with de novo HER2-positive MBC. Clinicians also need expert guidance on how to integrate clinical and nonclinical criteria into their decision-making, and exposure to strategies that enable patients to remain engaged in their care over the long-term.

Recommendation #4: Optimize Therapy Selection for Patients With Newly Diagnosed HER2-Positive MBC Who Were Previously Treated for Early BC
Clinicians need access to expert perspectives on the appropriate selection of therapies for patients who received TCHP and T-DM1 for early stage BC, including guidance on how best to define a treatment-free interval, and how to integrate novel agents into clinical practice.

Recommendation #5: Optimize CNS Disease Management
Clinicians need guidance on how best to define “low threshold” for performing diagnostic MRI in the setting of neurologic symptoms suggestive of brain involvement to ensure timely access to investigational and/or newly approved agents with potential benefit for CNS disease. Clinicians also need exposure to expert guidance on the optimal management of patients with brain-only progression as well as strategies for identifying radiation necrosis after radiation therapy and managing patients with leptomeningeal disease. Finally, education on emerging treatment options that have shown activity in patients with CNS metastases is also needed.

Recommendation #6: Optimize Therapy Selection for Patients With HER2-Positive MBC and Disease Progression Following Treatment With Current Standard of Care Therapies
Clinicians need exposure to expert perspectives on the appropriate selection of therapies for patients who progress following previous treatment of first- and second-line standard of care regimens THP and T-DM1, respectively, and education that will help them build familiarity with investigational agents/regimens that have shown clinical activity in heavily pretreated patients.

Recommendation #7: Optimize Therapy Selection for Patients With Low HER2 Expression
Clinicians need exposure to expert guidance on accurate strategies to define HER2 status and emerging therapeutic options for patients with low HER2 expression.

Recommendation #8: Increase Familiarity With Novel Agents

Clinicians need education on novel agents being developed for the treatment of HER2-positive MBC, including their toxicity profiles and mechanisms of action. An increase in familiarity with investigational agents could help to increase clinician comfort with and confidence in using agents sooner after regulatory approval.

Recommendation #9: Define and Initiate Palliative Care Discussions

Patients with HER2-positive MBC have complex needs that require support to minimize distress and deterioration in quality of life. Clinicians need guidance on the breadth and availability of oncology-led or palliative specialist–led palliative care options, the timing of palliative care discussions, and the impact of palliative care on quality of life.

Study Design and Methodology

Background

The management of and prognosis for patients with HER2-positive BC drastically improved after the introduction of the HER2-targeted monoclonal antibody trastuzumab. Thankfully, the field is still advancing rapidly, and new HER2-targeted options have improved the survival and quality of life of patients with advanced or MBC. The CLEOPATRA and EMILIA studies established THP and T-DM1 as new standards of care for first-line and second-line therapies, respectively. However, analyses of cases entered into the CCO MBC Interactive Decision Support Tool suggest that many patients with HER2-positive MBC are still not being treated optimally when compared with expert consensus recommendations (**Figures 1 and 2**).[1]

Figure 1. First-line treatment choice for de novo disease.

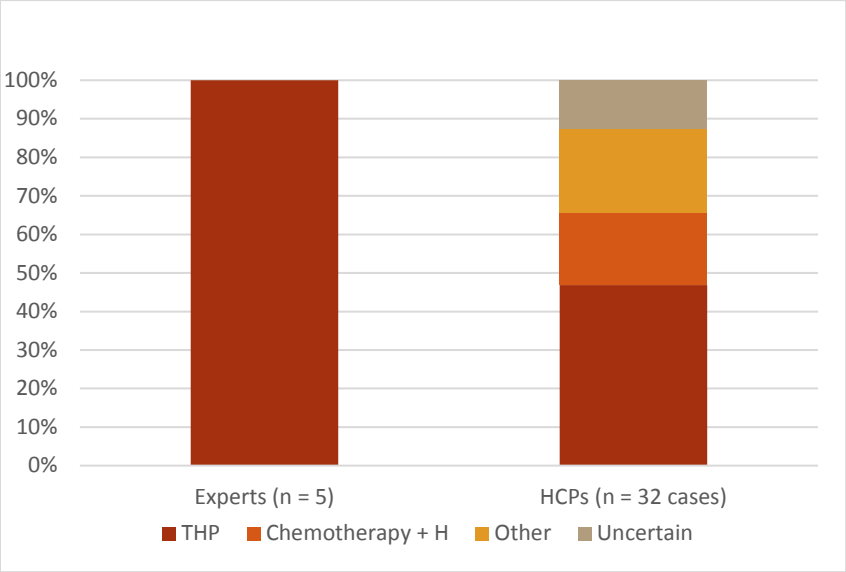
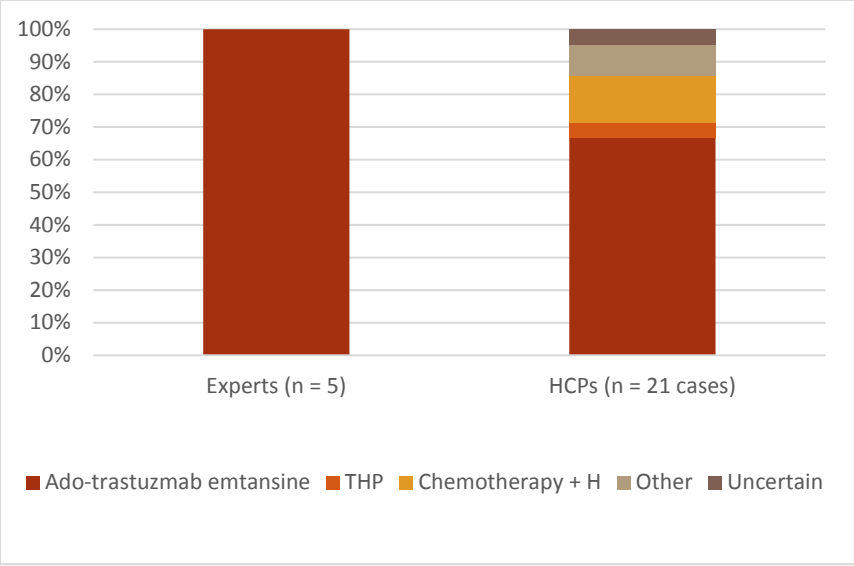


Figure 2. Second-line treatment choice after THP.



With new and next-generation HER2-targeted agents such as the TKIs tucatinib and neratinib along with antibody–drug conjugates in late-stage clinical development, the optimal choice and sequencing of HER2 therapies in MBC is highly likely to become even more challenging for healthcare providers. In addition, approximately 30% to 50% of patients with advanced HER2-positive BC will develop CNS metastases.[2] The limited penetration of trastuzumab and pertuzumab into the CNS can substantially hinder their efficacy in these patients. However, TKIs such as tucatinib and neratinib have established activity in HER2-positive BC brain metastases (BCBM).[3,4] Sara A. Hurvitz, MD, FACP, wrote in a recent editorial that "*patients with BCBM have a worse quality of life, reduced [PFS], and shorter [OS] compared with those without CNS involvement. Identifying regimens to improve outcomes for this poor prognostic subset of patients remains a considerable unmet need in [BC]*."

Clinicians will soon be challenged to understand and integrate emerging research into clinical practice. It will be critical to assess their understanding of the mechanisms of action and the role of novel HER2-targeted therapies in clinical investigations for patients with HER2-positive advanced BC. The HER2-targeted agents pertuzumab and T-DM1 currently approved in this setting, as well as neratinib and tucatinib, are being investigated in combination with each other, immunotherapies, and endocrine therapies in patients with HER2-positive and/or hormone receptor–positive MBC. Among heavily pretreated patients with HER2-positive MBC with and without brain metastases, tucatinib in combination with T-DM1 appeared to have an acceptable toxicity and promising efficacy.[5] Tucatinib is also being investigated in combination with capecitabine and trastuzumab, which has demonstrated acceptable toxicity and preliminary antitumor activity[3] and is being further studied in the double-blinded, randomized, multi-center HER2CLIMB trial (NCT02614794). In addition, ongoing clinical investigations of next-generation, novel HER2-targeted agents as monotherapy or in combination, along with novel antibody–drug conjugates, such as trastuzumab deruxtecan[6,7] and trastuzumab duocarmazine,[8] have shown the promise of relevant clinical activity in pretreated patients, with some of the agents/combinations showing preliminary activity in BCBM and/or low HER2-expressing tumors. Other well-tolerated and promising HER2-targeted agents include margetuximab[9] and DHES0815A.

To provide targeted education that adequately prepares clinicians to confidently and safely use these emerging HER2-targeted agents, a clear understanding of the current educational needs of healthcare providers is needed.

Study Design

Following a review of the literature and CCO internal data, this two-phase, mixed-methods needs assessment study was designed to include qualitative telephone interviews (Phase 1) and an online survey (Phase 2). Phase 1 of the study explored gaps in the knowledge, skills, and clinical confidence of US-based healthcare providers responsible for treatment decisions for patients with HER2-positive MBC. Phase 2 examined practice trends among clinicians within the United States. The study design included informed consent and measures to ensure protection and confidentiality for participants. Participants were offered an ethically acceptable level of compensation (ie, fair market value, but not enough to create coercion) to increase the number of participants and improve the statistical power as well as the likelihood that our study cohort is representative of the general US oncology specialist healthcare provider population.

Qualitative Phase

Semi-structured interviews were designed to explore intuitive decision-making factors influencing clinical reasoning.[10] We conducted a series of confidential, 30- to 45-minute telephone interviews, directed by an interview topic guide based on literature review, faculty input, and synthesis. Interviews were transcribed verbatim and imported into NVivo 12 for Mac (*QSR International*), a software package designed to support the systematic analysis of unstructured textual data. Analysis was based on grounded theory and an open-ended process of constant comparison that generates themes, descriptive patterns, and hypotheses as an ongoing, iterative process.[11] This approach included 4 components:

1. Data immersion and familiarization
2. Descriptive coding and node generation
3. Thematic coding and analysis
4. Subgroup analysis by demographic and other relevant attributes

The transcript content was coded into descriptive categories, or “nodes,” that were tagged to sections of text. Following descriptive node generation, a second round of coding identified potential themes of relevance until we achieved thematic saturation. Indicators of themes included words, phrases or segments of text that were used in a similar fashion by respondents across or within interviews, and that pointed to an emerging idea or concept. Qualitative findings were also examined for educationally significant differences among subgroups (ie, practice setting, specialty, designation) and reported where relevant. The conclusions for the overall group are, for the most part, relevant across all subgroups.

Quantitative Phase

We fielded an in-depth quantitative survey to identify practice trends concerning integrating new agents and therapeutic advances in the care of patients with HER2-positive MBC, sources of information consulted for best practices and/or education, gaps in knowledge, competence, and performance, and barriers to the adoption of new treatment options.

Oncology clinicians treating HER2-positive MBC were recruited to complete a 10- to 15-minute online survey. Sara A. Hurvitz, MD, FACP, Director, Breast Cancer Oncology Program, Associate Professor of Medicine, Division of Hematology/Oncology, Department of Medicine, David Geffen School of Medicine

at UCLA and Sara M. Tolaney, MD, MPH, Assistant Professor of Medicine, Harvard Medical School, Associate Director, Susan F. Smith Center for Women's Cancers, and Director, Clinical Research, Breast Oncology, Dana-Farber Cancer Institute—both nationally recognized experts in HER2-positive MBC—worked with educational and survey design/assessment experts to develop case scenarios and clinical questions to assess gaps in optimal patient management, trends in care, knowledge of clinical trials and investigational agents, and self-identified barriers to optimal care.

Recruitment

Invitations to participate in both phases of the study were sent through email to a list of CCO members as well as lists specific to radiation oncologists, neuro-oncologists, and midlevel providers. CCO Oncology membership includes more than 163,000 clinicians worldwide, including more than 26,000 physicians in the United States, of whom more than 16,000 define themselves as having a specialized interest in medical oncology or hematology/oncology. The lists for radiation oncologists, neuro-oncologists, and midlevel providers included 4245, 3783, and 3184 clinicians, respectively. Multiple targeted emails were sent to each group in an effort to maximize participation.

Participant Characteristics

Demographic Characteristics of Participants

We conducted qualitative interviews between June 25 and August 20, 2019. For the qualitative phase, we recruited 30 clinicians who described themselves as practicing in US academic centers, community cancer centers, private practice, or community-based settings (**Table 1**). A majority of interview participants were physicians with a decision-making role with regards to treatment; 7 participants were Advanced Practice Providers (Advanced Practice Nurses or Physician Assistants) and 1 was a nurse practitioner (NP). Many of the community-based clinicians were affiliated with a community or academic hospital. The quantitative survey was conducted between July and August 2019 and yielded 347 US-based participants (**Table 1**).

Table 1. Demographic Characteristics of Participants

	Qualitative (n = 30)		Quantitative (n = 347)	
Position	**n**	**%**	**n**	**%**
Physician	22	73.33	128	36.89
Nurse Practitioner	1	3.33	15	4.32
Physician Assistant	1	3.33	13	3.75
Advanced Practice Nurse	6	20	28	8.07
Nurse Navigator	--	--	19	5.48
Pharmacist	--	--	63	18.16
Nurses	--	--	81	23.34
Specialty	**n**	**%**	**n**	**%**
Medical oncology	14	46.66	94	29.75
Hematology/oncology	11	33.33	109	34.49
Radiation oncology	5	16.66	28	8.86
Surgical oncology	--	--	7	2.22
Neuro-oncology	--	--	0	0
Neurosurgery	--	--	1	0.32
Primary care	--	--	17	5.38
Pharmacy	--	--	46	14.56
Other	--	--	14	4.43
Years of practice	**n**	**%**	**n**	**%**
< 5	NA	NA	70	22.15
5-10	NA	NA	67	21.20
11-15	NA	NA	35	11.08
16-20	NA	NA	35	11.08
21-30	NA	NA	59	18.67
> 30	NA	NA	50	15.82
Practice setting	**n**	**%**	**n**	**%**
Academic	8	26.66	66	20.89
Community/hospital/ health system owned	13	43.33	150	47.47
Physician owned	7	23.33	57	18.04

Federal government owned	--	--	5	1.58
Other	2	6.66	38	12.03
BC patients/month	**n**	**%**	**n**	**%**
< 5	NA	NA	76	24.05
5-10	NA	NA	48	15.19
11-15	NA	NA	52	16.46
16-20	NA	NA	27	8.54
21-30	NA	NA	42	13.29
> 30	NA	NA	71	22.47

Roles and Responsibilities

One half of the interview participants saw patients with a range of solid tumors and one half specialized in or mainly saw patients with BC. The roles of interview participants in managing patients with HER2-positive MBC differed by degree/professional qualification (**Table 2**).

Table 2. Self-Reported Role by Degree/Professional Qualification

MD	APN/MSN/PA	NP
Treatment determination	Initial evaluation	Infusion administration
Collaboration lead	Patient education	Patient education
Clinical trial identification	Symptom management	Symptom management
	Navigation	

Practice Gap #1: Disparities in Using a Multidisciplinary Approach to Decision-Making and Treatment Planning

A multidisciplinary approach to cancer care that relies on the expertise of all relevant disciplines to discuss optimal disease management is recommended by experts and clinical practice guidelines. Clinicians with access to tumor boards are more likely to describe treatment planning as a collaborative or multidisciplinary process. Clinicians without access to multidisciplinary planning or other clinical decision support resources are more likely to view themselves as primary decision-makers when it comes to treatment planning for patients with advanced HER2-positive BC.

Treatment Planning as a Collaborative Process

Almost one half of interview participants (n = 14) participated in tumor boards. Although some of these participants also described themselves as primary decision-makers, overall, this group was more likely to describe treatment planning as collaborative or multidisciplinary, and used words such as "team" and "consensus" to describe the process.

> *We have a **multidisciplinary breast tumor board**, so usually we run the patient through that and/or we discuss them on the phone between ourselves.* [provider 16, MD, oncology, community]

> *A lot of those patients are presented at the breast tumor board. So, whatever the treatment we are doing or we'd recommend to the patient is **usually a consensus or at least most oncologists agreed upon** at that meeting.* [provider 18, MD, radiation oncology, community]

> *It's quite comprehensive. Our physicians sit at our weekly tumor board meetings that are located at the hospital and you have a dynamic team of physicians that are part of patient care, from surgeons to pathologists and **all of the care team members that are involved in making diagnoses for patients** based on what their findings are, with radiologists. And so those decisions are made together, as a team.* [provider 15, APN, hematology/oncology, community]

Participants viewed the tumor board as an especially pertinent clinical decision support resource in the setting of early HER2-positive BC but also emphasized how important and necessary the tumor board is becoming as a resource to support decision-making in advanced disease. A discussion of metastatic cases at a tumor board provides an opportunity to review pathology, imaging, and evolving standards of care for patients with complex disease as well as to clarify metastatic biopsy sites and identify potential clinical trials. One academic interview participant described a weekly tumor board initiative that concentrates solely on patients with metastatic disease.

> *We're probably unique in that, in the last year, **we've actually formed a metastatic tumor board** where we only discuss metastatic cases, so we do that once a week. It's partially to get everybody's idea **because the care of metastatic patients is becoming so complicated and it's also helped us a lot with clinical trial screening and enrollment.*** [provider 26, MD, oncology, academic]

Primary Decision-Makers in Treatment Planning

Most interview participants said they collaborated with other clinicians and specialists in treatment planning, which typically included breast surgeons or general surgeons focused on BC, radiation oncologists, and pathologists. However, more than one half (n = 16) described themselves as primary decision-makers in treatment planning for patients with HER2-positive BC ("the oncologist is the main quarterback"). Radiation oncology clinicians also described the medical oncologist as "in charge of systemic therapy."

> *[My] primary role is the administration and management of systemic treatment around HER2-positive breast cancer. So* ***choosing therapy, ordering therapy, administering therapy, managing toxicity, managing expectations****…*[provider 14, MD, hematology/oncology, community]

> *I'm a physician, so* ***I'm the decision maker from diagnosis to the treatment*** *and all the journey through the treatment.* [provider 6, MD, hematology/oncology, private practice]

> *I'm the doctor.* ***I'm the primary decision-maker****. I make all the recommendations*. [provider 12, MD, hematology/oncology, private practice]

> ***It's mainly up to the medical oncologist to assign the treatment****. That's how [decisions are made] for the care of their patient.* [provider 1, APN, oncology, community]

Communication Among Clinicians

Interview participants who had access to tumor boards noted that communications among specialists about treatment for patients with advanced disease usually occurred in person at the tumor board itself. In the absence of a tumor board discussion (eg, if a decision were made before the tumor board occurred), communications among team members most commonly occurred via telephone calls, as well as secure text message platforms or electronic medical records. Community clinicians or clinicians in private practice were more likely to communicate with other specialists on a case-by-case basis rather than using a multidisciplinary approach as a rule of thumb, and described having access to specialists in radiation oncology or neurosurgery via hospital affiliation or through their specialist network.

> *If they have something wrong with them that will need the services of a radiation-oncologist, I just pick up the phone and call them. It depends.* [provider 12, MD, hematology/oncology, private practice]

> *It depends on the situation—if we need a neurosurgeon, if we need a thoracic surgeon, if we need pain specialists, so it depends on a case-by-case basis.* [provider 7, MD, hematology/oncology, private practice]

Treatment Planning

The medical oncologists we interviewed acknowledged that "while each case is different" there is a common range of clinical factors that they (and colleagues, if participating in tumor boards) consider when determining treatment for patients with advanced HER2-positive BC. These factors included:

- Expected response
- Duration of disease control
- PFS
- OS
- Types of adverse events
- Frequency of adverse events
- Hormone receptor–positive status
- Comorbidities
- De novo metastatic disease
- Previous adjuvant/neo-adjuvant therapy
- Performance status
- Disease stage
- Extent of metastatic disease

Radiation oncology clinicians had less to say about the initial treatment for patients with de novo or previously treated metastatic disease. One physician noted the following:

> *Their HER2-positive status doesn't really affect the radiation decision as far as whether it's a curative treatment or a palliative treatment. We know that HER2-positive patients generally have more aggressive disease, so that's something to think about when thinking about recommending or not recommending treatment. But the type of treatment that's recommended is not that drastically different than somebody that's HER negative, as, you know, HER2 positivity is not really a predictor of outcome with radiation*. [provider 21, MD, radiation oncology, community]

Communication With Patients

Clinicians with access to tumor boards noted that following tumor board discussion, they would typically have a treatment planning discussion with the patient that reflected the extent of the patient's disease as well as team consensus about treatment. Medical oncologists reported that they typically met with patients in person to offer treatment recommendations based on either tumor board consensus or, for medical oncologists with no access to tumor boards, to offer their own recommendations based on patient history, disease characteristics, and previous treatment.

APNs and NPs described their role in communication with patients as "*reinforcing*" what the medical oncologist has already discussed as based on information and orders documented in and available via electronic medical records. Some interview participants also pointed to the increasing role of nurse navigators to coordinate care and help patients navigate through the treatment process.

> *The oncologist will directly communicate that with the nurse navigator and if the patient is going to receive an infusion, the nurse navigator is going to talk with our precertification department,*

making sure everything is covered and the patient will be set up and scheduled and that the nurse navigator will call the infusion team after the patient is scheduled and the patient will come to the department. [provider 10, APN, oncology, community]

Setting Expectations

Medical oncologists described in considerable detail their approach to discussing treatment recommendations and setting expectations for patients (**Table 3**).

Table 3. Examples of How Medical Oncologists Set Patient Expectations in Treatment Planning
In the first meeting when I see somebody with metastatic breast cancer, I tell them that, unfortunately, at this point, their disease is not curable, meaning that there will never be a time where I can tell them that their breast cancer's not going to come back and that there will never be a time that I can recommend that they go off treatment. With that being said, I do say that metastatic breast cancer is very treatable and we are getting more and more drugs to treat this disease every year and it's sort of something that we manage as a chronic disease for as long as we can and as best as we can. And then I say something like, "The goals of your care at this point are to prolong your life and give you the best quality of life for as long as possible." [provider 26, MD, hematology/oncology, academia]
We lay down all the treatment options and from the beginning very well plan what is a prognosis going to be, what they should look for the outcome in the future. [provider 6, MD, hematology/oncology, private practice]
Well, the first thing we say is that the median overall survival of these patients has more than quadrupled in the last decade or two, so nowadays patients are living, on average, 5 years. So we say that to the patient that, "We think we're going to change your disease into a chronic disease." We don't say, "We're going to cure you," but we'll say, "This disease can be treated for many, many years and some patients may go 10 years." [provider 7, MD, hematology/oncology, private practice]
You want to initially establish with them that this is an incurable condition and whether it's chemotherapy plus or minus targeted therapy, they'd likely be on something for the rest of their life. [provider 8, MD, oncology, private practice]

While oncologists generally told patients upfront that HER2-positive MBC is incurable ("*we're honest from the beginning*") most viewed metastatic disease as a chronic, treatable disease and described "*laying out all the options to help patients make a decision they're comfortable with*."

Clinicians ranged in how they specifically addressed the prognosis, from telling patients at the time of diagnosis of metastatic disease, *"there is no cure,*" to quantifying the prognosis, as described here by a physician:

> *I am discussing their prognosis on a few data points. One is what are the chances of response—60%, 80%—based on the data that has been accumulated and is readily available to me…*[provider 14, MD, hematology/oncology, community]).

A radiation oncologist also noted that he discussed treatment success with patients in terms of "*the percentage of control of their cancer*" and with consideration of risk vs benefit:

> *You know, we talk about side effects and complications and the percentage of severe complications and all of those things and then we come to a conclusion about whether the patient wants to proceed.* [provider 21, MD, radiation oncology, community]

In contrast, for some clinicians, there was a general sense that most patients are not looking for quantifiable data on prognosis, but rather, a "*general sense of kind of a vague concept of 'how long have I got*?'" As such, 1 clinician noted "*you have your clichéd phrases that you help pacify the patient and then you hope for the best*." [provider 24, MD, oncology, academia]

APNs and NPs were less likely to have conversations with patients about prognosis and generally ceded such discussions to the medical oncologist. However, APNs and NPs emphasized the importance of setting immediate goals with patients before initiating systemic therapy and 1 APN described a tool her practice uses to gauge how patients want to handle challenging information.

> *In our practice, we have a sheet, a wishes sheet (My Wishes), and then we read the wishes**, what they would like and how comfortable they feel about being told that they are dying**. We do this, you know. We discuss that with every patient now regardless if they're metastatic or not.* [provider 1, APN, oncology, community]

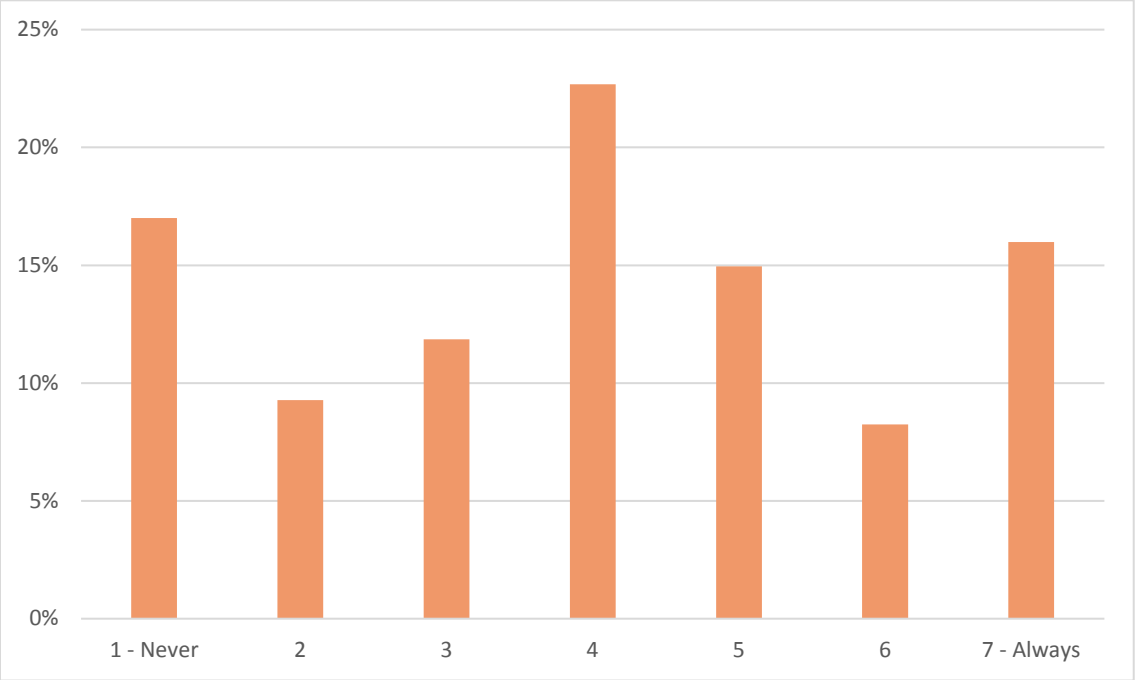
Practice Gap #2: Deficits in Clinical Trial Referral

Participation in clinical trials is encouraged by clinical practice guidelines and experts in an effort to optimize outcomes for patients with cancer and to promote discovery of new therapies. Although clinicians say they discuss clinical trials with patients, they vary in the timing of such discussions, and the estimated percentage of patients that clinicians said they were able to refer for clinical trial is low.

Clinical Trials in Treatment Planning

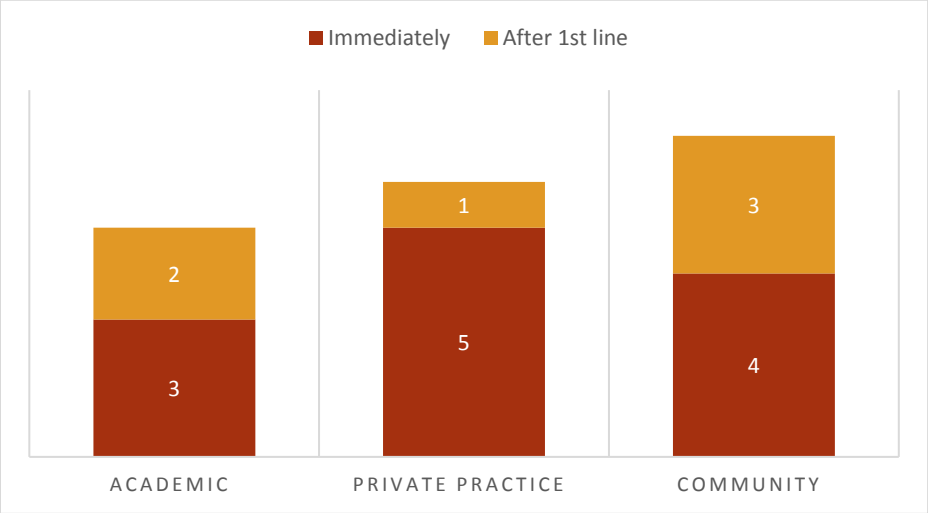
Survey data show that only 1 in 6 clinicians said they always discuss clinical trials with their patients and approximately 25% indicated that they rarely or never discuss clinical trials (**Figure 3**).

Figure 3. Percentage of clinicians discussing clinical trials with patients (n = 194).



In interviews, more than one half of the medical oncology clinicians said they usually discussed clinical trials with their patients as an option early in treatment planning and revisited the potential for trial enrollment at progression (**Figure 4**). The remaining medical oncology clinicians we interviewed said they typically discussed clinical trials following failure of first-line therapy in the metastatic setting (**Figure 2**).

Figure 4. Timing of clinical trial discussion by medical oncology clinicians (n = 18).



APNs/NPs and clinicians working in radiation oncology were unaware if their radiation oncology physicians or medical oncology colleagues discussed clinical trials with patients at any point in treatment planning.

While only one of the radiation oncology clinicians we interviewed indicated that the potential for clinical trial referral was an option for their patients (this provider had participated in a national hippocampus-sparing trial), survey data suggest that approximately one half (55%) of radiation oncology specialists recommend trials to their medical oncology colleagues.

Clinicians broadly agreed that with few exceptions, patients rarely asked them about clinical trials.

Clinical Trials in Initial Treatment Planning

Clinicians who said they usually discussed clinical trials with their patients as an option early in treatment planning and revisited the potential for trial enrollment at progression appeared to feel a responsibility to consider clinical trials for their patients with HER2-positive MBC in an effort to improve patient care.

> *I tend to think about clinical trials as early on as possible.* ***At basically every treatment decision, I will be looking to see if there's a clinical trial that makes more sense*** *than what I might be offering. I'm pretty proactive about looking at clinical trials and seeing where something might be more beneficial than what I currently have available.* [provider 11, MD, hematology/oncology, private practice]

> ***The clinician has a responsibility to know what clinical trials are available at their institution****, so that you kind of broach the topic having one in mind, because that is, I think, a difficult concept for patients to wrap their head around if they're just kind of wrapping their head around the diagnosis. I introduce the concept of clinical trials and let them know that we have an interesting trial for them, but probably go more so into detail about the specific trial when they come back, after their staging studies.* [provider 24, MD, oncology, academic]

If there is a clinical trial available, ***then the first option would be to enroll****. Definitely something that I encourage.* [provider 2, MD, hematology/oncology, academic]

However, the estimated percentage of patients that interviewed clinicians said they were able to refer for clinical trial was low (approximate range: 1% to 20%). In practice, even among those who said they discussed clinical trials at the initial treatment planning visit, clinical trial referral was more likely to occur at the second or third line of therapy.

You know, as we go down the line and ***we're exhausting standard treatments, then people are much more receptive to seeking out clinical trials,*** *but I do try to have that conversation right at the beginning if I feel like the person is going to be receptive.* [provider 4, MD, hematology/oncology, community]

Private practice and community clinicians offered the additional caveat that although some of their patients might be eligible for clinical trial referral at a tertiary center, distance would likely pose a barrier to participation.

We know how these ***patients are living far away from big cities and they don't want to travel****, many of them don't have cars, so you have to put things in perspective and if I have a standard of care that can give you 60 months of survival, I don't think clinical trials are feasible.* [provider 7, MD, hematology/oncology, private practice]

Clinical Trials After First-line Treatment Failure

Clinicians who waited to discuss clinical trials until later lines of therapy felt that the current standard approaches (dual-HER2 trastuzumab/pertuzumab-containing therapy, T-DM1–containing therapy, and neratinib- or lapatinib-containing therapy) were effective for most patients, depending on disease and patient characteristics.

I would say that I'm usually not bringing up clinical trials at the first or second meeting in metastatic HER2-positive breast cancer, because ***we have a very clear cut sort of first-line regimen that provides an overall survival benefit and there's rarely any trials in the first-line setting*** *and most patients are going on the standard of care best therapy in the first line.* [provider 26, MD, hematology/oncology, academic]

I always discuss clinical trials, to be very open to, in the metastatic HER2 setting. I'm a little reluctant to talk about it, you know, in the first couple of months, because we have such good upfront drug therapy right now and I don't have a great first-line trial right now. So, personally, I ***tend to talk about trials as we go forth in the subsequent months and so forth****. I typically am not a big fan of doing it right away in this particular disease. I typically wait in this setting, just because so much is going on and I think you have to do it****. It's a marathon journey****, I tend to not just sprint and do everything at once.* [provider 25, DO, oncology, community]

Oftentimes, ***the discussion for clinical trial usually happens much later****, because we have such great effective treatments today that it's possible that the patient continues to have a beneficial effect for a very, very long time on current therapy before we are in the clinical trial world. So it*

depends on how the disease in the patient is behaving. [provider 14, MD, hematology/oncology, community]

Practice Gap #3: Deficits in Selecting Optimal First-line Therapy for Patients With de novo HER2-Positive MBC

Many clinicians appropriately chose THP and HP maintenance as initial therapy for de novo HER2-positive MBC; however, potential overtreatment in the de novo setting is evident, with approximately one half reporting they would also add local therapy (surgery or radiation) to the treatment regimen.

Current Standard of Care for de novo HER2-Positive MBC

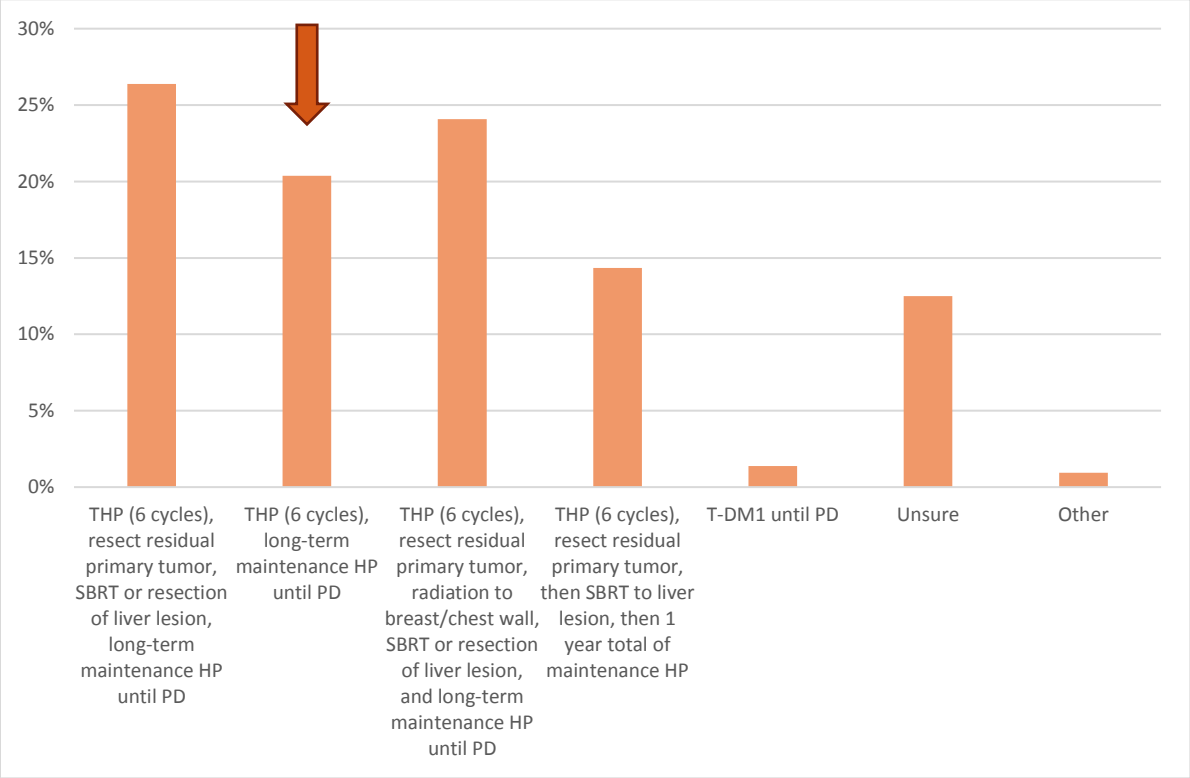
Based on the positive results of the phase III CLEOPATRA trial, the current standard of care for patients diagnosed with de novo HER2-positive MBC is initial therapy with THP followed maintenance HP until progression or intolerance.[11] Experts indicated that, although reasonable in some cases, additional local therapy might represent overtreatment. Upon disease progression following THP plus HP, the standard of care is the antibody–drug conjugate T-DM1 based on positive results of the phase III EMILIA trial.[12]

Case #1: Newly Diagnosed de novo HER2-Positive MBC

A 54-year-old woman presented to her primary care doctor with a 4-cm breast mass and a palpable ipsilateral axillary lymph node. Biopsy of the breast mass demonstrated an ER-negative, PgR-negative, HER2-positive (3+) invasive ductal carcinoma and fine-needle aspiration of the lymph node was positive for carcinoma. Staging studies revealed a 2-cm liver lesion, the biopsy of which was ER negative, PgR negative, and HER2 positive (3+), consistent with her BC.

Which of the following treatment approaches would be most appropriate for this patient?

Figure 5. Selection of optimal therapy for newly diagnosed de novo HER2-positive MBC (n = 216).



Expert preference for this newly diagnosed patient with HER2-positive MBC is THP for 6 cycles followed by long-term HP maintenance (**Figure 5, indicated by arrow**). Experts indicated that although THP for 6 cycles followed by surgical resection and/or radiation therapy and long-term HP maintenance therapy would be reasonable in some cases, additional local therapy might represent overtreatment placing the patient at increased risk of complications from their treatment. Breast cancer expert Sara Tolaney, MD, MPH, was "*surprised that so many were doing local therapy for patients with de novo metastatic disease that was more than just oligometastatic.*"

Clinician Rationale for de novo Therapy Selections

In interviews, most clinicians similarly identified THP (a taxane, paclitaxel or docetaxel, plus trastuzumab and pertuzumab) as their preferred therapy for patients presenting with de novo metastatic disease. Clinicians pointed to performance status, functional status, extent of disease, symptoms, tolerability of the THP regimen, age, and preexisting neuropathy as being rationale for this choice, as well as patient desire for systemic therapy. Many clinicians viewed de novo therapy as "*pretty standard*" and echoed the sentiment of one oncologist who noted "*there's not a whole lot that's going to affect what I give them in the first line*."

Although the THP regimen was frequently mentioned, other chemotherapy agents that clinicians cited included navelbine (hair loss–sparing), nab-paclitaxel (on the grounds that there are some data showing equivalence to taxanes), and carboplatin.

> *Everybody kind of agrees that dual blockade is the best option with chemotherapy. We can discuss sometimes which is the best partner for the dual blockade, which chemotherapy will be the best partner, paclitaxel, docetaxel, or sometimes we use vinorelbine.* [provider 5, MD, oncology, academic]

Three APNs identified dual HER2 blockade as standard in the de novo metastatic setting but were less clear about which specific combinations oncologists were likely to recommend. In patients whose disease was also hormone receptor positive, the approach that clinicians most frequently mentioned was to introduce hormone-based therapy following completion of chemotherapy, alongside dual HER2 blockade.

Nonclinical Factors

Clinicians reported that they collected a range of information from patients to support decision-making via medical history, review of systems, and, in some cases, patient preference questionnaires. Most of this information pertained to clinical issues such as symptoms and comorbidities. However, few of the clinicians we interviewed described how they used nonclinical factors in their decision-making for de novo metastatic patients. Typical responses to this question include this remark from an oncologist, who said:

> *Nonclinical factors, not a whole lot**. I can't think of anything nonclinical, so to speak**. I mean, one can say the desire of the patient to receive therapy, and so on.* [provider 14, MD, hematology/oncology, community]

The nonclinical factors most frequently cited were convenience for the patient, patient willingness to go through treatment, psychosocial issues, social issues (eg, transport, family support), and insurance coverage. Clinicians who factored nonclinical information into their decision-making provided the following rationales:

> *So, depending on **how old a patient is, is she still working and wants to continue working, if she has young kids,** other relationship issues, I think all that information is very important to have.* [provider 23, MD, oncology, private practice]

> ***We always take the patient's consideration into effect**. The family's a little bit, but the patient comes first. So that's really it: trying to make sure that the patient is comfortable with what we do. And I mean, we have some that go, "No, I'm not going to do it," and that's their choice.* [provider 9, APN, oncology, academic]

> *If people have a hard time getting to and from our center or if they're going to not have good family support during therapy, **we might consider less aggressive therapies or more convenient therapies**.* [provider 16, MD, oncology, community]

Therapy Selection in HER2-Positive MBC That Is Also Hormone Receptor Positive

Current Standard of Care for de novo Hormone Receptor–Positive/HER2-Positive MBC

In patients with hormone receptor–positive, HER2-positive MBC, clinical guidelines recommend treatment with dual HER2 blockade plus chemotherapy followed by the introduction of hormone-based therapy after chemotherapy is completed.

The most common practice described by the clinicians we interviewed concerning the treatment of hormone receptor–positive, HER2-positive advanced BC involved adding endocrine therapy to HER2 blockade and/or introducing hormone-based therapy to dual HER2 blockade following completion of chemotherapy. This approach (typically fulvestrant/trastuzumab or aromatase inhibitor/trastuzumab) was considered standard by clinicians for patients with small disease burden, no visceral crisis, and who might not desire chemotherapy. CDK4/6 inhibitors were also mentioned by a small group of private practice and community-based clinicians.

> *If the patient is tolerating Taxotere, **I will continue to use it as long as I can use it**. **At that point, I'll switch over to hormone plus dual HER2** if the disease is under control and continue with that until disease progression and then switch out altogether to Kadcyla. So the only difference is utilization of hormones at some point, either before progression or after progression.* [provider 14, MD, hematology/oncology, community]

> ***Usually these patients will get a hormonal therapy in the maintenance phase**, more or less, not as the primary treatment, because the data has been limited. We have a few studies here and there using an AI plus anti-HER2, more in the elderly who didn't want chemotherapy or were not eligible for chemotherapy. The responses certainly were inferior to chemotherapy, but you can certainly use it in the situation where you cannot use or the patient doesn't want chemotherapy.* [provider 7, MD, hematology/oncology, private practice]

After induction treatment, when the response has been the maximum, we change chemotherapy for endocrine therapy plus blockade*. But if the patient is kind of old, she's been pre-treated, or she's not willing to go through chemo side effects, and if there is a high expression of hormone receptors, we go for endocrine therapy plus doing a blockade but plus anti-HER2 therapy.* [provider 5, MD, oncology, academic]

Practice Gap #4: Challenges in Selecting First-line Therapy for Newly Diagnosed MBC in Patients Previously Treated for Early BC

Many clinicians are unsure which first-line therapy is appropriate for patients who received TCHP (docetaxel/carboplatin plus trastuzumab, and pertuzumab) and T-DM1 for early-stage BC. Clinicians also vary in how they define a treatment-free interval, which is an important factor in choosing subsequent therapy at the time of progression to metastatic disease. Clinician uncertainty about therapy selection is noticeably greater concerning treatment for metastatic disease following therapy with adjuvant T-DM1 or for patients whose disease recurs after a longer treatment-free interval, which some clinicians defined as after more than 6 months while others defined it as after more than 12 months.

Standard of Care for Early HER2-Positive BC and Impact on Management of Newly Diagnosed MBC

Many patients are diagnosed with earlier stages of HER2-positive BC and may be treated with neoadjuvant or adjuvant trastuzumab/pertuzumab in combination with chemotherapy, as well as extended adjuvant therapy with neratinib in some high-risk patients.[13,14] More recently, the FDA also approved T-DM1 (May 2019) as adjuvant therapy for these patients.[15] Thus, clinicians are increasingly encountering patients with newly diagnosed HER2-positive MBC with previous exposure to trastuzumab, pertuzumab, T-DM1, and neratinib, and are facing the challenge of deciding how to treat these patients upon recurrence with metastatic disease in the absence of a standard-of-care treatment. Current approved treatment options for patients who progress to metastatic disease following treatment for early stage HER2-positive breast cancer include rechallenge with a previous treatment regimen in some select cases, lapatinib plus capecitabine, trastuzumab plus chemotherapy, or chemotherapy. However, most patients eventually experience disease progression with these treatment regimens, thus new options are clearly needed.[16]

New Therapies in Clinical Development for Pretreated HER2-Positive MBC

Therapies under development that have shown promise in the setting of pretreated HER2-positive MBC, whether for early BC or MBC, include improved HER2-targeted TKIs, monoclonal antibodies, and antibody–drug conjugates. In the phase III NALA trial, neratinib, an irreversible pan-HER TKI, in combination with capecitabine significantly improved PFS vs lapatinib plus capecitabine in patients who had received at least 2 regimens targeting HER2 (HR: 0.76; P = .0059, with 12-month PFS rates of 29% vs 15%, respectively).[17] Tucatinib, an oral, selective HER2-targeted TKI, has also demonstrated early phase activity in this setting, achieving an ORR of 48% and PFS of 8.2 months in combination with T-DM1, and an ORR of 61% and PFS of 7.8 months in combination with capecitabine and trastuzumab.[5,18] Furthermore, because of its selectivity for HER2, tucatinib has demonstrated fewer EGFR-related toxicities than many of the other HER2-targeted TKIs.[16] The combination of tucatinib plus capecitabine and trastuzumab is being evaluated in the ongoing randomized phase II HER2CLIMB trial.[19]

Clinician Rationale for Therapy Selection for Newly Diagnosed MBC Following Treatment for Early BC

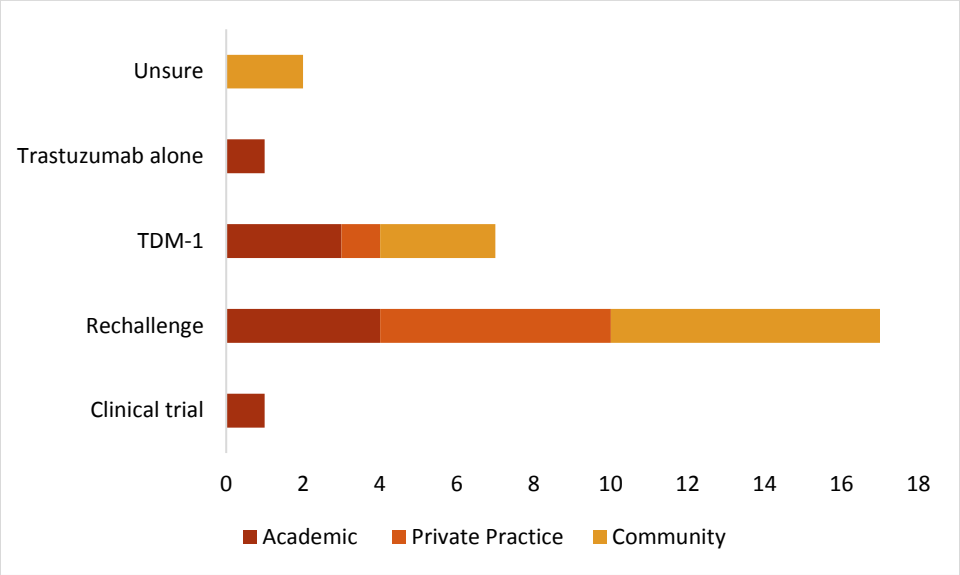
We asked clinicians to explain their rationales for choosing therapy for patients with newly diagnosed MBC who were previously treated for early BC. **Table 4** describes the range of responses that clinicians provided.

Table 4. Clinician Rationales for Therapy Selection Following Treatment for Early BC
The rationale is what you think is the best option based on the level of response, the type of therapy that she had, the receptor status, the level of response, the duration of therapy, the level of side effect. All of that would play a role. So the idea is to maximize and use something that most likely the patient will respond to, whether they have previously responded to it, whether they have achieved a tremendous response, minimal response, near complete response. All of that stuff will play a role. [provider 14, MD, hematology/oncology, community]
The rationale is, if the treatment-free interval is longer, then still, there is a likelihood of responding to the same treatment. And that tells me the prognosis is probably better. If treatment field is shorter, that tells me it's excessive disease. That helps me to prepare the patient also. Say you have a bad disease—the likelihood of treatment for longer time is small, possibly. [provider 6, MD, hematology/oncology, private practice]
All what we decide is based on large phase III trials, and that didn't come from 1 or 2 years, over many, many years of research that we have these milestone phase III trials that set in stone what I'm talking about. [provider 7, MD, hematology/oncology, private practice]
Things like patients' clinical factors, performance status or comorbidities or volume in extended disease, impact treatment decisions…as far as burden of disease in HER2-positive breast cancer, that does not affect my treatment decisions as much as it does in, say, estrogen receptor-positive breast cancer. Because the first, second, and third lines all have efficacy that is not based on volume of disease. [provider 26, MD, hematology/oncology, academic]
When you have someone who's been already treated, then you have to see what their time to progression was, what their treatment-free interval was. That is very important and plus what they had already been treated with. So a lot of times patients, if they've had taxanes before, they may come in already with some treatment-related symptoms from taxanes, such as neuropathies. If they have gotten any anthracyclines or Herceptin in the past, they may have already some cardiac issues. So, yeah, I think you have to be very careful when you're then treating patients with metastatic disease what kind of symptoms may be related to their treatment before. [provider 23, MD, oncology, private practice]

Therapy Following Adjuvant/Neoadjuvant HP

The general consensus following neoadjuvant or adjuvant treatment with trastuzumab or pertuzumab among medical oncologists we interviewed was that "if it's been a while" a rechallenge with HP was feasible for patients with metastatic disease (**Figure 6**). Medical oncology APNs and radiation oncology clinicians were unsure of available options, said they would use trastuzumab alone or T-DM1, or look for a clinical trial.

Figure 6. Therapy following neoadjuvant/adjuvant trastuzumab/pertuzumab (n = 28).

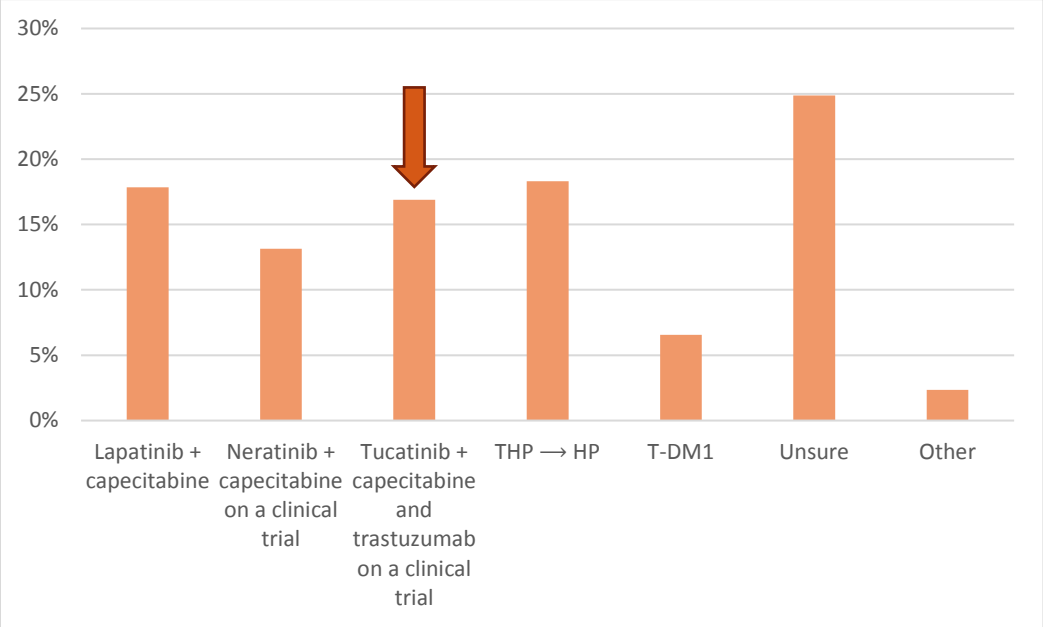


Case #2: Therapy Following Adjuvant T-DM1 for Early BC

A 58-year-old woman who was treated for T2N1 ER-negative, PgR-negative, HER2-positive (3+) invasive ductal carcinoma received preoperative TCHP and was found to have residual disease in the breast and lymph node. She subsequently received adjuvant T-DM1 for 14 cycles. Two years later, she presented with right upper quadrant discomfort and was found to have liver metastases. Biopsy confirmed the liver metastasis was ER negative, PgR negative, HER2 positive (3+).

Which of the following treatment regimens would be most appropriate for this patient?

Figure 7. Appropriate therapy selection for patient newly diagnosed with HER2-positive MBC who previously received TCHP and T-DM1 for early-stage disease (n = 213).



Expert preference for this newly diagnosed patient with HER2-positive MBC who previously received TCHP and T-DM1 for early stage disease would be to enroll them on a clinical trial of tucatinib plus capecitabine and trastuzumab (**Figure 7, indicated by arrow**). Experts indicated that other reasonable options include lapatinib/capecitabine, neratinib/capecitabine on a clinical trial, or THP followed by maintenance HP.

Rationale for Therapy Selection After T-DM1 for Early BC

Clinician uncertainty was noticeably greater concerning treatment for metastatic disease following therapy with adjuvant T-DM1 for early BC. While a small group of interviewed clinicians said they might circle back to HP, rechallenge with T-DM1, or make a switch to lapatinib, the majority of clinicians expressed uncertainty about next steps (**Table 5**). In fact, less than one half of interviewed clinicians said their practice is even to use T-DM1 in the adjuvant setting for patients with early BC who were treated with neoadjuvant HER2-targeted therapy and then had residual disease. Most interviewed radiation oncology clinicians were unfamiliar with T-DM1 and APNs were unaware of options in this setting.

Table 5. Uncertainty Concerning Approach to Therapy Following T-DM1 for Early BC
We'd look at could we do another anti-HER2-neu—I mean, again, it would depend on how long ago they had it and how well they responded to it. So we could, you know, consider doing some endocrine manipulation or CDK inhibitor if they're ER/PR positive, or ***trying a different anti-HER2-neu agent****. So I think those would all be on the table for consideration, but which one we would pick I think would just depend on the patient's individual clinical situation*. [provider 16, MD, oncology, community]
*If they progressed on T-DM1 then, yeah****, it becomes questionable what you should use****. I'd probably try to use Perjeta triplet in those patients and if they progressed on Perjeta then I think I'm going to go to T-DM1*. [provider 11, MD, oncology, private practice]
*That's a really tough question and I haven't even seen that yet. If they have residual disease and they've already had Herceptin and Perjeta and then they've already had T-DM1 and then if they progress****, it would really depend on what the treatment-free interval was, how long after they progressed, what their repeat receptors look like****. Again, I would biopsy them again, I would repeat the receptors and go from there.* [provider 26, MD, hematology/oncology, academia]
*Now, we do know that T-DM1 can be used as part of consolidation therapy after initial Herceptin-Perjeta neo-adjuvant treatment, that there may be T-DM1 consolidation after their breast surgery and then they may, at some point, develop stage IV disease****. Nobody is quite sure yet whether they should be restarted on Herceptin-Perjeta, whether they should be restarted on T-DM1****. Nobody is quite sure what to do with that woman. I would be influenced by the cardiac status. I would be interested by how long the free interval was. So, for example, if someone had consolidated T-DM1 and maybe they had stage IV disease 9 months later, I'd say they're done with Herceptin, Perjeta, and T-DM1. They may just be refractory to those agents. So another very unlikely possibility is lapatinib with capecitabine, particularly if the relapse occurred in the brain—but again, that's an extremely unlikely scenario for us.* [provider 12, MD, hematology/oncology, private practice]

Sara Tolaney, MD, MPH, was "*not surprised by the confusion in the approach for patients who have had adjuvant HP and/or T-DM1, given the lack of data in this setting and unclear optimal disease-free interval for re-exposure to these agents.*"

Defining Treatment-Free Interval With HER2-Targeted Therapy for Early BC

The duration of a treatment-free interval factors into clinical decision-making when determining therapy for patients previously treated with trastuzumab/pertuzumab in the (neo)adjuvant setting. **Although the FDA currently defines this interval as 6 months, many experts adopt a treatment-free interval of either 6 or 12 months.** Interviewed clinicians varied in how they defined "treatment-free interval," a definition that included 1 month, 6 months, 12 months, or 2 years (**Table 6**).

Table 6. Rationales for Therapy for Newly Diagnosed MBC Following Adjuvant/Neoadjuvant HP	
Rechallenge With HP	**Switch to T-DM1**
If it's been a while, we would generally re-give it or re-challenge—I mean, give it again, if it's been many years. [provider 16, MD, oncology, community]	*If you develop metastatic disease at a later date, then we don't go back to that regimen, we start—we usually use Kadcyla or a clinical trial. We're going to get Kadcyla, we're not using Herceptin. Well, the Herceptin is in the Kadcyla because it's a conjugate; it's got Herceptin and a chemo helper*

	drug in it but it's just 1 medication. [provider 19, NP, oncology, private practice]
If it is more than a year, usually we go back. Remember, they are going to be on anti-HER2 for a year anyway, either Herceptin or Herceptin plus Perjeta and now we have even neratinib approved for extended adjuvant, so when you say "adjuvant therapy," that can go on for 2 years. So I'm talking about from the end of the adjuvant therapy. If it's been more than a year, you can certainly go back to Herceptin and chemo again and do it with Perjeta. [provider 7, MD, hematology/oncology, private practice]	*If it is a short recurrence, then I probably would do T-DM1. If it is a longer duration recurrence, then I would probably—I don't think I would revisit pertuzumab if they've already seen it, but certainly trastuzumab and any other cytotoxic therapy I think would be appropriate.* [provider 24, MD, oncology, academic]
It would depend on what they progressed on. You know, primarily, if they had progressed on, like, Herceptin alone, I would maybe consider using Perjeta in combination or perhaps T-DM1 if they progressed. [provider 11, MD, oncology, private practice]	*Generally, if someone has received pertuzumab and trastuzumab both in adjuvant and neoadjuvant settings then I'll go to T-DM1 as the first-line therapy in the metastatic setting.* [provider 13, MD, hematology/oncology, community]
This is an area that we just don't really have any answers to right now. It's become a real problem. However, depending on what their treatment-free interval was—so, say that they had been treated and they progressed 2 years after having their treatment, that's a patient that I may retreat again with Taxotere, Perjeta, and Herceptin. [provider 23, MD, oncology, private practice]	*If the patient has not had a duration or less than a year's worth of remission duration, I would consider using Kadcyla in those patients*. [provider 14, MD, hematology/oncology, community]
	It would depend how long ago their adjuvant therapy was. I mean, more than 6 months or less than 6 months, then you would go to second line vs try to re-challenge them with Herceptin. [provider 2, MD, hematology/oncology, academic]

Therapy at Recurrence Within 6 Months Following Initial Treatment

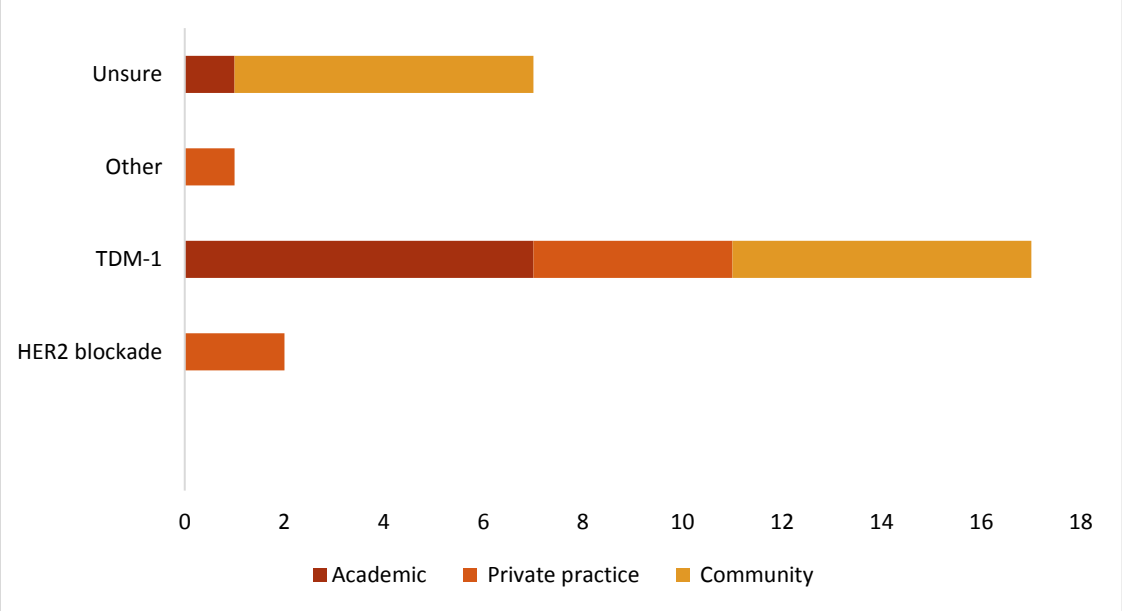
Clinicians expressed greater certainty in their likely treatment selections for patients whose disease recurs within a short treatment-free interval (which, as mentioned above, some clinicians defined as within 6 months while others defined it as within 12 months) following any previous treatment (**Table 7**). In this scenario, T-DM1 was the clear choice for oncologists and 1 radiation oncologist (**Figure 8**). Nonphysicians were unsure about potential options in this scenario.

Table 7. Rationale for Therapy Selection at Recurrence Within 6 Months After HER2-Targeted (Neo)Adjuvant Therapy for Early BC

Dual HER2 Blockade
Probably if they are HER2-positive, if they have received only Herceptin as an adjuvant therapy, did not see Perjeta, I may add Perjeta. [provider 6, MD, hematology/oncology, private practice]

It would depend on what they progressed on. You know, primarily, if they had progressed on, like, Herceptin alone, I would maybe consider using Perjeta in combination. [provider 11, MD, oncology, private practice]
T-DM1
If they are less than 6 months, I would probably use an alternative agent—Kadcyla or otherwise—again, depending on what they have received previously. If they have received Kadcyla and it's less than 6 months since completion, I would be looking at lapatinib or neratinib. [provider 14, MD, hematology/oncology, community]
Kadcyla, that would be my first-line option for someone if it's been less than 6 months. [provider 2, MD, hematology/oncology, academic]
So then it becomes harder because I feel like they're going to progress really soon. So if they were getting Herceptin-pertuzumab, then I would move on to Kadcyla. But if it's a patient who's kind of looking well, feeling well, and it's just scans that are beginning to look scary, then sometimes I'll just reuse what we did before. [provider 4, MD, hematology/oncology, community]
Well, it depends on what was the free interval between the cessation of their adjuvant/neo-adjuvant treatment and the demonstration of stage IV disease. If it's less than a year, then I'm typically not going to use Herceptin and Perjeta again. I might go right to T-DM1. [provider 12, MD, hematology/oncology, private practice]
Other
Less than 6 months, then we get concerned about resistant mechanisms. So what I was starting to say is that's when I may look at their estrogen receptor. That's going to be really important in assessing these patients, because now that neratinib has finally finished the NALA study and has shown some benefit in metastatic disease, that might be the scenario that I would consider. [provider 23, MD, oncology, private practice]

Figure 8. Therapy selection at recurrence within 6 months (n = 27).

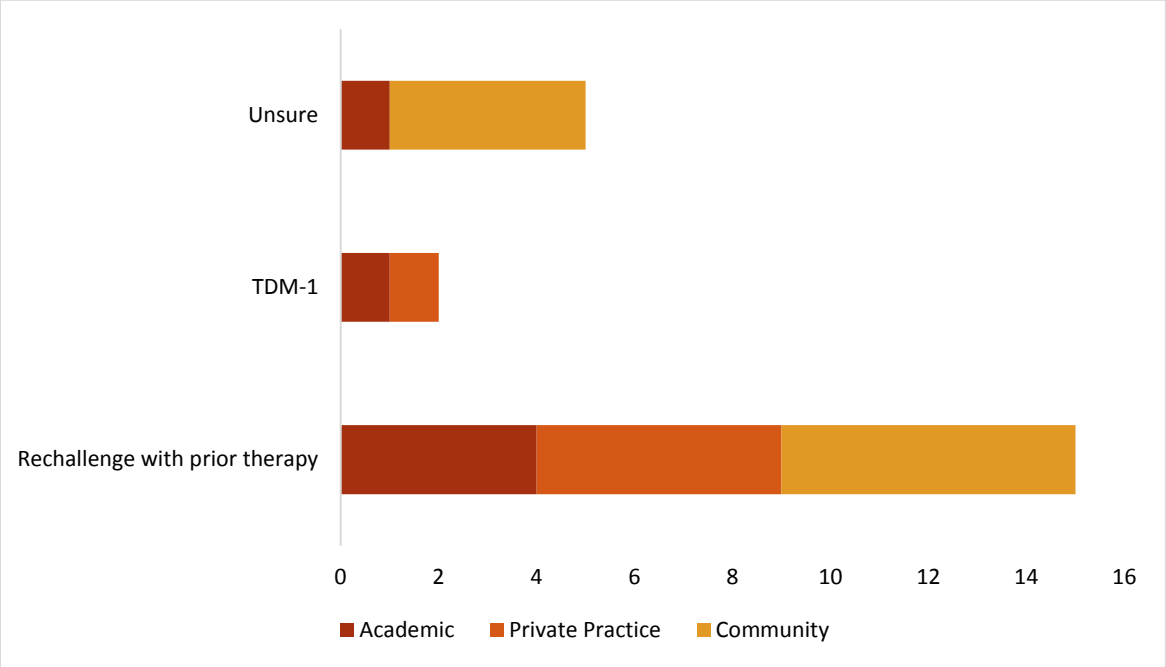


Therapy at Recurrence More Than 6 Months Following Initial Treatment

Interviewed clinicians were mixed in their views on which therapy they would likely select for patients whose disease recurs after a longer treatment-free interval following any previous treatment (which, as mentioned above, some clinicians defined as after more than 6 months while others defined it as after more than 12 months) (**Table 8; Figure 9**). Nonphysicians and radiation oncology clinicians were unsure about potential options in this scenario.

Table 8. Rationale for Therapy Selection at Recurrence More Than 6 Months Following Initial Treatment
Rechallenge with Previous Therapy
So, depending on if it's greater than 6 months, I will go back to the same treatment which we have done before. [provider 6, MD, hematology/oncology, private practice]
I often re-use whatever regimen I was on. A common scenario is they're on the 4-drug regimen, their scans are really good and I take off the chemotherapy and they're just on Herceptin-pertuzumab or just on Herceptin and if I'm able to get many months out of this, if I start seeing growth of lesions or whatever on a CAT scan, then I just reintroduce that chemotherapy and that way I can just get a year or more out of the same drugs without exhausting my first line of drugs. But if I do, then sometimes I just switch out my chemotherapy without moving on to Kadcyla, so I might switch from taxane to something else, like a Xeloda or a Navelbine or something without changing the Herceptin-Pejeta, especially if it's sort of a small recur, small progression, or not a major progression, just to try to get more mileage out of the medication. [provider 4, MD, hematology/oncology, community]
I think if they've been on treatment for 12 months and they had a good response to the prior option, meaning while they were on that option they tolerated the treatment well, I'll likely give it a shot with that same option again, especially if there's not rip-roaring disease causing a lot of visceral crisis and things like that. [provider 11, MD, oncology, private practice]
The only thing that really matters and the only thing that should matter is how long they relapsed after their last receipt of Herceptin. I believe in the CLEOPATRA trial you could go on if you had relapsed at least after 12 months after your last dose of Herceptin. So if they had adjuvant Herceptin and relapsed more than a year later, I would still give them the CLEOPATRA regimen. [provider 26, MD, hematology/oncology, academic]
Oftentimes we'll give chemo plus either Herceptin and/or pertuzumab. [provider 13, MD, hematology/oncology, community]
I would definitely do trastuzumab, pertuzumab, docetaxel. [provider 25, DO, oncology, community]
T-DM1
So the HER2 that we were using before, we may not—even whether it's 6 months or 1 year—I tried to not use the same drug again. We would like to change to some other lines of conjugate monoclonal antibodies and then again, looking at chemo, what they've got, whether they've got hormonal chemotherapy, what type, and then what type of options we have—but I would've mostly changed the HER2-neu treatment that the patient got the first time and then change it to a different one. [provider 20, MD, oncology, academic]
I would try Kadcyla, maybe—try to see if I can use that then. [provider 2, MD, hematology/oncology, academic]

Figure 9. Therapy selection at recurrence more than 6 months after initial therapy (n = 22).



Practice Gap #5: Challenges in Managing Patients With HER2-Positive MBC and CNS Disease

A majority of clinicians would switch systemic therapy in a patient with brain-only progression, in contrast to the expert recommendation to continue with the same systemic therapy and treat CNS metastases with local therapy. Managing patients with leptomeningeal disease and identifying radiation necrosis after radiation therapy are significant challenges in the management of CNS disease for clinicians in all specialties, including radiation oncology. Most clinicians are imaging symptomatic patients when they present with metastatic disease vs at baseline. Few clinicians, even radiation oncologists, are aware of investigational therapies that have shown activity in patients with CNS metastases after available standard-of-care options.

Standard of Care for Patients With HER2-Positive MBC and CNS Disease

Upwards of 40% to 50% of patients with HER2-positive disease eventually develop CNS metastases during their disease course.[16] Because of this high incidence, it is recommended that clinicians have a low threshold for brain MRI screening if CNS disease is suspected.[23] Patients who do develop brain metastases should receive appropriate local therapy, whether surgery, whole-brain radiotherapy, or stereotactic radiosurgery, and if indicated, systemic therapy. However, patients whose systemic disease is controlled should remain on their current systemic therapy while receiving local therapy for their CNS disease.

Investigational HER2-Targeted Therapies With Promising CNS Activity

With such a high incidence of CNS metastases and because current standard-of-care therapies for HER2-positive MBC are not CNS penetrant, better options for the prevention and treatment of brain metastases are needed in this setting.[16] Due to their small size and improved ability to penetrate through the blood–brain barrier compared with current standard-of-care therapies and other investigational agents, HER2-targeted TKIs are the most promising candidates for this purpose. In fact, both neratinib and tucatinib have demonstrated CNS activity in patients with pretreated HER2-positive MBC. Most recently, neratinib plus capecitabine was shown to reduce time to intervention for CNS metastases vs lapatinib plus capecitabine in the phase III NALA trial (22.8% vs 29.2%, respectively; P = .043), suggesting that neratinib is more effective in the CNS than lapatinib.[17] Tucatinib in combination with capecitabine and trastuzumab showed a promising ORR of 42% (5/12) in patients with measurable brain metastases in a phase I study. In combination with T-DM1, it showed a brain-specific ORR of 36% in patients with measurable disease and a median PFS of 6.7 months among the 30 patients with brain metastases.[5,18]

Baseline Screening for CNS Disease

As per the updated American Society of Clinical Oncology guidelines,[23] most of the clinicians we interviewed, including radiation oncology clinicians, said that patients typically receive an MRI scan when they begin to exhibit symptoms indicative of CNS disease (eg, changes in vision, falls, headaches, coordination changes).

> *I would say most of the time the medical oncologists that are seeing the patient hear about certain complaints—let's say headaches, nausea, neurologic deficit—and then they order an MRI and then, if they find something that's suggestive of metastatic disease, then they get referred to us for palliative radiation.* [provider 21, MD, radiation oncology, community]

A small group (n = 8) of clinicians across practice settings prefer to screen patients at baseline when they present with metastatic disease as part of the typical workup (**Table 9**).

Table 9. Rationale for Baseline CNS Disease Screening
My typical workup would include usually a CAT scan of the chest, abdomen, and pelvis and a bone scan. I, personally, do do a brain MRI on every patient with metastatic HER2 breast cancer. I think the rate is high for brain metastases, and I always get a heart echocardiogram as well on the patient, for cardiac clearance for their therapy. [provider 25, DO, oncology, community]
If they're metastatic, they're scanned from head to toe. PET scan to see how active the tumor is. CAT scan, MRI, not all of them, but one of the other—just scan the brain, a whole-body scan to see where all the tumor has travelled to. [provider 1, APN, oncology, community]
Most of the time I would start with CAT scan chest, abdomen, pelvis, and bone scan. Sometimes when they are found to have some concern from metastatic disease, they may have already come to me with some imaging, CT, and then we may obtain a PET scan and then proceed with the biopsy. If they can tolerate MRI, then I usually prefer the MRI with and without contrast. If they can't tolerate MRI, then I try to do CT of the head with contrast. [provider 8, MD, oncology, private practice]

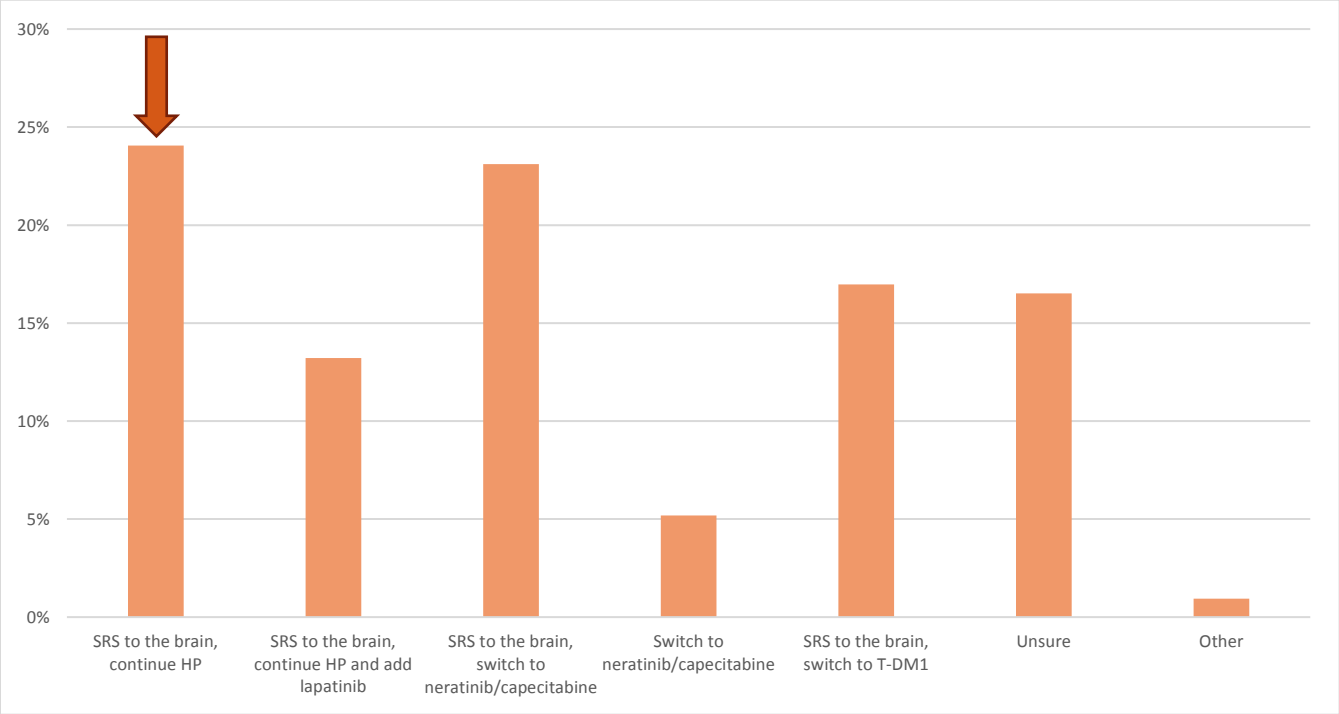
A majority of interviewed clinicians say they monitor patients for CNS disease symptoms and have a low threshold for suspicion of brain metastases ("*at the slightest hint of any concern of CNS disease we'll get an MRI brain*"). Once patients are symptomatic, they liaise with radiation oncology and schedule imaging every 3-6 months throughout the treatment duration.

Case #3: Therapy Selection for Patients With CNS Disease

A 63-year-old woman is treated for hormone receptor–positive, HER2-positive MBC to liver/lungs with THP ⟶ HP. After 18 months, her disease progresses with 3 new lesions in the brain, each approximately 1 cm. There is no evidence of disease outside of the CNS.

Which of the following treatment options would be most appropriate for this patient?

Figure 10. Appropriate therapy selection for patients with CNS progression but stable systemic disease (n = 212).



Experts indicated that local therapy to brain metastases while continuing the current systemic therapy was optimal for this patient with CNS progression but stable systemic disease (**Figure 10**). A majority of survey respondents chose to combine local therapy and a switch of systemic therapy in contrast to the expert recommendation to continue with the same systemic therapy and treat with local therapy. Sara Tolaney, MD, MPH, was "*surprised that so many were switching [systemic] therapy with CNS only progression.*"

The clinicians we interviewed said that they collaborate with radiation oncologists and/or neurosurgeons to manage patients with CNS disease and determine the appropriate primary management modality. Localized radiation, whole brain radiation, and surgery (gamma knife) were the main approaches to primary management described by clinicians across setting and specialty. In line with survey data, interviewed clinicians varied in whether they would continue anti-HER2 therapy, stop systemic therapy, or switch agents during radiation therapy (**Table 10**).

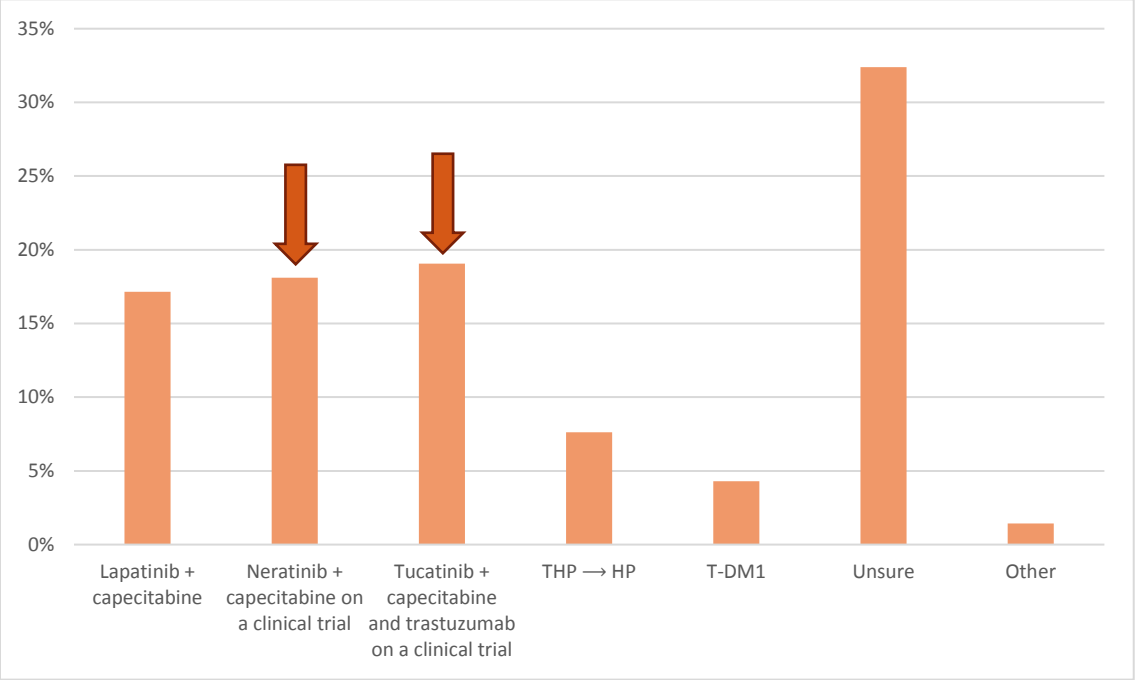
Table 10. Perspectives on Systemic Therapy During Radiation
Continuing Anti-HER2 Therapy
If we can radiate it without causing too much neurotoxicity, I would recommend radiation and then try to continue—if they have systemic disease too, then continue with the treatment. If not, we've also sometimes done Herceptin directed therapy to lepto-meningeal disease. [provider 2, MD, hematology/oncology, academic]
We would just typically treat them, you know, the same way, so the brain mets really wouldn't influence very much what we did. You know, in most cases we still would give the same type of chemotherapy regardless of if they have brain mets or not. [provider 16, MD, oncology, community]
The role of systemic therapies are relatively—systemic therapy for—just for the brain mets, it's not a great option. The reason is all the therapies, they don't go into the brain. So the main treatment is still radiation. [provider 6, MD, hematology/oncology, private practice]
They send the referral to us, we see the patient and I tell them—well, I tell the patient what I recommend and I also send a note to the medical oncologist about what the treatment plan is for the treatment of the brain mets. And then we coordinate as far as whether they're going to continue systemic therapy simultaneously or there might be a break during their treatment. That decision is usually made mostly by medical oncologists, although I don't necessarily discourage continuing systemic therapy, especially HER2 -directed, single -agent therapy during radiation treatment. [provider 21, MD, radiation oncology, community]
Switch Systemic Therapy
Depending on how much disease there is, we follow up with targeted radiation or whole-brain radiation. And then, systemically, I mean, those are the patients that you would like to use a small TKI and that's where neratinib may have more of a benefit, or perhaps using different chemotherapy that I know will cross the blood-brain barrier. [provider 23, MD, oncology, private practice]
So let's say a woman was on Herceptin-Perjeta and they develop brain mets that get treated with resection or radiation or both. Should we switch to Kadcyla, should we think about lapatinib, which we know has brain penetration? I would probably stop the Herceptin and Perjeta. I'm not sure they get into the brain as well as the other 2 drugs. But I have to tell the truth, I would have to review the literature on whether or not continued Herceptin-Perjeta is worthwhile in a person who had resected brain mets. [provider 12, MD, hematology/oncology, private practice]

Case #4: Investigational Therapies With Activity in Patients With CNS Metastases

A 58-year-old woman who was treated for T2N1 ER-negative, PgR-negative, HER2-positive (3+) invasive ductal carcinoma received preoperative TCHP and was found to have residual disease in the breast and lymph node. She subsequently received adjuvant T-DM1 for 14 cycles. Two years later, she presented with right upper quadrant discomfort and was found to have liver and CNS metastases. Biopsy confirmed the liver metastasis was ER negative, PgR negative, and HER2 positive (3+).

Which of the following treatment regimens would be most appropriate for this patient if CNS lesions were treated with local therapy as appropriate?

Figure 11. Clinician awareness of investigational therapies in patients with CNS disease (n = 210).



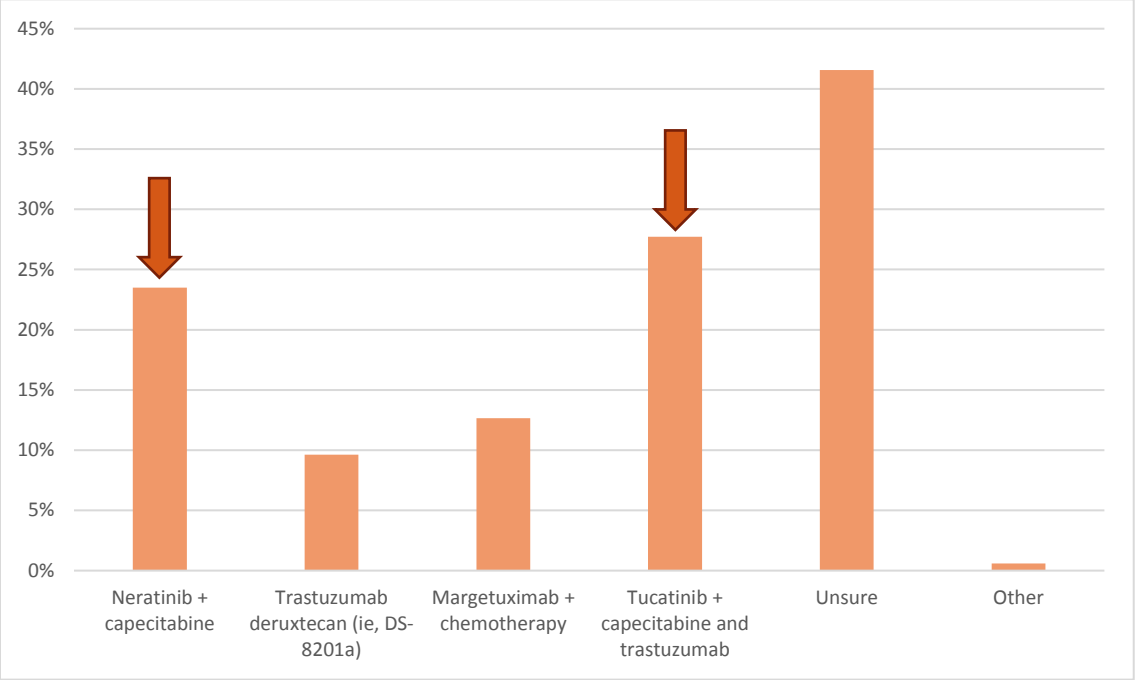
Experts indicated that enrolling this patient on a clinical trial evaluating 1 of 2 investigational HER2-targeted TKIs (neratinib or tucatinib) would be the optimal next step in the management of this patient with HER2-positive MBC and CNS metastases who received THCP and T-DM1 for early disease (**Figure 11, indicated by arrows**). A majority of survey respondents were unsure what treatment approach would be best for this patient or chose approaches that were not recommended by the experts.

Systemic Therapy in CNS Disease

To gain an understanding of the degree to which clinicians are aware of CNS-active agents under investigation for the treatment of pre-treated HER2-positive MBC, we asked survey respondents the following question.

Which of the following agents has/have shown preliminary antitumor activity in the CNS for patients with progressive HER2-positive MBC and mildly symptomatic brain metastases after previous treatment with trastuzumab, pertuzumab, and T-DM1 (select all that apply)?

Figure 12. Clinician awareness of regimens with activity in patients with progressive HER2-positive MBC and CNS disease (n = 166).



Consistent with survey responses to Case #4, only approximately 25% of respondents were aware that neratinib plus capecitabine and tucatinib plus capecitabine and trastuzumab have shown activity in patients with new CNS metastases after 2 previous lines of HER2-targeted therapy (**Figure 12, indicated by arrows**).

Breast cancer expert Sara A. Hurvitz, MD, FACP, was "*struck by the lack of consensus (and general confusion) about how to treat patients with CNS disease, [including] the lack of knowledge regarding new agents,*" a sentiment echoed by Sara Tolaney, MD, MPH.

Most Challenging Aspects of Managing Patients With CNS Disease

Survey respondents ranked the most to least challenging aspects in their care of patients with HER2-positive MBC and CNS metastases, with management of leptomeningeal disease followed by identifying radiation necrosis emerging as the most challenging (**Table 11**).

Table 11. Management Challenges in Patients With CNS Disease (n = 193)

Management Challenges, %	Most Difficult	⟷		Least Difficult
Managing patients with leptomeningeal disease	41.62	15.14	27.03	16.22
Identifying radiation necrosis following radiation therapy	13.90	34.76	31.55	19.79
Choosing between SRS vs WBRT	21.08	25.95	20.54	32.43
Choosing between surgical resection and SRS vs both for oligometastatic lesions	23.81	24.87	20.11	31.22

Interviewees expanded on this suite of challenges to include cognitive decline, steroid management, quality of life, trigger for discussing palliative care/life expectancy, speech and mobility impairment, symptoms (eg, headaches, dizziness, weakness, fatigue), behavioral changes (eg, depression), localized pain (eg, from gamma knife pain), lack of therapeutic efficacy, and social and functional issues (eg, loss of income, ability to work, insurance) (**Table 12**).

Table 12. Challenges Associated With CNS Disease

Clinical Challenges
Poor survival, worsening quality of life, quickly, short survival and so on. [provider 14, MD, hematology/oncology, community]
We have to put them on steroids so they're already in a weakened state from their systemic therapy. So the steroid, the addition of the steroid is a little bit challenging to manage, especially if they have side effects from their systemic therapy, which is usually diarrhea and fatigue. [provider 17, APN, radiation oncology, academic]
Controlling the disease is hard. I mean, we are talking now as like it is so easy, but many times this is a major problem and controlling the disease is a problem. You may give radiation, you may get control of a few months and then, 3 or 4 months later, it's progressing again. [provider 7, MD, hematology/oncology, private practice]
Functional Challenges
When brain mets are present, there's an overall level of progression that, you know, you start to see in the patient and they're not quite prepared for that, going from being completely mobile and independent, and some patients have a lot of weakness and dizziness and problems with vision. [provider 15, APN, hematology/oncology, community]

Most of them, it affects their ability to work. So they have a loss of income, sometimes a loss of insurance. It's really not so much symptom management; it's more functionality and being able to carry on regular activities with daily living. And being able to provide for themselves or their families. [provider 22, APN, radiation oncology, community]

Necrosis

Unfortunately, we don't have a very good way to tell whether it is necrosis or progression of disease. So there's some special MRI sequences we can do, but the results and now from even according to the literature, it's not really satisfying, a lot of time you still just don't know. So, in those situations, you either follow the patients and do another scan, because if it's necrosis eventually they become silent. If it's a tumor, it's going to continue to progress. [provider 18, MD, radiation oncology, community]

We see isolated brain mets more in HER2-positive patients who have received HER2-directed therapy as the first sign of relapse compared with HER2-negative patients…which is a shame because if you see an isolated relapse years after initial treatment, then it raises the issue of whether treatment directed towards the CNS with CNS-penetrating capabilities would be beneficial and, unfortunately, we don't have that yet. [provider 21, MD, radiation oncology, community]

Radiation Oncology Perspectives

The radiation oncologists (n = 2, both community) we interviewed viewed radiation as important palliative treatment in the metastatic setting, but also noted recent data suggesting a survival benefit of radiation in patients with oligometastases. Said one radiation oncologist: *I don't think that has been applied in routine daily practice, but I think that's something coming on the horizon*. [provider 18, MD, radiation oncology, community]

These clinicians held different perspectives on the role of and lesion cut-offs for stereotactic radiosurgery (SRS) vs whole-brain radiation. One noted that while whole-brain radiation has applicability in the context of very widespread metastases, the trend is to avoid whole-brain radiation therapy because of adverse events. She felt that SRS is becoming more routine for up to as many as 10 lesions on the basis of single institution studies. However, a radiation oncology APN pointed out that payer concerns pose barriers to SRS.

> *Insurance is a different issue and with a lot of them I'm very frustrated. You know, they have certain guidelines. Like, for example, some insurance companies say, "Okay, 3 brain metastases you can do radiosurgery, 4 you can't," and I can't and I hate to be forced into giving whole-brain to a patient when I know there are better options available.* [provider 17, APN, radiation oncology, academic]

Another radiation oncologist felt that the safety and efficacy of radiosurgery has only been proven in patients with up to 4 lesions.

> *We don't have randomized data that radiosurgery is as safe as whole brain. We've done patients with radiosurgery with more extensive disease, but usually, you know, we sort of cap it around 10 at the most. Anybody with less than 4, I strongly recommend radiosurgery to preserve their cognitive function, since there's no benefit to whole brain as far as survival, although there's benefit to whole brain in terms of control of their disease elsewhere in their brain, not in the radiosurgery-treated location.* [provider 21, MD, radiation oncology, community]

Both radiation oncologists typically recommended stopping chemotherapy during whole-brain radiation.

> *Normally, I don't have any restriction or I don't change their medication they are taking. Maybe sometimes I'll put them—I'll see if we're adding a medication, just to control the edema if they have symptoms of intracranial pressure, but otherwise I don't change their medication. I don't like to do whole-brain radiation concurrent with chemotherapy, so sometimes, if it's okay with the medical oncologist, they will stop the chemotherapy during the course of radiation therapy.* [provider 18, MD, radiation oncology, community]

> *I don't think that being on HER2-directed therapy is a contraindication to getting radiation, so I don't encourage stopping that treatment. However, if they're on Herceptin coupled with a systemic agent, then I usually would recommend withholding the systemic agent other than Herceptin or whatever the HER2-directed therapy may be. So most of the time they continue the HER2-directed therapy, but stop the chemotherapy.* [provider 21, MD, radiation oncology, community]

These community clinicians collaborated with their medical oncology colleagues via tumor boards and telephone. They were aware that their oncology colleagues were using T-DM1 through tumor board discussions and had a general perception that oncologists in their practice are early adopters ("they adapt very quickly").

> *Our medical oncologists have just started using it, so we've just started seeing that. I don't have a lot of experience, because those patients are new on that treatment…I'm kind of aware of the data because I went to a meeting and they presented data, it seems very promising.* [provider 18, MD, radiation oncology, community]

However, radiation oncology clinicians were unsure if their oncology colleagues were using novel investigational agents outside clinical trial participation (a typical response was "*My guess? I think they do*.")

Practice Gap #6: Challenges in Selecting Optimal Therapy for Patients With HER2-Positive MBC and Disease Progression Following Treatment With Current Standard of Care Therapies

Clinicians are challenged to identify optimal third-line therapy following progression after THP and T-DM1 for HER2-positive MBC and are unfamiliar with investigational agents/regimens that have shown clinical activity in heavily pretreated patients.

Lack of a Standard of Care in the Third-line Setting for HER-2 Positive MBC

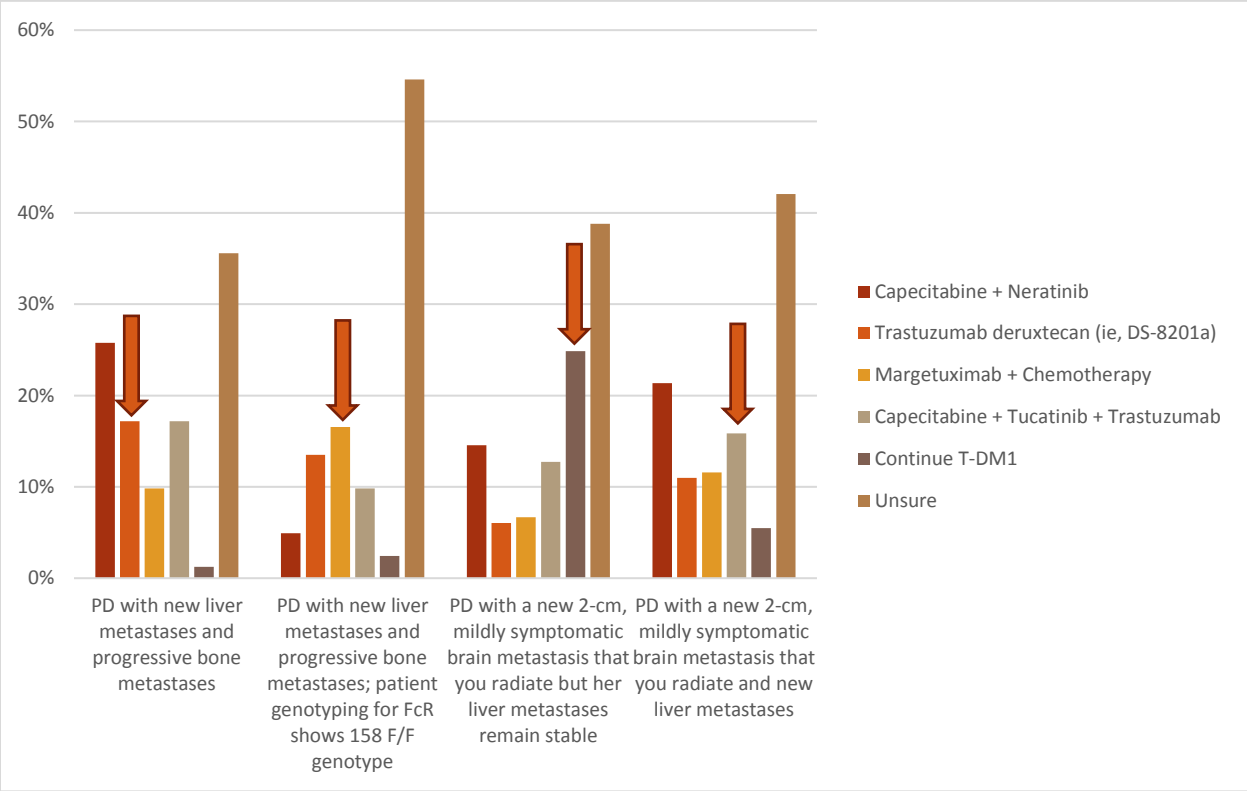
Despite strong standard-of-care options for the first- and second-line treatment of HER2-positive MBC, there is currently no standard-of-care therapy for the treatment of HER2-positive MBC after trastuzumab, pertuzumab, and T-DM1.[16] As introduced above, several novel HER2-targeted agents are under active investigation to fill this unmet need as well as to find better options for the prevention and treatment of CNS metastases. The HER2-targeted TKIs tucatinib and neratinib both have shown efficacy in patients who had received at least 2 regimens targeting HER2 and against CNS disease.[5,17,18] Furthermore, the HER2-targeted antibody margetuximab plus chemotherapy demonstrated a small but significant improvement vs trastuzumab plus chemotherapy in the phase III SOPHIA trial (5.8 vs 4.9 months; HR: 0.76; *P* = .033), with patients carrying a FCγRIII CD16A-F allele appearing to experience the greatest benefit.[24] There are also several improved HER2-targeted antibody–drug conjugates in clinical development. As mentioned above, trastuzumab deruxtecan (DS-8201), the closest new anti-HER2 antibody–drug conjugate to the clinic, showed an ORR of 54.5% in patients with HER2-positive MBC who were pretreated with T-DM1, as well as trastuzumab and pertuzumab in the majority of patients, with median duration of response and PFS not yet being reached.[6] Trastuzumab deruxtecan is being evaluated in phase III trials.[25.26]

Case #5: Choice of Therapy After 2 Previous Lines of HER2-Targeted Therapy

A 59-year-old woman with ER-negative, HER2-positive BC and metastases to her bones received first-line THP, and then developed progressive disease in her liver for which she received second-line T-DM1 for 8 months until again experiencing progressive disease.

Given the known limited activity of currently available regimens in the third-line setting, please indicate your top preferred choice of third-line therapy for each of the following clinical scenarios for this patient whose disease progressed while receiving T-DM1, assuming that all of the listed agents are available.

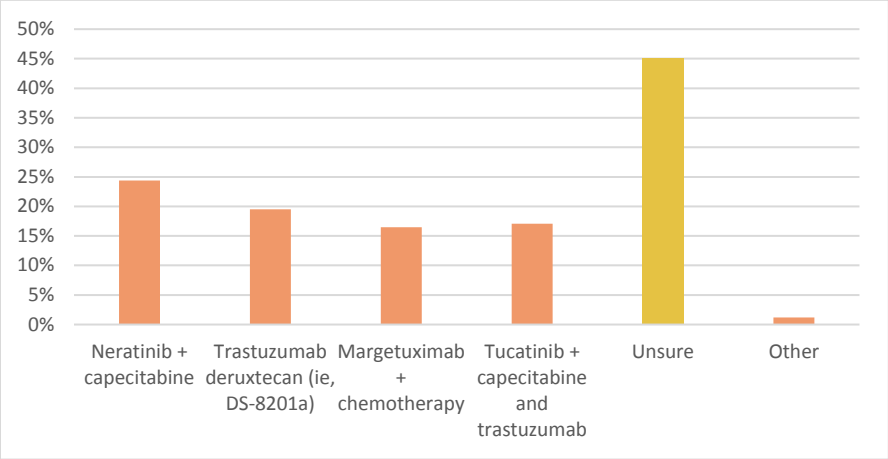
Figure 13. Preferred choice of third-line therapy in select patient scenarios of disease progression on T-DM1 (n = 165).



Arrows indicate reasonable options as defined by clinical experts (**Figure 13**). Surveyed clinicians are challenged to identify optimal third-line therapy following progression after THP and T-DM1.

Furthermore, surveyed clinicians were asked to select all of the investigational regimens that have demonstrated activity in the setting of progression after THP and T-DM1 (**Figure 14**).

Figure 14. Awareness of investigational agents in patients who received 2 or more previous lines of anti-HER2 therapy for MBC (n = 164).



Consistent with survey responses to Case #5, surveyed clinicians were unaware that there is evidence of clinical activity in heavily pretreated patients for ALL 4 of the investigational agents/regimens listed.

Contextualizing Therapy at Progression

Interviewed clinicians defined progression in the following ways:

- Unable to achieve median PFS
- Not responding to 2-3 cycles of treatment
- Symptomatic or radiographic progression as per RECIST criteria
- Changes in tumor markers.

Many of these clinicians were using T-DM1 as second-line therapy, but therapy beyond this setting was much more complex to ascertain. A small group said they were using novel or investigational agents at this point in therapy. **Table 13** illustrates the perspectives of clinicians concerning therapy at progression after multiple HER2-targeted therapies.

Table 13. Perspectives on Optimal Third-line Therapy

Chemotherapy and HER2 Blockade
In HER2-positive breast cancer, it's quite often that they can go for a third- and fourth-line treatment if they have a good performance status, or even if their performance status is not that good. I mean, apart from various comorbidities or age-related or factors that you cannot change with treatment, mostly all the patients go for a third-line treatment option, and particularly with an anti-HER2 therapy, either chemotherapy or an oral chemo-free option, just to ensure more quality of life. [provider 5, MD, oncology, academic]

If they have received hormonal therapy along with HER2-directed therapy, then they will switch to chemotherapy. If they already received one sort of chemo, I will switch to a different kind of chemotherapy. [provider 6, MD, hematology/oncology, private practice]
The best sequence. Let me think about that. So I think a lot of times that past chemo plus HER2-targeted agents in the first-line, past T-DM1. I think at that point a lot of it just becomes discussion of kind of toxicity and which chemo regimens they would or wouldn't want to have based on side effects plus Herceptin, really, essentially. [provider 13, MD, hematology/oncology, community]
If I have a sort of algorithm it's primarily going to be Perjeta-based treatment first, followed by T-DM1–type treatment second, followed by something like lapatinib third, and then probably a variety of Herceptin/chemo combos in fourth and fifth and so on afterwards. [provider 11, MD, oncology, private practice]
Novel/Investigational Agents
Targeted therapies, like Tykerb or—I don't know that there's a lot of targeted therapies approved for HER2, other than the Herceptin and Kadcyla. We've given pertuzumab to them in the adjuvant setting, so we're not reintroducing that. So, Kadcyla and then we do capecitabine, they're a load of Tykerb and look for trials. I mean we usually have trials available for those type of patients and that's why we have a fairly good number of ladies on trials. [provider 19, NP, oncology, private practice]
Depending on what they have been on, I usually try to use—yes, I still consider to use Perjeta and Herceptin in first line if I can, depending on what they've had before, if anything, and then follow up with Kadcyla as second line. And that's when I've tried to send patients for clinical trial for some of the other drugs that are being developed. [provider 23, MD, oncology, private practice]
If the patient progresses, then Kadcyla followed by either neratinib or lapatinib-containing therapy, so lapatinib plus capecitabine or neratinib plus capecitabine, depending on what we feel is the best tolerable regimen, as well as with metastasis neratinib may be favored in that situation. [provider 14, MD, hematology/oncology, community]
We still go with anti–T-DM1, we go to anti–T-DM1. If, again, if we don't see a quick response, we quickly go to the TKI therapy. And in this case we have now 2, actually. We have neratinib for adjuvant therapy, but actually, neratinib is a drug. I was a PI on first-line metastatic disease with neratinib over 10 years ago, but that study never showed life so the drug never got approved for the metastatic setting. And, finally, they found a way to approve it in the so-called "extended adjuvant" therapy, but now we start so see some more data in the metastatic setting, so there is no doubt it's a more potent drug than Tykerb, but it's also potentially more toxic to the GI tract. [provider 7, MD, hematology/oncology, private practice]
[We] go through the Herceptin, Perjeta, taxane, T-DM1…there certainly are third-line options. I mean, the most common third-line option is lapatinib/Xeloda. The NALA trial was just presented at ASCO 2019 and that compared neratinib/Xeloda with lapatinib/Xeloda. The results for neratinib/Xeloda were a little bit better, including a little bit better intracranial efficacy, so in terms of brain metastases, but neratinib/Xeloda is extremely hard to tolerate in terms of diarrhea. I have not had very much success with that regimen. [provider 26, MD, hematology/oncology, academic]

Practice Gap #7: Challenges in Treating Patients With Low HER2 Expression

There was broad consensus among interviewed clinicians that they would not treat patients with low or indeterminate HER2 expression with anti-HER2 therapies and low awareness that there are emerging therapeutic options for patients with low HER2 expression.

Treatment Selection in Patients with MBC and Low HER2 Expression

The results of the phase III NSABP B-47 trial demonstrated that patients with "HER2-low" early BC, defined as IHC1+/2+/ISH-, did not benefit from adjuvant trastuzumab and therefore should be treated as if they are HER2-negative.[20] Fortunately, new investigational HER2-targeted antibody–drug conjugates are showing promising efficacy in this patient population.[16] Trastuzumab deruxtecan (DS-8201) achieved an ORR of 50% (17/34) in patients with MBC and low HER2 expression in a phase I study.[6] Trastuzumab duocarmazine (SYD985) has also shown activity in this setting, achieving an ORR of 27% in hormone receptor–positive, HER2-low MBC and an ORR of 40% in hormone receptor–negative, HER2-low MBC.[21,22]

Clinician Rationale for Therapy Selection in Patients With MBC and Low HER2 Expression

Although many of the clinicians we interviewed noted that the best way to determine HER2 status remains an evolving question for research vs a practical concern in clinical settings, there was broad consensus that they would not treat patients with low or indeterminate HER2 expression with anti-HER2 therapies.

> *You hit the mark or you don't. If you don't hit the mark you're not HER2 positive.* [provider 24, MD, oncology, academic]

> *This was studied extensively in an NSABP trial and it was totally negative. There is no value of anti-HER2 in these patients.* [provider 7, MD, hematology/oncology, private practice]

Medical oncologists noted cytotoxic chemotherapy without HER2-directed therapy as the most common management approach and were aware of emerging therapies that might be appropriate for patients with low expression (only 1 clinician referred explicitly to trastuzumab deruxtecan). A few private practice and community-based oncologists reported that they would, in some equivocal cases, consider continuation of HER2-blockade in the metastatic setting.

> *We bring this up at tumor board all the time.* ***The guidelines would say don't treat. If you're asking me what I do, I sometimes will offer them just Herceptin****. I'll give them Herceptin and docetaxel, as an example. I have definitely seen some weak—some lower positive —I've seen responses subjectively, and I think there is some data. It's not huge data, but there are some data points to support some patients benefit. My rationale is Herceptin has very low toxicity, so I would offer it to the patient and watch their heart test every 3 months.* [provider 25, DO, oncology, community]

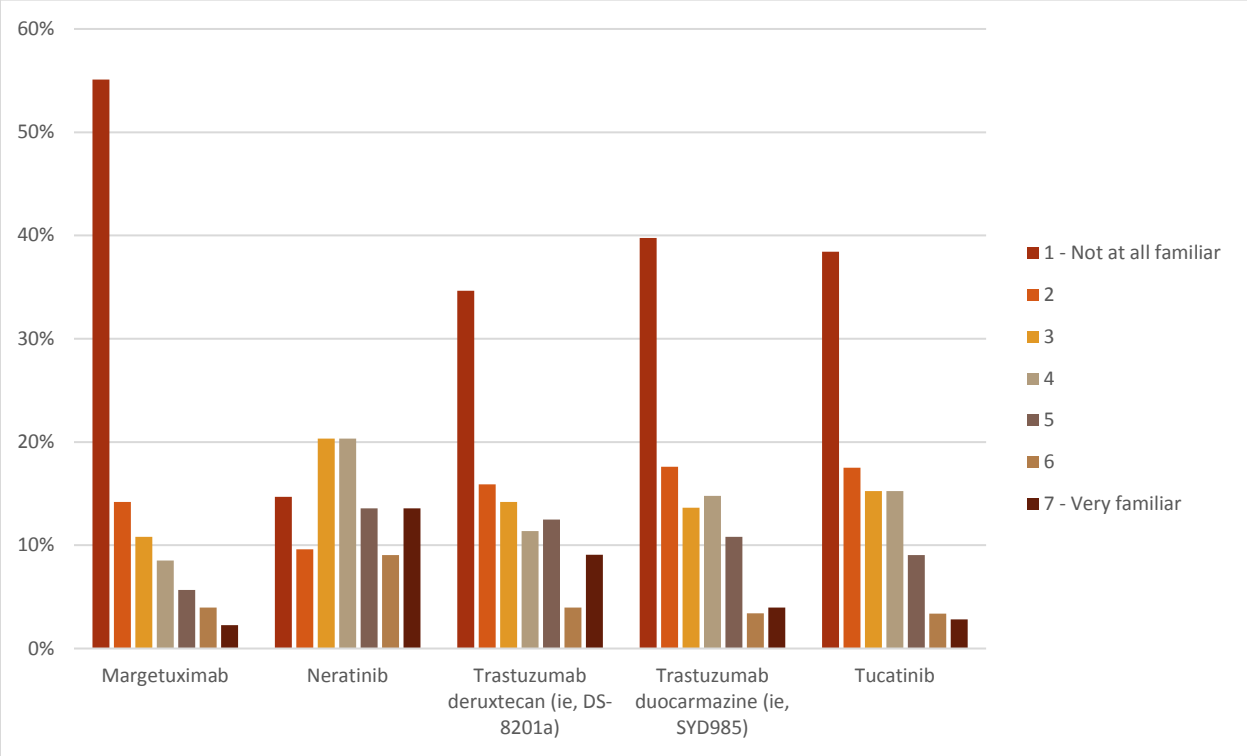
APNs were generally unaware of how low expression is treated in their practice setting.

Practice Gap #8: Deficits in Familiarity With Novel Agents

Clinicians are largely unfamiliar with novel agents being developed for the treatment of HER2-positive MBC or their associated toxicity profiles, and in interviews, their mechanisms of action. A majority consider only FDA approval based on phase III clinical data as sufficient evidence to incorporate a new agent or regimen into their practice for patients with HER2-positive MBC.

Survey data show that most clinicians are unfamiliar with several investigational agents currently being evaluated for HER2-positive MBC in ongoing randomized phase II and III trials (**Figure 15**). The highest level of familiarity among clinicians was with neratinib, which is currently approved by the FDA as extended adjuvant therapy for patients with HER2-positive early-stage BC.[27]

Figure 15. Awareness of investigational therapies in randomized phase II/III trials (n = 177).



Furthermore, only 30% of survey respondents (n = 156) were able to identify tucatinib as a more selective HER2 TKI compared with lapatinib and neratinib, both of which are currently approved for different indications in patients with HER2-positive BC.

This trend of unfamiliarity with investigational agents was mirrored among interviewed clinicians as illustrated by **Table 14**. Although approximately one third of interviewees mentioned being aware of either investigational HER2-targeted TKIs or antibody–drug conjugates, few were able to identify specific drugs in these classes or describe their mechanisms of action. Clinicians most frequently referred to neratinib. Notably, clinicians who referred to specific drugs by name were involved in clinical trials.

Both Sara Tolaney, MD, MPH, and Sara A. Hurvitz, MD, FACP, were surprised by how many clinicians were unfamiliar with the new drugs and their mechanisms of action, with Sara A. Hurvitz, MD, FACP, remarking, "*Being in the field, I thought that everyone had heard about these agents…but the general lack of knowledge…certainly supports the need for CME programs*" on this topic.

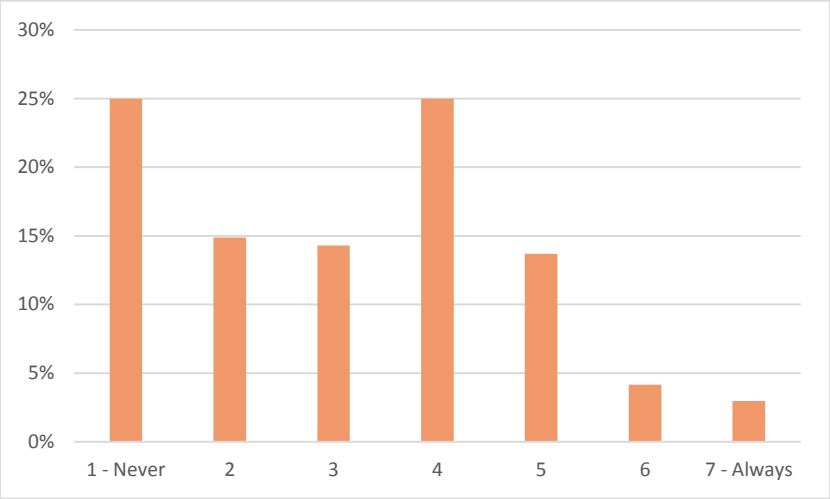
Table 14. Clinician Identification of Novel/Investigational Agents

Antibody–Drug Conjugates
There's another one that's coming down the pike, it's a Seattle Genetics product. I don't remember it right off the bat. [provider 14, MD, hematology/oncology, community]
Off the top of my head, I would just say the TULIP trial. [provider 2, MD, hematology/oncology, academic]
I mentioned trastuzumab diotoxin-something—I forgot its full name. Again, it looks very compelling data, the one I saw, and it's already moved to phase III trial. [provider 7, MD, hematology/oncology, private practice]
I'd say—somewhat. There's some exciting novel agents coming down the pipeline which I've sort of heard about with regards to specific antibodies targeting HER2. You know, the 8201 really is the one that I've heard the most about. What's stuck out in my mind is just the fact that they're targeting HER2-low disease as well. [provider 13, MD, hematology/oncology, community]
TKIs
I'm sure I've heard the spiel but…[provider 19, NP, oncology, private practice]
I think that there are TKIs, which are obviously affecting downstream signaling, but I wouldn't know much beyond that. [provider 11, MD, oncology, private practice]
The ones that target HER2. So, give me an example. Nothing immediately comes to mind. [provider 12, MD, hematology/oncology, private practice]

Scenarios Under Which Clinicians Will Use New Agents

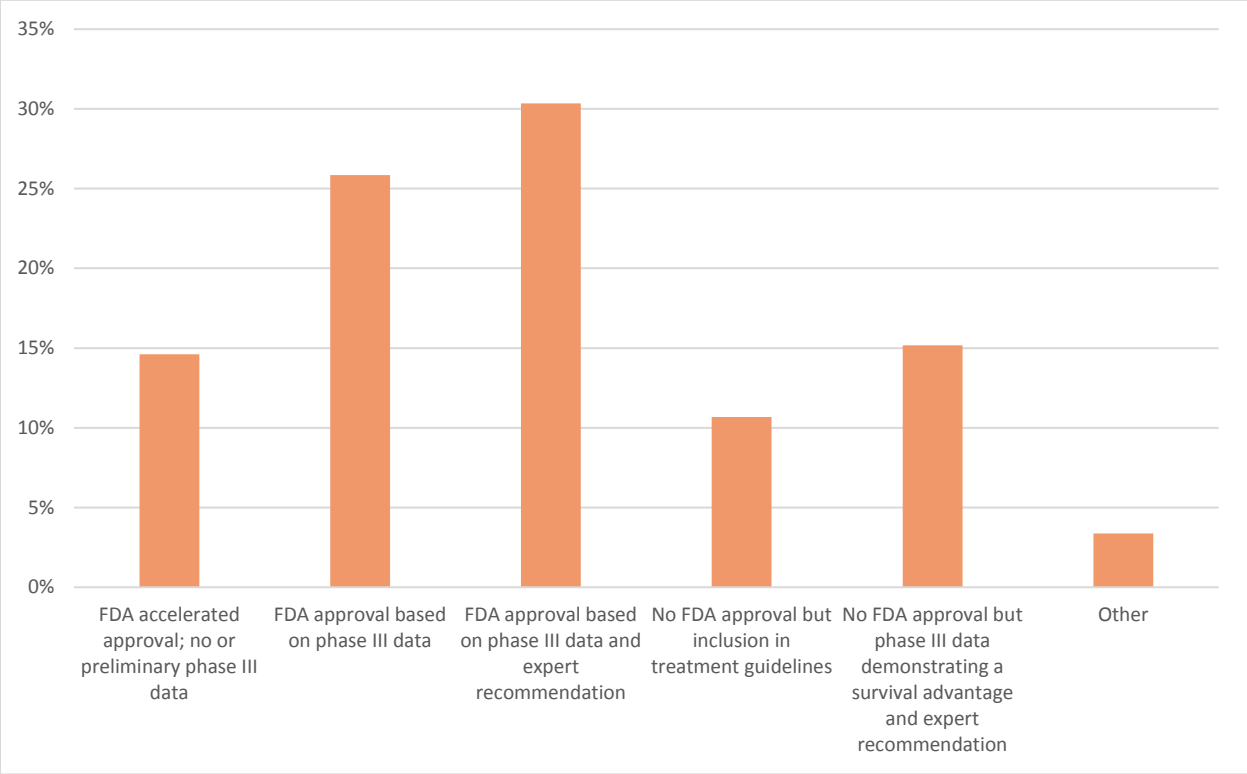
Over one half of surveyed clinicians are unlikely to use newly approved or investigational therapies if they are not familiar with how the agents work (**Figure 16**). Given the lack of familiarity of clinicians with the agents under development for HER2-positive MBC noted earlier (ie, neratinib, tucatinib, margetuximab, trastuzumab deruxtecan, and trastuzumab duocarmazine), it is unlikely that they would consider these agents as options for their patients on a trial or when they become available in the clinic.

Figure 16. Likelihood of using new agents if unfamiliar with drug class or mechanism of action (n = 168).



More than one half of survey respondents (55%; n = 130 respondents) indicated that they consider FDA approval based on phase III evidence sufficient evidence to incorporate a new agent or regimen into their practice for patients with HER2-positive MBC (**Figure 17**).

Figure 17. Preferred level of evidence for using new agents (n = 178).



The clinicians we interviewed provide additional context to the trends observed in the survey. A majority across setting and specialty noted they would use novel agents if accompanied by phase III clinical data, and the rest said they would when approved by the FDA and when other treatment options were exhausted (**Table 15**). One interviewed clinician, who described himself/herself as an "*early adopter,*" said that they would use investigational agents in practice following treatment with T-DM1, or following third-line treatment.

Table 15. Rationale for Using New Agents

FDA Approved
In terms of using new drugs that are approved, I feel very comfortable doing that based on both safety and efficacy data. [provider 26, MD, hematology/oncology, academic]
Once they're FDA approved, usually, that's when we integrate them into our treatment pathways. [provider 16, MD, oncology, community]
Phase III Clinical Data
Phase III trials are preferred where you are getting, you know, the investigational agent vs the standard of care. [provider 2, MD, hematology, academic]
I think the best is phase III clinical trials. But sometimes we can start looking at the phase II and the mature data again of phase III. [provider 6, MD, hematology/oncology, private practice]
They do if there is strong data over—let's say—Herceptin's been around for a while and if there's data suggesting that the treatment is superior or—either instead of or in combination, particularly when it comes to survival, OS, and then possibly as a second or third line of treatment if the first line fails. [provider 21, MD, radiation oncology, community]
Other Treatment Exhausted
At the tail end, either if they are just cycling too fast through their therapies or they are just not responding to therapy when biomarker wise and analyzing off-path, they really should be responding but they're not, then I feel like maybe they just need different drugs that we don't have as part of standard regimen. [provider 4, MD, hematology/oncology, community]
I would say any patient who has disease progression beyond the—I would say the top 3. So you always get concerned about the HER2-positive patient that should have had a durable response who's seen pertuzumab, who has seen T-DM1. Yeah, those are the patients that you kind of need to think a little bit out of the box. [provider 24, MD, oncology, academic]
Investigational
Very, very likely. I'm very excited about that. The question—so, I'm an early adopter, so if there's an opportunity, as I mentioned. So then the next question you might ask is: where if I might use and so on. And so then my answer would be post Kadcyla, before even neratinib or lapatinib, based on what I feel, what I perceive is the better efficacy and the better tolerability. So, basically, Herceptin, Perjeta chemotherapy, hormones, whatever the case may be, followed by Kadcyla, followed by novel agent. [provider 14, MD, hematology/oncology, community]

Identification of Adverse Events Associated With HER2-Targeted Agents

Many surveyed clinicians were not able to identify the most concerning adverse events associated with various agents used in the treatment of patients with HER2-positive MBC as well as agents under investigation in this setting (**Table 16, most concerning adverse events for each agent highlighted in gold**). This was particularly evident among agents that have no currently FDA-approved indications (ie, trastuzumab deruxtecan, margetuximab, and tucatinib). According to clinical experts, a lack of knowledge about an agent's toxicities and their management can be another barrier to uptake of new agents.

Table 16. Identification of Concerning Adverse Events Associated With Agents Used in HER2-Positive MBC (n = 154)

Adverse Events, %	Pertuzumab	T-DM1	Neratinib	Trastuzumab deruxtecan (DS-8201a)	Margetuximab	Tucatinib
Diarrhea	49.35	9.74	49.35	9.74	9.74	19.43
Infusion-related reaction	25.90 (rare)	15.83	6.47	22.30	33.09	4.32
Interstitial lung disease	11.11	14.81	14.81	16.30	11.11	6.67
Increased AST/ALT	10.22	35.04	18.25	10.95	8.76	12.41
Neuropathy	11.19	29.85	8.21	12.69	8.96	8.96
Thrombocytopenia	7.14	35.00	13.57	12.14	10.71	11.43
General myelosuppression	12.14	28.57	17.14	20.00	14.29	12.14

Practice Gap #9: Inconsistencies in Defining Quality of Life and Palliative Care

Although quality of life factors into discussions about goal and expectation setting, there is little consensus among clinicians about how best to define quality of life. Similarly, clinicians view palliative care as an important component of addressing quality of life but vary in how they define palliative care and when they initiate discussions about palliative care with their patients.

Quality of Life

Clinicians identified several factors as being linked to quality of life, including disease control, toxicities, and pain. Clinicians factored quality of life into discussions about goal and expectation setting but varied in how they defined quality of life (**Table 17**).

Table 17. Defining Quality of Life

Quality of life is something that is not obvious from the data*. Not all studies have looked at quality of life, so I would say we would kind of summarize that the most important quality-of-life determinant is (a) is the disease able to be controlled and (b) [what is] the type of toxicity one would expect from the treatment? So if we are diligent and appropriately following and managing the side effects then, hopefully, we can maintain quality of life and minimize the deterioration and if we control the disease, we will also maintain the quality of life. That is what is expected, but in terms of numerical and statistical results, we don't always have that.* [provider 14, MD, hematology/oncology, community]
It's whatever the patient defines it as and that changes along their disease trajectory*. We see it change. Something that's unacceptable in their mind at maybe the time of initial diagnosis becomes acceptable when they are faced with maybe stopping treatment and going on to kind of a hospice-type situation. So we have to constantly re-evaluate that.* [provider 17, APN, radiation oncology, academic]
A lot of docs get patients really fixated on bloodwork and markers and this and that and my approach is different from that. I'm very patient centered, so it's like, "How are you feeling?" and "How is this disease affecting your activities of daily living?" and that's what I measure. [provider 23, MD, oncology, private practice]

APNs and NPs were more likely to view quality of life as less of a fixed entity and more as a consideration that changes as patients move through treatment options. APNs and NPs also described quality of life as something they would be more likely to explicitly discuss with patients than would oncologists or other specialists.

Palliative Care

Clinicians viewed palliative care as an important component of addressing quality of life but varied in how they defined this concept. Clinicians seemed split on defining palliative care as equivalent to supportive care or defining it as end-of-life planning (**Table 18**). Others distinguished symptom management in early treatment from end-of-life planning, but referred to both as palliative care. As one PA put it:

> *It's really interesting you bring that up, because I was just at ASCO and they were talking about the difference between palliative and supportive care and that* ***they're using them interchangeably when they're really not****.* [provider 9, APN, oncology, academic]

Clinicians also differed in their timing of discussing palliative care with their patients. Broadly, discussions about palliative care occurred either at the initial treatment planning visit or later in the disease/treatment trajectory as therapy failed. The timing of palliative care discussion likely hinges on how clinicians define palliative care. Clinicians who viewed palliative care as symptom management and/or supportive care throughout the treatment trajectory were more likely to introduce palliative care into early discussions with patients and to view it as integral to oncology care. Clinicians who viewed palliative care as end-of-life planning were more likely to initiate a discussion about palliative care after multiple lines of treatment (**Table 18**).

Table 18. Definitions for Palliative Care
Palliative Care as Symptom Management
*What I usually do in patients regardless of the breast cancer or the type of cancer, when you are dealing with advanced cancer, whether the patient is symptomatic or asymptomatic**, I usually encourage and make sure that they are seen and been plugged in with a palliative care specialist**, not only about symptom management but also managing the expectation, managing anxiety, and all of the other things that come with the cancer diagnosis.* [provider 14, MD, hematology/oncology, community]
*We actually frame it from the standpoint of that **it's an extra layer of support**. That it does not mean hospice. We are pretty upfront with that, that it's another team member or members to manage their symptoms, to optimize their quality of life basically.* [provider 17, APN, radiation oncology, academic]
***We talk about palliative care at the very beginning of the stage IV disease discussion**. In fact, we refer newly diagnosed stage IV patients to our palliative care to fine-tune any of the kind of symptomatic treatments that they're already on. We've learned that early use of palliative care, both medicinal as well as psychosocial support, makes patients live longer and live better, so that's a standard of care in our cancer center.* [provider 12, MD, hematology/oncology, private practice]
Palliative Care as End-of-Life Planning
***End of life planning is during later end of cancer journey**, not from the beginning because a lot of patients, they don't want to hear from the start but they are willing to listen at the later point of their treatment journey.* [provider 6, MD, hematology/oncology, private practice]
***We talk about if they're getting towards the end of what we can offer them medically**—like, if they've had multiple lines of therapy and they continue to progress, then we typically say, "Well, this is like a third-line therapy and the results from this might not be so good, so it's also an option to not do the therapy, just do best supportive care, palliative care, where we're just trying to minimize symptoms related to cancer, but we're not actively treating it with anything." So we kind of usually introduce that when we think we're getting towards someone who has less than 6 months to a year to live, we start talking about those types of things*. [provider 16, MD, oncology, community]
*It depends on the situation. If I have an elderly patient coming in a wheelchair, of course we'll talk about end of life from day 1, but when I'm talking to a young patient—and we have a lot of people in their 40s and 50s—and here **we're telling them the survival median is 5 years, you can go 10 years, especially if they have limited metastatic disease, they are not going to be interested in hearing this at all.*** [provider 7, MD, hematology/oncology, private practice]

Main Clinical Challenges in the Optimal Treatment of HER2-Positive MBC

The top 3 clinical challenges that interview participants identified as barriers to optimal treatment and patient management were disease progression, symptom management, and CNS disease (Figure 18).

Figure 18. Frequency of reported clinical challenges in interviews (n = 26).

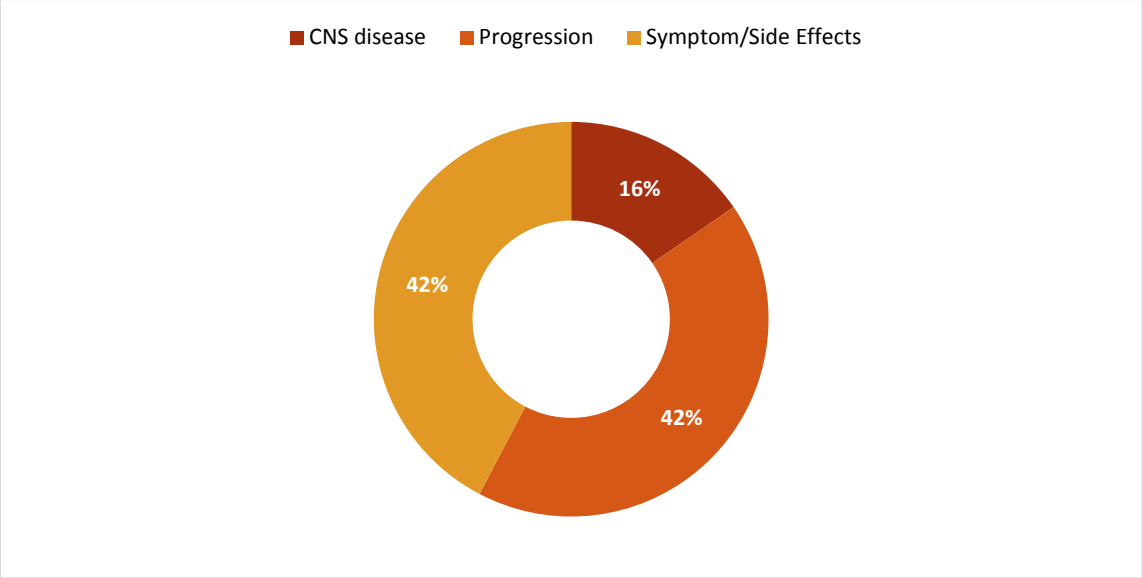


Table 19 summarizes how participants described these challenges.

Table 19. Clinician Descriptions of Barriers to Optimal Treatment

Symptom and Adverse Event Management
▪ *I guess I would say some of the symptoms. Symptoms management with those patients as far as, you know, some of the therapies can cause the diarrhea pretty bad. So that would be 1 of the main ones and just the fatigue, just the not feeling well. Less often any cardiac stuff.* [provider 17, APN, radiation oncology, academic]
▪ *Occasionally, we start to see a cardiac problem. I mean, when you start to see a drop in ejection fraction, etc, which may happen, sometimes you have to do what's best for the patient and sometimes we have changed therapy to the oral TKIs because of that.* [provider 7, MD, hematology/oncology, private practice]
▪ *Symptom management. You know, side effect management. Dealing with the fear of recurrence. Helping patients manage being able to still function while going through treatment. When someone's got to have chemotherapy and surgery, radiation, how am I going to help them to continue to function in the workplace, possibly, as we're talking mostly women here, if they have families, if they have children, you know. These are all the challenges. Helping them deal with all the emotional impacts of it. You know, self-image issues with losing hair, with losing breasts, all these body image changes. It's a lot.* [provider 10, APN, oncology, community]
▪ *A lot of my younger patients, they do tend to have more side effects, maybe because I'm using more chemotherapy or the fact that they just don't get breaks, like others can. They kind of move from one line to the next line in fairly rapid succession. So side effect management becomes pretty hard for a lot of people. There's a lot of back and forth to the clinic. Sometimes I have to admit*

them to the hospital. Management of diarrhea is pretty challenging and that tends to be a not uncommon side effect on anti-HER2 drugs. So that becomes difficult because it requires a lot of education, people are very hesitant taking Imodium or lomodal or whatever. So there's just a lot of back and forth. [provider 4, MD, hematology/oncology, community]

Progression

- *Number 2 is patients who become refractory or progress on Kadcyla. Although we have at least 1 other option or 2 other options, the duration of response is short, the toxicity is significant and that's not—there is room for improvement in those particular patients for outcome.* [provider 14, MD, hematology/oncology, community]
- *With HER2, we usually can kind of extend people's lives by years, but eventually they all can usually end up succumbing to the disease and so that's a challenge when you're dealing with younger patients and they have families and they're worried about passing and leaving—you know, who's going to take care of their kids or their parents or whoever else they're kind of taking care of. So it's challenging to deal with that.* [provider 16, MD, oncology, community]
- *The challenges are that the literature sometimes is more limited about the success rate of radiation in particular cases that may not be so common and the follow up for patients with HER2-positive cancer's not as long as the HER2 negative because even though it's been around for, now, nearly, maybe a decade and a half or so, we still don't have as much follow up as we do with other patients*. [provider 21, MD, radiation oncology, community]
- *A lot of the drugs that we use for metastatic disease only have been moved up earlier in treatment and so my concern has always been, when the patient progresses, when they have metastatic disease and they progress and we've used so many of this drug already upfront, how we're going to have to treat that. Also, patients may have a limit to their insurance allocation and drugs are so expensive and women are living so long with metastatic disease that they get to that limit, then how are they going to pay for treatment?* [provider 23, MD, oncology, private practice]

CNS Disease

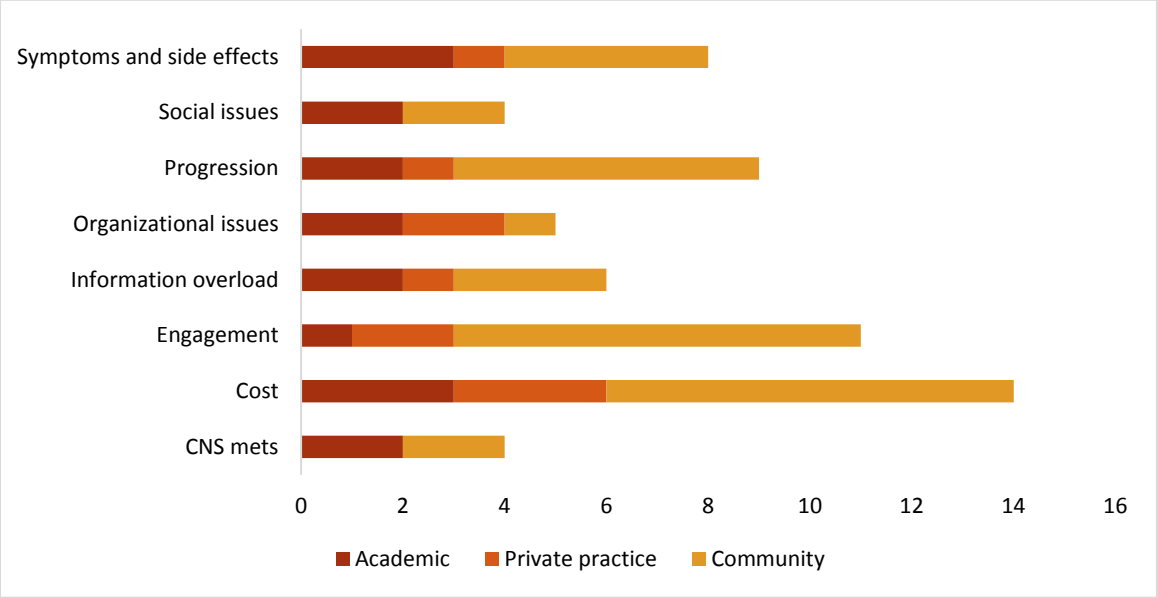
- *Number 1 on my list would be brain metastases. You know, depending on the study that you look at, 30% to 50% of women with metastatic HER2-positive breast cancer will have brain metastases and we have many, many drugs that treat HER2-positive breast cancer, but we do not have many drugs that cross the blood–brain barrier and are effective in the treatment of breast cancer once it's spread to the brain. So that's a huge clinical problem and even though we've made strides in the OS of HER2-positive breast cancer over time, we actually have not yet made strides in women who develop brain mets; their survival is still about 2 years after formation of a brain met. And we're getting there. There are some drugs coming down the pipeline. One of them is called tucatinib, neratinib has CNS penetrability, so does lapatinib. T-DM1, which is the second line, which is standard of care in the second line, has some CNS activity as well.* [provider 26, MD, hematology/oncology, academic]
- *Brain metastases is a big issue and the agents are not as effective in the brain. I think that's a big problem*. [provider 26, DO, oncology, community]
- *The biggest clinical challenge, in my mind, is occurrence of or progression of CNS disease, intracranial metastasis, CNS metastasis. Those patients have a poor prognosis. Currently, existing therapy, very few of them have good data and a few of them good activity, so there's a tremendous unmet need, which may be fulfilled in the near future or at least to some extent would be filled by some of the newer active agents that are coming down the pike.* [provider 14, MD, hematology/oncology, community]
- *HER2 positive, they tend to metastasize to the brain, so sometimes if they have brain mets, that becomes an issue*. [provider 2, MD, hematology/oncology, community]

Patient Engagement

- *The other challenge is to keep patients engaged. In my experience with these patients, the first 6 months to a year they are very engaged; beyond that, the enthusiasm sort of cools down and they are coming in all the time, getting treatment. You have to keep them energized. You have to remind them what we are doing here to keep them involved, because this is a long therapy and it gets boring and some patients lose interest. Like, "Okay, I feel fine, I don't know if I want to keep doing this." It's our job to keep them engaged.* [provider 7, MD, hematology/oncology, private practice]
- *I do think categorically when you're first meeting patients that are HER2 positive and telling them the duration of therapy, everybody's face sinks when you tell them it's going to be a year of therapy, but it doesn't carry over to noncompliance. Everybody's compliant, but there is this moment when they're like, "A whole year?," so you have to get people to buy in.* [provider 24, MD, oncology, academic]
- *The biggest challenge, I would say, in advanced cancer ends up being engagement with palliative care. You know, I think we try to encourage patients to see palliative care earlier. I think there's still a stigma around palliative care being mostly for hospice only. And so I think often times they end up getting seen by palliative care later than I would've liked despite kind of encouraging it early on. And I see that's quite the biggest barrier that I see that really impacts patient quality of life.* [provider 13, MD, hematology/oncology, community]

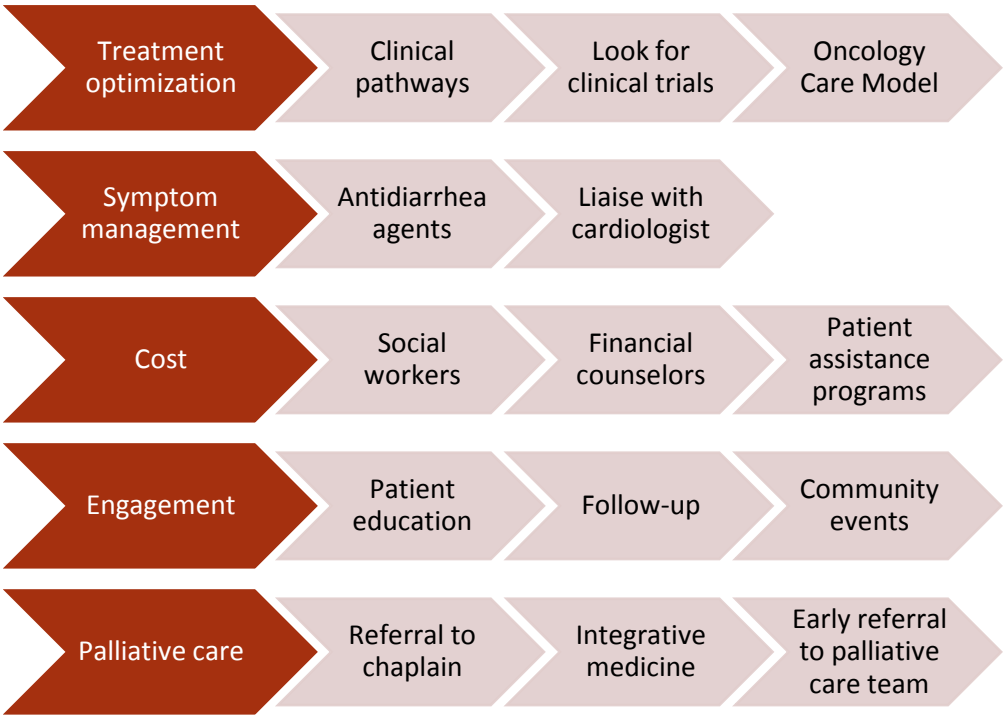
In addition to the cost of treatment, interviewed clinicians also pointed to a range of other social, organizational, and interpersonal challenges, such as how best to: 1) keep current with novel and investigational therapies; 2) sustain patient engagement across the treatment trajectory; and 3) address cost and access to treatment (**Figure 19**). The top priorities for radiation oncology clinicians were cost, patient engagement, and managing radiation adverse events.

Figure 19. Frequency of challenges mentioned by interviewed clinicians (n = 61).



Interviewed clinicians noted the following range of strategies that their practice settings are using to address the challenges they described (**Figure 20**).

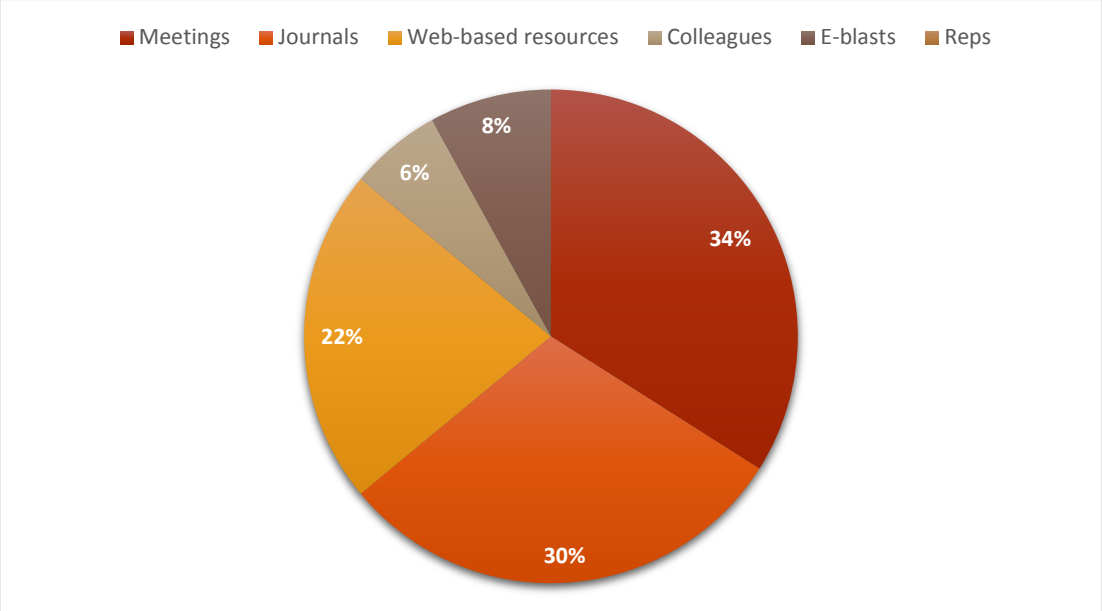
Figure 20. Stated strategies to address practice challenges.



Preferred Educational Sources and Formats

Figure 21 shows the range of information sources that interviewed clinicians rely on to stay current with treatment and management developments in HER2-positive MBC.

Figure 21. Preferred education sources reported in interviews (n = 50).



The *Journal of Clinical Oncology* and the *New England Journal of Medicine* were the most frequently cited journals; many also cited ASCO Post and Oncology Nurse Advisor as reliable sources of information. Oncologists cited ASCO, San Antonio Breast Cancer Conference, and the American Association for Cancer Research conference as frequently attended meetings. Radiation oncology clinicians cited the American Society of Radiation Oncologists annual meeting. Participants also emphasized the importance of conversations with peers in tumor boards and locally organized weekly or monthly meetings as important spaces for discussions about patient management as well as sources of information about new agents, clinical trial data, and other management issues. UpToDate, Clinical Care Options, Research to Practice, OncLive, and Medscape were cited as frequently accessed online resources.

Time was a major factor in participant selection of educational format. Participants valued the accessibility and immediacy of online tools, information, and resources, but they preferred being able to go to meetings, interact with colleagues, discuss cases, and learn from subject matter experts. Podcasts and webcasts were valued for their easily digestible formats "*with a human touch*."

Most participants identified in-person meetings as the pre-eminent learning scenario, followed by online resources such as webcasts and downloadable slide presentations.

> *I want to hear it first hand, so that's why I am at ASCO every year, but I also follow the latest and the greatest that is being presented and published and so on. But I also appreciate greatly the Clinical Care Options' review, the slide sets, the summary of the data, as well as the video from some of the symposia that are available along with slides and so on. So I appreciate all of that.* [provider 14, MD, hematology/oncology, community]

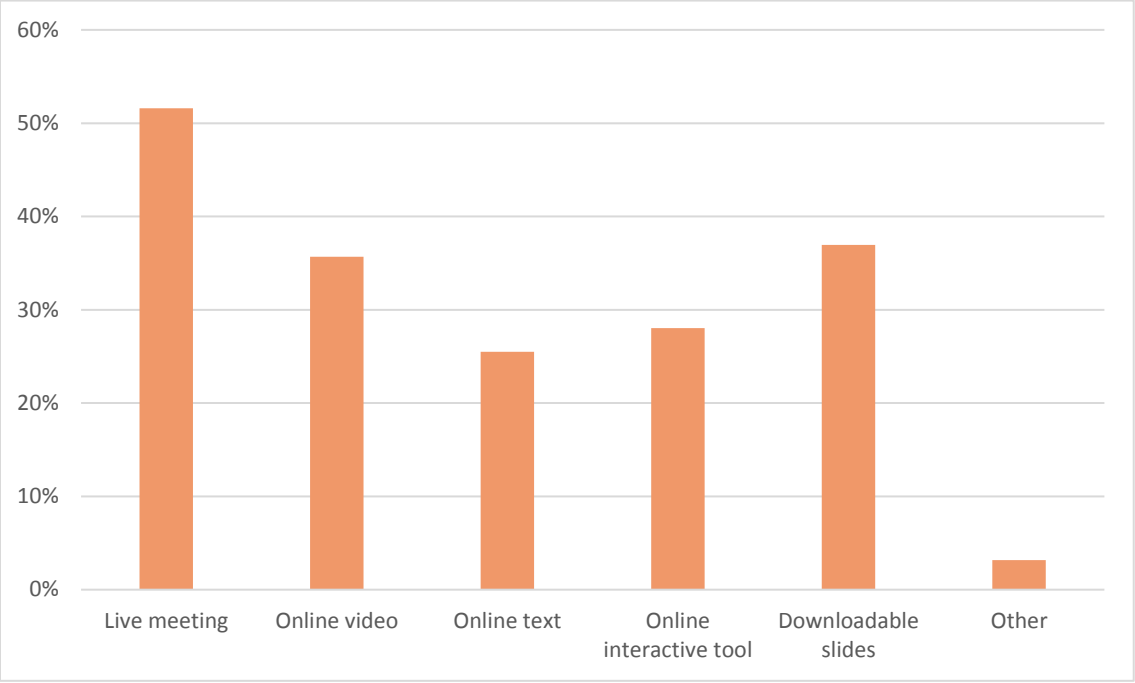
> *I love meetings, especially the breakout sessions. I like going to a lot of the pharma presentations; so I know they're biased, but still you get a lot of information and you can ask direct questions.* [provider 9, APN, oncology, academic]

> *Well, for convenience, preference is online, but if it's a new drug that I'm responsible for administering, I do like a site visit, especially for something that's new.* [provider 10, APN, oncology, community]

> *I learn more visually, so I like looking at when someone's talking and you have slides in front of you, so that helps.* [provider 2, MD, hematology/oncology, academic]

Survey results regarding preferred education sources echoed that of the interviews (**Figure 22**).

Figure 22. Preferred education sources reported in the survey (n = 157).



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