

AJMC® conducts video interviews with stakeholders to gain perspectives from experts on various policy issues and therapeutic areas.

PANELISTS



KEVIN KALINSKY, MD, MS

Associate Professor of Medicine
NewYork-Presbyterian Hospital/
Columbia University Medical Center
New York, NY



SARAH SAMMONS, MD

Assistant Professor of Medicine
Duke Cancer Institute, Duke University
Durham, NC



BHAVESH SHAH, RPH, BCOP

Senior Director of Specialty and
Hematology/Oncology Pharmacy Services
Boston Medical Center Health System
Boston, MA

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

www.ajmc.com

AJP1087



Defining Value in the Treatment of Brain Metastasis in Metastatic Breast Cancer

Brain metastasis in metastatic breast cancer (mBC) can be silent, and it is fairly common for patients to be asymptomatic. But mBC has substantial direct and indirect costs for patients, insurance payers, and society. The goals of therapy for mBC with brain metastasis are to improve symptoms, stabilize or reduce the tumor burden, maintain quality of life, and improve overall survival. New therapies can provide value by reducing the risk of distant metastasis, preventing central nervous system relapse, and improving quality of life. This article discusses the risk factors, comorbidities, diagnosis, economic burden, and treatments for brain metastasis in mBC, based on recent Insights video interviews with Kevin Kalinsky, MD, MS; Sarah Sammons, MD; and Bhavesh Shah, RPh, BCOP. To watch the full interviews, visit ajmc.com/insights.

OVERVIEW AND BURDEN OF BRAIN METASTASIS IN METASTATIC BREAST CANCER

HER2-Positive Breast Cancer

Breast tumors with high levels of the growth-promoting protein HER2 are characterized as HER2-positive breast cancer. Although these tumors tend to grow quickly and spread, they often respond to therapy directed at HER2.¹ According to Sarah Sammons, MD, "historically, 20 or 30 years ago, HER2-positive breast cancer had one of the highest risks of spreading distantly and progressing to metastatic disease. HER2-positive early-stage breast cancer is now one of the most curable breast cancers...given the highly effective therapies we have." Patients with early-stage HER2-positive breast

CLINICAL COMMUNICATIONS

Senior Vice President Jeff Prescott, PharmD	Project Manger Lindsay Caporrino
Assistant Director, Content Services Angelia Szwed	Associate Editors Jill Pastor-Mohr Amanda Thomas
Clinical Project Manager Lauren Burawski, MA	Assistant Editor Daniel Greaves

COPY & PRODUCTION

Copy Chief Jennifer Potash	Copy Editors Cheney Baltz Georgina Carson Rebekah Harrison Kirsty Mackay Ron Panarotti
Copy Supervisors Rachelle Laliberte Paul Silverman	Creative Director, Publishing Melissa Feinen
Scientific & Medical Quality Review Editor Stacey Abets, PhD	Art Director Julianne Costello
Senior Copy Editor Kelly King	

SALES & MARKETING

Vice President Gil Hernandez	National Account Managers Robert Foti Ryan O'Leary
Senior National Account Managers Ben Baruch Megan Halsch	National Account Associate Kevin George

OPERATIONS & FINANCE

Circulation Director Jon Severn circulation@mjhassoc.com	Vice President, Finance Leah Babitz, CPA
	Controller Katherine Wyckoff

CORPORATE

Chairman & Founder Mike Hennessy Sr	Senior Vice President, Operations Michael Ball
Vice Chairman Jack Lepping	Senior Vice President, I.T. & Enterprise Systems John Moricone
President & CEO Mike Hennessy Jr	Vice President, Human Resources and Administration Shari Lundenberg
Chief Financial Officer Neil Glasser, CPA/CFE	Vice President, Mergers & Acquisitions Chris Hennessy
Chief Marketing Officer Michael Baer	Executive Creative Director, Creative Services Jeff Brown
Executive Vice President, Global Medical Affairs & Corporate Development Joe Petroziello	
Senior Vice President, Content Silas Inman	

cancer usually receive trastuzumab- or sometimes pertuzumab-based chemotherapy and then undergo surgery. If they have residual disease, patients typically receive the antibody-drug conjugate (ADC) trastuzumab emtansine (T-DM1). Patients who, after surgery, have a complete response or no residual disease are maintained on trastuzumab-based therapy for a year.² “With this most up-to-date treatment regimen, even in the highest-risk early-stage breast cancer patients, about 88% of them will not have any disease come back at 3 years, which is really tremendous,” said Sammons. Unfortunately, she added, that still leaves “a small portion of patients with high-risk, early-stage disease that progresses and becomes metastatic.”

Progression to Metastatic Disease

According to Bhavesh Shah, RPh, BCOP, HER2-positive breast cancer is a very aggressive disease. It is second only to non-small cell lung cancer in causing brain metastasis. “An estimated 60% of the deaths of patients with HER2-positive disease are from progression to the brain,” said Shah.

Sammons stated that a large portion of the patients with HER2-positive metastatic breast cancer (mBC) have de novo metastatic disease, in which “their early-stage disease is not caught soon enough. By the time their disease is diagnosed, they have metastatic disease already, which is disease that has spread beyond the breast and regional lymph nodes.” Common locations of metastasis include the liver, lung, bones, lymph nodes, and brain.

Kevin Kalinsky, MD, MS, and Sammons stated that approximately 50% of patients with mBC will develop brain metastasis; all patients with HER2-positive mBC should be considered at risk. Shah added that Hispanic, Black, Latino, and elderly patients are at much greater risk of developing central nervous system (CNS) disease in mBC or HER2-positive disease.

Current research suggests a fairly short period of time after diagnosis for the development of brain metastasis. According to Sammons, the RegistHER study (NCT00105456) used a large database of approximately 1000 patients with HER2-positive mBC and determined that the initial brain metastasis occurred at around 13 months after diagnosis in those who were receiving treatment.³

These results were supported by those of the CLEOPATRA trial (NCT00567190), in which patients undergoing treatment developed brain metastasis by approximately 15 months, said Sammons.⁴ Based on this timing, Sammons stated that patients who will likely develop a brain metastasis during first- or second-line therapy for metastatic disease “speak

to the need for us to bring agents that penetrate the blood-brain barrier [BBB] into earlier lines” of therapy. Kalinsky echoed this, indicating that the ability of therapeutic agents to cross the BBB is also “an issue for patients with early-stage breast cancer, as we’re hoping to decrease the likelihood of developing metastases, including CNS metastasis.”

DIAGNOSIS AND DISEASE PRESENTATION

Symptoms

Brain metastasis can be silent, and it is fairly common for patients to be asymptomatic. However, most brain metastases are diagnosed based on neurological symptoms that can include headaches; dizziness; slurred speech; weakness in a unilateral extremity (eg, an arm or a leg); numbness or tingling in a unilateral extremity, and numbness, tingling, or weakness on 1 side of the face.

Kalinsky stressed the importance of asking patients whether they are having any sort of neurological symptoms. “Sometimes [brain metastasis] can present with...more mild symptoms. A patient may, for instance, have some headaches or not quite feel themselves. But [symptoms] can be more extreme: seizures and/or weakness, and/or sensory loss, or any sort of associated cranial abnormalities that can develop,” he said. “One of the greatest symptomatic burdens of brain metastasis is seizures,” Shah said. “Some patients may require seizure prophylaxis. Long-term consequences of seizures include neurocognitive decline, difficulty in articulating words, and a change in speech pattern.” He added that the number of metastases can range from a few to innumerable. Development of leptomeningeal disease portends a poor prognosis.

Disease Monitoring

According to Sammons and Kalinsky, current National Comprehensive Cancer Network (NCCN) guidelines recommend a screening MRI only in patients with neurological symptoms,² but institutional approaches differ. “At our institution, it’s not something that we commonly do in the absence of brain metastasis,” said Kalinsky. “But this issue [will likely be revisited] given that we have...better therapeutics...that offer better systemic control and that patients may have asymptomatic CNS metastasis.” Therefore, if there is a concern about brain metastasis or a recommendation from radiology, and no contraindications for a brain MRI or insurance issues exist, Kalinsky said an MRI would be ordered.

CLINICAL AND ECONOMIC BURDENS

The clinical and economic burdens of brain metastasis and its treatment are high. “When we treat patients with CNS metastasis, and they have a limited clinical burden and we’re able to give some local therapy and keep it under control, it doesn’t necessarily impact adherence and cognition,” said Kalinsky. However, patients can have a high burden of disease due to the severity of disease or the treatments they are receiving, such as whole brain radiotherapy. There is substantial concern for “acute and more late effects of toxicity from whole brain radiotherapy that can really impact patients’ memory, and they can become increasingly forgetful,” noted Kalinsky. “It can be very hard to treat the patient [and] hard for the family to help manage that patient.”

Sammons added that depression, anxiety, and decreased quality of life occur in patients with mBC with brain metastasis. Moreover, Shah added that increasing intracranial pressure can not only affect patients’ quality of life but also put them at substantial risk for venous thromboembolism.

Shah remarked that health care utilization, including hospitalization and intensive care unit (ICU) stays, in patients with brain metastasis is double that of patients with breast cancer and no brain metastasis. Furthermore, health care disparities exist among racial minority groups and older patients, leading to even more utilization of health care resources in these patient populations.

TREATMENT OPTIONS FOR mBC WITH BRAIN METASTASIS

Goals of Therapy

“The goals of therapy for mBC with brain metastasis are to improve symptoms, stabilize or reduce the tumor burden, maintain quality of life, and improve overall survival [OS],” said Kalinsky.

Initial Therapy

Initial nonpharmacological therapies for brain metastasis include locally directed therapy with surgical resection, stereotactic radiosurgery, and whole brain radiation therapy.⁵ According to Kalinsky, “if the number of brain metastases is small and limited, we can often give just local therapy, such as stereotactic radiotherapy or Gamma Knife surgery. If patients [are receiving] systemic therapy and their systemic disease [is largely] under control, but they had some small progression in the brain, we often continue that systemic therapy and treat the metastases locally until we see that they are no longer under control.” Because many toxicities are associated with whole brain radiation, it is reserved for patients who have a large volume of brain metastasis, a new tumor, or metastases that are large in size, he said. Unfortunately, HER2-positive mBC is aggressive, and intracranial progression often occurs within 1 year.⁶

Agents With CNS Activity

“One advantage of treating patients with HER2-positive mBC is that we have a number of agents,” said Kalinsky, but “not all those drugs have great CNS penetration.” Shah noted that cytotoxic chemotherapy and

monoclonal antibodies, such as trastuzumab and pertuzumab, do not cross the BBB. T-DM1 does not cross the BBB very well either. Sammons stated that for a long time, lapatinib plus capecitabine was one of the only options for patients with HER2-positive mBC with brain metastasis.

Historically, clinical trials have excluded patients with brain metastasis. Obviously, brain metastasis leads to a poorer outcome, and, according to Shah, “you don’t want to influence [a trial’s] results [by including] a very poor-risk patient population.”

Sammons said that they have “seen a change since both the American Society of Clinical Oncology [ASCO] and the FDA...have encouraged [including] patients with brain metastasis very early on in the drug development process.” The tucatinib trials are a “very good example of that for investigators moving forward. [Their inclusion] only strengthened the results and strengthened their approval and certainly

made it more appealing for clinicians to prescribe that drug for their patients, [although it] certainly led to...inferior outcomes,” she said.

According to Kalinsky, the treatment armamentarium for HER2-positive mBC has expanded to include other tyrosine kinase inhibitors (TKIs), such as neratinib and, most recently, tucatinib and the ADC trastuzumab deruxtecan.^{2,5} For third-line therapy and beyond, Kalinsky acknowledged that it is an “open space for what agents to use.”

Clinical Trial Results

LANDSCAPE

LANDSCAPE (NCT00967031) was an open-label, multicenter study in patients with HER2-positive mBC and previously untreated brain metastasis. Patients received lapatinib plus capecitabine until disease progression or unacceptable toxicity.⁷ “It was a smaller trial, with 45 patients enrolled,” said Sammons. “The primary end point was intracranial response rate...and this was one of the earlier trials to show intracranial efficacy of any compound in HER2-positive breast cancer. It showed a very respectable intracranial response rate of about 65% with lapatinib and capecitabine.”⁷

Shah added, “The median time to CNS progression was approximately 5.5 months, and median OS was about 17 months.”⁷

“Some of the issues with this regimen included things like diarrhea and...skin reactions, including hand-foot syndrome, that we can see with capecitabine,” said Kalinsky.

Grade 3 hand-foot syndrome and diarrhea each occurred in 20% of patients,⁷ Shah continued. “All the supportive care that you need to do with capecitabine, you need to do with lapatinib and capecitabine,” he said. The pill burden is substantial, as well, and it must be considered in this patient population. “[These] patients [may have] neurocognitive

“The goals of therapy for [metastatic breast cancer] with brain metastasis are to improve symptoms, stabilize or reduce the tumor burden, maintain quality of life, and improve overall survival.”

– Kevin Kalinsky, MD, MS

dysfunction, and then you're giving them 10, 12, 15 pills a day," said Shah, and what's more, "capecitabine pills are pretty large."

HER2CLIMB

According to Kalinsky, the results of the pivotal HER2CLIMB study (NCT02614794) led to the approval of tucatinib in 2017 and to a "landscape change for patients with HER2-positive mBC."

"HER2CLIMB was a...randomized, placebo-controlled clinical trial of tucatinib or placebo added to trastuzumab and capecitabine in patients with HER2-positive mBC," described Sammons. "One of the most important things about the trial was that all patients had received trastuzumab and pertuzumab, and all patients had had prior T-DM1. Also, about 50% of the patients in the trial population had brain metastasis. And probably more importantly, a large portion of that 50% had...either untreated brain metastasis, so their brain metastasis had not undergone surgical resection or radiation, or they had progressive metastasis, meaning they had undergone surgery or radiation but the brain metastasis was still growing. We've never seen a...trial include [these] high-risk patients before, and that was really very exciting."⁸

Shah reiterated this point, noting that with approximately 600 patients, the trial "was pretty large...and unique in regard to the number of...patients with brain metastases."⁸

One-year progression-free survival (PFS) was significantly higher in the tucatinib/combination group (33.1%) compared with the placebo/combination group (12.3%; $P < .001$). Two-year OS was 44.9% versus 26.6% in the tucatinib and placebo groups, respectively ($P = .005$). In the subgroup of patients with brain metastases, 1-year PFS was 24.9% in the tucatinib group versus 0% in the placebo group ($P < .001$).⁸

The estimated 1-year CNS PFS was 40.2% in the tucatinib group and 0%

in the placebo group. The tucatinib combination was associated with a significant reduction (68%) in the risk of CNS progression or death compared with the placebo combination (HR, 0.32; 95% CI, 0.22-0.48; $P < .0001$). Median CNS PFS was 9.9 months in the tucatinib arm versus 4.2 months in the placebo arm.⁶

At baseline, approximately 40% of patients with brain metastasis had stable brain metastases and 60% had active brain metastases.⁶ According to Shah, "looking at patients with stable versus active [metastases], there was still this benefit. You're going to actually have a prolonged time for them to progress if they're on tucatinib versus...not being on tucatinib.

"One-year OS was about 70%, and median OS was 18 months. [There] was...a 42% risk reduction...so [these results are] meaningful and definitely practice changing," Shah stated.⁶

Added Sammons, "This is the first trial ever to show an OS benefit in patients with a history of brain metastasis and especially those with treated progressive or untreated brain metastasis."

The trial also included "a small subgroup of patients who had...CNS metastasis...[and hadn't] received radiotherapy," said Kalinsky. "Tucatinib compared with placebo [was associated with] a...delay in terms of the need for utilization of radiotherapy."⁶ Shah noted that diarrhea and elevated aminotransferase levels occurred more frequently in the tucatinib arm compared with the placebo arm and should be monitored.

NALA

NALA (NCT01808573) was a randomized phase 3 trial designed to compare capecitabine plus neratinib versus capecitabine plus lapatinib in patients with HER2-positive mBC who experienced progression after at least 2 lines of therapy.⁹ Patients with asymptomatic or stable brain metastases were eligible for the study. A total of 621 patients were enrolled; approximately one-third had received prior trastuzumab, pertuzumab, and T-DM1 therapy. The coprimary end points were PFS and OS.⁹

Neratinib plus capecitabine significantly improved PFS compared with lapatinib plus capecitabine (8.8 vs 6.6 months; $P = .0059$).⁹ Although OS was numerically higher with the neratinib combination (24.0 months) versus the lapatinib combination (22.2 months), statistical significance was not demonstrated.⁹ Compared with those given lapatinib (29.2%), fewer patients given neratinib (22.8%) required intervention for CNS metastases.⁹

Capecitabine is a chemotherapy that has good CNS penetration, said Kalinsky. Sammons added, "Neratinib has fairly robust intracranial activity. Neratinib and capecitabine prolonged time to CNS intervention modestly over lapatinib and capecitabine."

This is an important end point, explained Shah, because it can delay the need for radiation, and "once a patient gets whole brain radiation, their quality of life won't be the same as before."

These results led to the inclusion of neratinib in the NCCN guidelines for patients with CNS metastasis, said Kalinsky.⁵

Diarrhea was the most frequent adverse event associated with both treatment regimens.⁹ Unfortunately, the impact of diarrhea seen with lapatinib and neratinib can often limit the combination's tolerability in patients with HER2-positive breast cancer, said Kalinsky.

Sammons and Shah mentioned the importance of dose escalation and prophylactic antidiarrheals (eg, loperamide) with these regimens. The CONTROL trial (NCT02400476) examined ways to mitigate diarrhea, including the use of budesonide and colestipol, which Sammons said is sometimes used in severe cases.¹⁰

DESTINY-Breast01

DESTINY-Breast01 (NCT03248492) was an open-label, single-arm, phase 2 trial of trastuzumab deruxtecan in patients with HER2-positive mBC who had previously received T-DM1. A total of 184 enrolled patients received the recommended dose of trastuzumab deruxtecan. Twenty-four patients (13%) had asymptomatic brain metastasis. Patients were very heavily pretreated, Sammons noted, with a median of 6 lines of prior therapy. Shah added that all patients had received trastuzumab and about two-thirds had received pertuzumab.¹¹

"Looking at patients with stable versus active [metastases], there was still this benefit. You're going to actually have a prolonged time for them to progress if they're on tucatinib versus...not being on tucatinib."

– Bhavesh Shah, RPh, BCOB

“The overall response rate, above 60%, was one that we have really never seen before in such a heavily pretreated population,” said Sammons. “We also saw PFS around 16 months, which is also nothing like we’ve ever seen before in a population like this, which was very exciting.”¹¹ Shah added that 97% of patients achieved disease control, with a median duration of response of about 15 months.¹¹

“It was arguably in breast oncology one of the most significant response rates that we have seen,” echoed Kalinsky. Trastuzumab deruxtecan “may have some ability to keep CNS disease under control, suggesting that maybe the payload is able to cross [the BBB] and treat CNS disease.”

Shah pointed out that the median time to response was about 1.6 months, “which is really impressive for patients who have significant refractory disease.”¹¹

“I think the main concern with trastuzumab deruxtecan is that it has some rare but very significant toxicity—in particular, the interstitial lung disease [ILD],” said Kalinsky. ILD occurred in 25 patients (13%) and was associated with 4 deaths,¹¹ “and we don’t have great predictors for who developed that toxicity,” he said.

The median time to onset was about 190 days, “a long time to wait for developing such toxicity,” said Shah. “It’s really important to monitor for ILD.”

Sammons noted that physicians are “using it certainly beyond the third line...but we still have some details to work out in how to best identify patients who might be at risk for ILD.”

Treatment Implications From Recent Studies and New Drug Approvals

The HER2CLIMB regimen “is clearly a standard of care for our patients with HER2-positive disease,” stated Kalinsky. “New agents are contributing to changes in oncologists’ approach to treatment of mBC. I would consider utilizing a tucatinib-based regimen...possibly earlier on. And, if I have a patient who has significant systemic disease where I really need to get a response, I would consider trastuzumab deruxtecan,” he said.

PAYER CONSIDERATIONS

Value-Driven Care

New therapies can provide value by reducing the risk of distant metastasis, preventing CNS relapse, and improving quality of life. New agents that generate responses directly in the CNS and delay CNS progression could help mitigate some CNS adverse effects or delay interventions, such as whole brain radiation, noted Shah. “If you can prevent whole brain radiation, that is a value-driven outcome for any patient with this disease,” he said.

Shah also acknowledged the importance of early diagnosis, which can prevent hospitalizations and ICU stays. Early diagnosis also allows for better symptom control through the use of the most appropriate treatments, which can optimize outcomes.

“I think patient-centered value-based models are definitely up-and-coming in oncology,” said Shah. “If a patient receives optimal therapy first line and you’re preventing that progression, delaying that progression, or delaying that second-line therapy time to progression, you’re actually creating lower total cost of care.” Shah added that his institution

“internally develops our own pathways through our experts in breast cancer in collaboration with national guidelines.”

Access to Treatment

Among Medicaid and Medicare patients, the Medicaid patient population is probably the most complex, said Shah, because they have the most barriers to access and because mBC tends to affect African American and Latino patients more aggressively.

“So I think if I were a Medicaid payer, I would be more aggressively making sure that the treatments are optimized and the patients are receiving the appropriate treatment that would have long-term CNS PFS or OS for these patients,” said Shah. “In oncology, about 25% of patients decline their therapy because of cost sharing. Especially with oral agents, we know that there’s definitely going to be cost sharing, and [we have to consider] Medicare patients.” Ensuring that

all patients have access to all possible clinical support programs is important to increase the likelihood of adherence, he continued. “If you want patients to stay on drugs, there needs to be appropriate adherence...[and further,] that means that toxicity management needs to be done appropriately,” he said.

“So I think if I were a Medicaid payer, I would be more aggressively making sure that the treatments are optimized and the patients are receiving the appropriate treatment that would have long-term CNS [central nervous system] PFS [progression-free survival] or OS [overall survival] for these patients.”

– Bhavesh Shah, RPh, BCOP

CANCER CARE DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC

“[We have] been pretty vigilant about making sure our patients understand that risks [and potential outcomes related to] malignancy are much more than those of COVID-19 [coronavirus disease 2019],” said Shah. He noted that registry data released by ASCO and the American Association for Cancer Research indicate that there was no increase in patients’ risk of death as a result of their having COVID-19 and receiving specific chemotherapies. “I think that’s great, but I think we should continue to monitor that because I think we still have surges...but at least we have some preliminary evidence that shows that there’s not an increased risk of mortality for patients who have COVID-19 and have breast cancer and are receiving anticancer therapies or monoclonal antibodies such as trastuzumab or pertuzumab,” he noted.

During the pandemic, Kalinsky said, oncologists are increasingly treating patients with oral agents. “Having agents like tucatinib, neratinib, and lapatinib really proved to be helpful because we knew that patients could get active agents and not need to come into the infusion center,” he explained. The downside, however, is that not all patients

are adherent to oral agents, noted Kalinsky. When patients actually come into the infusion center, physicians at least know that they are receiving their medication.

At Sammons' institution, "a nursing program was implemented through a grant, in which nurses can go to patients' houses, collect their labs, and talk to them about any symptoms of therapy that they might be having," she described. For low-risk patients on CDK4/6 inhibitors and endocrine therapy, "that is a very, very reasonable model that I think we should all continue to pursue."

Value of Telehealth

Telehealth visits have been beneficial for patients who are stable on their treatment regimen or those who are on long-term oral therapies said Sammons. However, for the majority of patients with mBC, telehealth appointments can be difficult, and there is value in seeing patients face-to-face, especially those who are symptomatic or have a large disease burden, she said.

FUTURE DIRECTIONS AND EMERGING TREATMENT OPTIONS

The sequencing of treatments is an important question moving forward, said Sammons. "What's really unknown is if HER2-targeted TKIs will have any added efficacy" after a patient has already received one, she stated. Beyond TKIs and ADCs, she recommends continuing trastuzumab into further lines of therapy with alternate chemotherapy backbones.

Kalinsky noted that there is particular interest in data from phase 3 trials to see how trastuzumab deruxtecan compares with other agents. He said he also suspects that tucatinib "will continue to move up in terms of the lines of therapy that we use, including in the operable setting." Other therapies under investigation in mBC, he added, include immunotherapy and chimeric antigen receptor T-cell therapy. He remains "optimistic about what our therapeutic landscape looks like for patients with HER2-positive mBC, not only in preventing

metastasis but in treating patients who develop metastasis, and in those who have CNS disease."

Said Sammons, "It's unclear whether doing a screening MRI and identifying an asymptomatic brain metastasis early would impact outcomes." She hopes that this question will be answered in the near future.

Kalinsky noted that given the availability of agents that are active in the CNS and prolong survival, "that paradigm could shift over time."

"As more of these innovations come out, patients may be living longer, but it's also going to increase the cost to payers," Shah concluded. Manufacturers can "help these payers offset the costs of these innovations with...outcome-based contracting and value-based contracting to share the risk: both sides, manufacturer and payer." ■

REFERENCES

1. Understanding a breast cancer diagnosis. American Cancer Society. Updated September 20, 2019. Accessed November 4, 2020. <https://www.cancer.org/content/dam/CRC/PDF/Public/8580.00.pdf>
2. NCCN. Clinical Practice Guidelines in Oncology. Breast cancer, version 6.2020. Accessed September 8, 2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
3. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. *Clin Cancer Res*. 2011;17(14):4834-4843. doi:10.1158/1078-0432.CCR-10-2962
4. Swain SM, Baselga J, Miles D, et al. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA. *Ann Oncol*. 2014;25(6):1116-1121. doi:10.1093/annonc/mdl133
5. NCCN. Clinical Practice Guidelines in Oncology. Central nervous system cancers, version 3.2020. Accessed September 11, 2020. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf
6. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610-2619. doi:10.1200/JCO.20.00775
7. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol*. 2013;14(1):64-71. doi:10.1016/S1470-2045(12)70432-1
8. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382(7):597-609. doi:10.1056/NEJMoa1914609
9. Saura C, Oliveira M, Feng YH, et al; NALA Investigators. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol*. 2020;38(27):3138-3149. doi:10.1200/JCO.20.00147
10. Barcenas CH, Hurvitz SA, Di Palma JA, et al; CONTROL Study Investigators. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. *Ann Oncol*. 2020;31(9):1223-1230. doi:10.1016/j.annonc.2020.05.012
11. Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382(7):610-621. doi:10.1056/NEJMoa1914510

