Clinical Implications of Emerging Metastatic Breast Cancer Data from ESMO 2021: Interviews with Two Key Opinion Leaders

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Disclosure: Cortés is a consultant/advisor for AstraZeneca, Athenex, Bioasis Technologies Inc., BioInvent, Boehringer Ingelheim, Celgene, Cellestia, Clovis Oncology, Daiichi Sankyo, Eli Lilly and Company, Ellipses Pharma, Erytech, GEMoaB, Gilead Sciences, Inc., GlaxoSmithKline, HiberCell, Leuko, Menarini Group, Merck Sharp & Dohme, Polyphor, Reveal Genomics, S.L., Roche, Seattle Genetics, and Zymeworks; has received honoraria from Celgene, Daiichi Sankyo, Eisai, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Samsung Bioepis; research funding to the institution from Ariad Pharmaceuticals, AstraZeneca, Baxalta, Bayer, Eisai, F. Hoffman–La Roche, GMBH/Servier Affaires, GuardantHealth, Merck Sharp & Dohme, PIQUR Therapeutics, Pfizer, Puma Biotechnology, Queen Mary University of London, and Roche; has stock, patents, and intellectual property with Leuko (relative), MEDSIR, and Nektar Therapeutics; and has received travel, accommodation, and expenses from AstraZeneca, Daiichi Sankyo, Eisai, Novartis, Pfizer, and Roche. Curigliano has received grants and honoraria for advisory board involvement from AstraZeneca, Daiichi Sankyo, F. Hoffmann–La Roche, Genomic Health, Merck, Novartis, and Pfizer.

Acknowledgements: Medical writing assistance was provided by Brigitte Scott, MarYas Editorial Services, Cowlinge, UK.

Disclaimer: The opinions expressed in this article belong solely to the named interviewees.

Support: The publication of this article was funded by a medical educational grant from AstraZeneca to support the knowledge and practice of clinical and research oncology specialists in the evolving field of metastatic breast cancer and inform about the emerging data in this area.

Citation: EMJ Oncol. 2022;10[Suppl 7]:2-9.

Summary

Around 15–20% of breast cancers are characterised by amplification or overexpression of human epidermal growth factor receptor 2 (HER2), which is a biomarker of poor prognosis. Anti-HER2-directed agents in combination with chemotherapy are the mainstay of treatment of patients with HER2-positive metastatic breast cancer (HER2+ MBC). New and more effective therapies for HER2+ MBC are needed as this is still an incurable disease. Two key opinion leaders, Javier Cortés from Spain and Giuseppe Curigliano from Italy, discussed the current standard of care in HER2+ MBC and how data from the DESTINY-Breast03 trial presented at European Society for Medical Oncology (ESMO) 2021 support new approaches to second-line therapy. The treatment algorithm for HER2+ MBC is well-recognised globally, with most guidelines recommending as standard of care trastuzumab,

pertuzumab, and taxane (docetaxel) as first-line therapy, and trastuzumab emtansine (T-DM1) in second-line therapy. The unprecedented hazard ratio (HR) for progression-free survival (PFS) of 0.28 in DESTINY-Breast03 clearly indicates that trastuzumab deruxtecan (T-DXd) may now be considered as standard of care and is expected to move to the second-line setting. The overall survival (OS) data from DESTINY-Breast03 are immature; however, the PFS data are considered sufficient to encourage clinicians to prescribe T-DXd in second-line, rather than waiting for OS data. A median PFS of >19 months, as seen in the DESTINY-Breast01 trial, might be expected to translate to a similar duration in OS in heavily pre-treated patients; therefore, an OS of >29 months in this trial is impressive. Although DESTINY-Breast01 is a Phase II trial, the results are encouraging, and the OS results from Phase III trials, including DESTINY-Breast03 and DESTINY-Breast02, are awaited with interest. Preliminary responses in the TUXEDO-1 and DEBBRAH trials support the effectiveness of T-DXd in brain metastases in patients with HER2+ MBC. Cortés and Curigliano expect T-DXd to move to earlier lines, and to enter the early breast cancer treatment setting. They proposed there is the potential for some patients with metastatic disease with limited tumour burden who are treated with T-DXd to be cured.

INTRODUCTION

Female breast cancer has now surpassed lung cancer as the most commonly diagnosed primary malignancy and is the fifth leading cause of cancer-related morbidity worldwide, with around 2.3 million new cases and 685,000 deaths reported globally in 2020.[1,2] The 5-year relative survival rate for localised breast cancer is 99%, and that for breast cancer with distant metastases is 29%.[3] Around 15–20% of breast cancers are characterised by amplification or overexpression of HER2, which is a biomarker of more aggressive tumour behaviour, early metastasis, high recurrence rates, and poor prognosis.[4,5] Anti-HER2-directed agents in combination with chemotherapy are the mainstay of treatment of patients with HER2+ MBC.[5] Patients with early HER2+ breast cancer may relapse even after adjuvant trastuzumab-based treatment, and HER2+ MBC is still an incurable disease, with treatment benefit in metastatic disease diminishing from line to line; therefore, there is a medical need for new and more effective therapies for HER2+ MBC.[6]

For this article, EMJ conducted interviews in January 2022 with two key opinion leaders, Javier Cortés and Giuseppe Curigliano, both of whom have a wealth of experience and expertise in managing HER2+ MBC, to gain their perspectives on a range of topics in this area. The experts gave valuable insights into several pertinent issues in HER2+ MBC treatment and discussed significant recent developments in the field.

This article discusses the current standard of care for HER2+ MBC, the data from key clinical studies, and the potential impact of emerging therapies on patient management strategy. The potentially practice-changing data presented at ESMO 2021 are also explored.

CURRENT STANDARD OF CARE FOR METASTATIC BREAST CANCER

Cortés and Curigliano explained that the treatment algorithm for HER2+ MBC is clear and well-recognised globally. Most guidelines recommend as standard of care trastuzumab, pertuzumab, and taxane (docetaxel) as first-line therapy, based on the findings from the CLEOPATRA trial,[7] and the antibody–drug conjugate trastuzumab emtansine (T-DM1) in second-line therapy, based on the results of the EMILIA trial.[8] Anti-HER2-based therapy is recommended to continue in the third-line treatment setting, with the tyrosine kinase inhibitor tucatinib, based on the findings from the HER2CLIMB trial,[9-11] and the antibody–drug conjugate T-DXd, based on the results of the DESTINY-Breast01 trial,[12] the current preferred treatment options in this setting in the USA and Europe.

The key opinion leaders emphasised the importance of considering both regulatory and clinical perspectives in the management of patients with breast cancer. Although the above recommendations are from a regulatory perspective, new data presented at ESMO 2021,[13]

which were corroborated by results presented at the 2021 San Antonio Breast Cancer Symposium (SABCS),[14] support new approaches to second-line therapy from a clinical perspective, as described below.

DESTINY-BREAST03: INITIAL IMPRESSIONS

DESTINY-Breast03 (NCT03529110),[13-15] is a multicentre, open-label, randomised, Phase III study comparing the efficacy and safety of T-DXd versus T-DM1 in patients with HER2+ MBC who were previously treated with trastuzumab and taxane. It is the first reported randomised study of T-DXd in breast cancer. The primary endpoint was PFS, and secondary endpoints included OS, objective response rate, duration of response (DOR), PFS by investigator, and safety.[13-15]

From the data presented at ESMO 2021, the median treatment duration in DESTINY-Breast03[13] was 14.3 (range: 0.7–29.8) months with T-DXd versus 6.9 (range: 0.7–25.1) months with T-DM1. The HR for PFS was 0.2840 ($p=7.8x10^{-22}$), with median PFS not reached for T-DXd versus 6.8 months for T-DM1.[13] The estimated 12-month OS event rates were 94.1% (95% confidence interval [CI]: 90.3–96.4) for T-DXd and 85.9% (95% CI: 80.9–89.7) for T-DM1 (HR: 0.5546; 95% CI: 0.3587–0.8576; p=0.007172).[13]

Cortés highlighted that the data from DESTINY-Breast03[13-15] are immature in terms of OS, but are mature for both PFS and objective response rate. He expressed that the efficacy data are the best seen in the field of breast cancer, including for early and metastatic disease, and that the impressive improvement in PFS clearly indicates that T-DXd may now be considered as best standard of care.

Curigliano also commented on the remarkable PFS data from DESTINY-Breast03 presented at ESMO 2021,[13] highlighting the unprecedented HR of 0.28, which was confirmed at SABCS 2021.[14] He observed that the response rate was almost 70%, and that few patients progressed on T-DXd in the study.[13-15] Curigliano described the second generation antibody–drug conjugate T-DXd, which includes the same antibody as T-DM1, trastuzumab, as a highly potent and stable topoisomerase I inhibitor with a high therapeutic index. Agreeing with Cortés, Curigliano considered T-DXd to be the new standard of care for patients with HER2+ MBC following progression with trastuzumab and taxane, and expected T-DXd to be moved to the second-line setting. He hoped that it would eventually be moved into the first-line setting for patients with HER2+ MBC.

ARE THE PROGRESSION-FREE SURVIVAL DATA FROM DESTINY-BREAST03 SUFFICIENT TO SUPPORT WIDESPREAD SECOND-LINE USE OF TRASTUZUMAB DERUXTECAN IN PATIENTS WITH HER2+ METASTATIC BREAST CANCER?

Cortés recollected that the PFS data for trastuzumab, pertuzumab, and docetaxel combination therapy for HER2+ MBC in CLEOPATRA[7] were sufficient to encourage clinicians to prescribe these drugs, rather than waiting for OS data, which were available much later. Cortés predicted that this will also be the case for T-DXd in HER2+ MBC following the impressive PFS data from DESTINY-Breast03,[13-15] with T-DXd potentially being prescribed with regulatory support while further OS data are awaited. Furthermore, provided that there is an opportunity to prescribe the drug in compliance with regulations, Cortés stressed that it would be unfair for clinicians and patients to have to wait for OS data when there are impressive PFS data available.

Curigliano stated that the DESTINY-Breast03[13-15] PFS data are sufficiently convincing, and there is no need to wait for the OS data to confirm that T-DXd should be the new standard of care for patients with HER2+ MBC. He noted that there was a trend in OS benefit in the study, but as the follow-up was of short duration, further follow-up of at least another few months is needed before an OS benefit can be clearly seen. Curigliano corroborated the widespread positive opinion of T-DXd, stating that the PFS data and the unprecedented HR of 0.28 seen in DESTINY-Breast03[13-15] are sufficient to encourage clinicians to prescribe T-DXd as second-line treatment for patients with HER2+ MBC.

UPDATED SURVIVAL DATA FROM DESTINY-BREAST01

T-DXd was shown to have durable antitumour activity in patients with HER2+ MBC who progressed on or after T-DM1 in the open-label, Phase II DESTINY-Breast01 (NCT03248492).[12,16] At the primary data cut-off on 1st August 2019, the median DOR was 14.8 months (95% CI: 13.8–16.9) and median PFS was 16.4 months (95% CI: 12.7–not reached).[12] At the initial update (8th June 2020), confirmed overall response rate was 61.4%, median DOR was 20.8 months, median PFS was 19.4 months, and median OS was 24.6 months.[17]

The updated OS data for DESTINY-Breast01 were presented at ESMO 2021 by Saura Manich et al.[18] At data cut-off on 15th January 2021, the median duration of OS follow-up was 29.2 months (95% CI: 28.6–30.0).[18] With increased duration of follow-up, the updated median OS was 28.4 months (95% CI: 24.6–37.2), with 91 (49.5%) OS events. The estimated OS rate at 18 months was 75% (95% CI: 67–80) and at 24 months was 58% (95% CI: 51–65).[18]

Cortés postulated that a median PFS of >19 months might be expected to translate to a similar duration in OS in heavily pre-treated patients; therefore, OS of >29 months in DESTINY-Breast01 is a "great result."[18] Cortés provided this important reminder: "Although this OS result is good news in terms of the data, every OS event is the death of one of our patients, which is always bad news, and we forget this more times than we remember." Cortés added that although DESTINY-Breast01 is a Phase II study, the results are encouraging, and he awaits with interest the OS results from upcoming Phase III studies, including DESTINY-Breast03,[13-15] and DESTINY-Breast02.[19]

Curigliano pointed out that DESTINY-Breast01 was the first Phase I trial combined with an expanded Phase II study to investigate the activity of T-DXd in patients with HER2+ MBC, in whom the median number of previous lines of treatment for metastatic disease was 6 (range: 2–27).[12,16,17] According to Curigliano, the updated OS data presented at ESMO 2021[18] are impressive because there are patients living without progressive disease for almost 2 years. He considered that DESTINY-Breast01[12,16-18] provided important information on T-DXd that stimulated the planning and conduct of further trials to provide the evidence needed to improve the treatment landscape for HER2+ MBC.

TRASTUZUMAB DERUXTECAN IN PATIENTS WITH HER2+ METASTATIC BREAST CANCER AND BRAIN METASTASES

Brain metastases are frequently diagnosed in patients with HER2+ breast cancer, and increase patient morbidity and mortality.[20,21] At ESMO 2021, Bartsch[21] presented the preliminary results of TUXEDO-1 (NCT04752059),[22] a prospective, single-centre, single-arm, two-stage, Phase II study investigating T-DXd in patients with HER2+ MBC and active brain metastases. The primary endpoint in TUXEDO-1 was intracranial tumour response rate. By 1st April 2021, a total of 10 patients received at least one dose of T-DXd, with a median follow-up of 3.5 (range: 1–8) months, at which time nine patients were still on treatment.[21,22] T-DXd treatment yielded an intracranial response in five out of six patients (83.3%) enrolled in the first stage of the study, with three out of four progressing after prior local therapy, which supported progression of the trial to the second stage.[21,22]

Cortés explained that the blood–brain barrier is usually disrupted when there are brain metastases; therefore, drug penetration into the brain is likely. He proposed that all drugs that are effective for systemic metastases (e.g., in the liver and lungs) are also likely to be effective in the treatment of brain metastases. Cortés stated that the interesting preliminary responses in the proof-of-concept TUXEDO-1 support the effectiveness of T-DXd in brain metastases in patients with HER2+ MBC, and he highlighted the forward-thinking approach in this key trial.[21,22]

In addition, Curigliano noted that there were no patients with active brain metastases in the DESTINY-Breast03 trial;[13-15] however, there was an approximate 40% response rate following treatment with T-DXd in patients with metastases at diagnosis (baseline). Curigliano considered that the TUXEDO-1 results, together with emerging data on brain metastases from DESTINY-Breast03[13-15] and HER2CLIMB,[11] in

which survival benefits were described in this patient population, indicate the potential for T-DXd to be effective in the treatment of brain metastases.

The effect of T-DXd on brain metastases has also been explored in DEBBRAH (NCT04752059).[22-24] Preliminary data showed that T-DXd demonstrated efficacy in pre-treated patients with HER2+ MBC who had stable and progressive brain metastases after local treatment. Both Cortés and Curigliano were encouraged by these preliminary data on the effectiveness of T-DXd on brain metastases in this open-label, Phase II study.[22-24]

HOW IMPORTANT IS CLINICAL RESPONSE IN CLINICAL DECISION-MAKING?

Cortés emphasised that "patients are human beings, not machines," and although disease control is more important overall in MBC, clinical response is still meaningful and contributes to improved quality of life. Providing evidence to the patient of tumour response through imaging such as CT scans has a positive psychological impact, as patients 'feel' that the tumour is getting better, and this proof of tumour size reduction reinforces that their treatment is working. Clinical response may also be accompanied by alleviation of pain and other tumour-related symptoms, so the patient may start to feel physically better, resulting in improved quality of life and mental state. Cortés expressed how delighted he is to see patients with whom he has developed a bond over several years smile when they see a "beautiful response" on their scan following treatment. He referred to the "beauty of our speciality" and the professional satisfaction felt by oncologists when they are able to help their patients with particularly poor prognoses benefit from effective treatments, with some patients responding very well to treatment for years.

Curigliano also stated that in such an aggressive disease as HER2+ MBC, clinical response is important in clinical decision-making as there is the opportunity to achieve a rapid response and to improve the quality of life of patients. He stated that, for the first time in his professional life, there is the potential for some patients with metastatic disease with limited tumour burden to be cured. Curigliano emphasised: "An 80% response rate in a second-line setting, as seen in DESTINY-Breast03, is impressive. Imagine what can happen with a patient with a single lesion treated with T-DXd in first-line." He proposed that it is time to think about planning future trials to explore the potential curative role of T-DXd in patients with HER2+ MBC with limited tumour burden.

SAFETY PROFILES FOR METASTATIC BREAST CANCER THERAPIES AND THE IMPACT ON PATIENT MANAGEMENT

Cortés outlined that there are many therapies with different toxicity profiles for patients with MBC, and their use should be decided on a patient-by-patient basis. He declared that T-DXd in DESTINY-Breast03[13-15] had a better-than-expected safety profile compared with DESTINY-Breast01,[12,16-18] at least in terms of the development of interstitial lung disease (ILD), with 10.5% of patients with T-DXd developing ILD (most [9.7%] Grade 1 or 2; 0 Grade 4 or 5) versus 1.9% with T-DM1 (all Grade 1 or 2).[13] Cortés emphasised that these clinical trials represent a non-curative setting, in which the focus is on prolonging life, relieving symptoms, and maintaining or improving quality of life. In this setting, treatment toxicity plays a major role in quality of life. In contrast, in a curative setting, quality of life can be compromised for a short time during treatment, as it is known that the patient will be cured. Cortés referred to two types of toxicity: one is the toxicity that the patient feels (i.e., experiences symptomatically) such as diarrhoea or joint pain, which affects their comfort and quality of life; and the other is the toxicity that the patient does not feel (i.e., potentially asymptomatic) such as transaminitis or neutropenia, which may have significant clinical consequences. Both types of toxicity need to be addressed as part of a personalised or patient-focused clinical decision-making process.

Curigliano contemplated that the safety profile of a drug is also an expression of confidence of the prescriber to use the drug. He recalled that when paclitaxel was introduced in the clinical setting, there was a reported rare association with capillary leak syndrome, yet paclitaxel went on to become used worldwide. Curigliano clarified the importance of considering the balance between

the activity of a drug and its potential side effects, and stated that he does not believe that safety is a major issue when there is an opportunity to use drugs with a high therapeutic index. Curigliano reiterated there have been no fatal cases of ILD in patients taking T-DXd in DESTINY-Breast03,[13-15] which indicates that even a drug with potentially fatal toxicity like ILD can be given when measures are taken to increase patient awareness, educate clinicians on how to use the drug, and ensure careful lung monitoring.

TREATMENT CONSIDERATIONS FOR PATIENTS WHO ARE FRAIL

Cortés and Curigliano deliberated the efficacy-side effect balance of T-DXd versus T-DM1, and gave their thoughts on treatment for patients who are frail (i.e., elderly or particularly ill). Cortés advocated a patient-based, not community-based, approach to clinical decisions about treatment, particularly for patients who are frail or vulnerable. T-DM1 is a well-tolerated drug, but it is still associated with adverse events. Cortés recounted that the incidence of Grade 3 and 4 treatment-emergent adverse events for T-DM1 (approximately 40%) is similar to that for T-DXd (approximately 45%). In terms of important toxicities, such as ILD, Cortés rationalised that earlier treatment and regular clinical follow-up of treated patients should be recommended and should include lung imaging. He observed that the majority of ILD cases with T-DXd in DESTINY-Breast03[13-15] were Grade 1 or 2 lung changes that were usually reversible, only two patients (0.8%) had Grade 3 ILD, and there were no reports of Grade 4 or 5 ILD. In terms of treatment of patients who are frail, Cortés declared that the clinician needs to determine why the patients are frail (e.g., do they have an important lung disorder?), evaluate and monitor comorbidities during treatment and follow-up, and then balance the pros and cons of treatment for each patient. He asserted that patients who are frail can be treated with T-DXd, provided that there are no contraindications to the drug in terms of underlying chronic lung disease, and with the instigation of continuous, careful monitoring of the patient.

Curigliano clarified that T-DM1 still has a role in the treatment of HER2+ MBC. For example, patients who progress on T-DXd could be rechallenged with T-DM1. For patients who are elderly, frail, or very unwell, Curigliano did not believe that the safety profile of T-DXd is an issue, and even for patients with extensive metastatic disease, age is not a contraindication for T-DXd. Patients who are very frail and cannot tolerate T-DXd treatment could be given maintenance treatment with trastuzumab, with treatment decisions made on a case-by-case basis.

TRASTUZUMAB DERUXTECAN USE IN THE CLINIC

Cortés explained that he has had the opportunity to treat patients with T-DXd as part of a clinical trial in a first-line (DESTINY-Breast09 [NCT04784715])[25,26] or second-line (DESTINY-Breast12 [NCT04739761])[27,28] setting. He also recounted his experience of treating patients with T-DXd outside of a clinical trial in the third-line setting. He highlighted that treatment discontinuation rarely occurs, and the majority of patients continue on T-DXd without dose reduction. Provided there are no contraindications, Cortés stated that he intends to treat all of his patients with HER2+ MBC with T-DXd in the future.

Curigliano has administered T-DXd to patients with HER2+ MBC after several lines of treatment, and noted that only very rarely has there been a need to reduce the dose. Only one patient in Curigliano's experience has developed ILD, with no fatal consequence. Treatment was discontinued for this patient, not because of aggressive ILD, but to be compliant with the manufacturer's recommendations to discontinue treatment if ILD develops. Curigliano aims to prescribe T-DXd to as many refractory patients with HER2+ MBC as possible.

EMERGING MOLECULES FOR HER2+ METASTATIC BREAST CANCER

Cortés indicated that there is a plethora of emerging new drugs and treatment regimens for patients with HER2+ MBC, including tyrosine kinase inhibitors, such as pyrotinib,[29] which has been approved in China. Pyrotinib is currently being evaluated in combination treatments for patients with HER2+ MBC.[29] Immunotherapy is being studied with different combinations

of antibody–drug conjugates and monoclonal antibodies, including the ongoing Phase III KATE3 study of T-DM1 plus atezolizumab or placebo in patients with previously treated HER2+ and programmed death-ligand 1-positive locally-advanced or metastatic breast cancer.[30] Further research of interest in this field involves defining the role of cyclin-dependent kinase 4 and 6 inhibitors,[31,32] for which there are ongoing pivotal trials, including PATINA,[33] in which trastuzumab, pertuzumab, and palbociclib are being evaluated in combination in the first-line treatment setting.

According to Cortés, the most exciting research is in the use of antibody–drug conjugates, including T-DXd and trastuzumab duocarmazine.[34,35] Data presented at ESMO 2021 from TULIP[35] showed improvement in PFS, but important toxicity with trastuzumab duocarmazine. In this Phase III study, centrally reviewed median PFS was 7.0 months (95% CI: 5.4–7.2) for trastuzumab duocarmazine versus 4.9 months (95% CI: 4.0–5.5) for physician's choice treatment (HR: 0.64; 95% CI: 0.49–0.84; p=0.002).[35] Important toxicity with trastuzumab duocarmazine included ILD or pneumonitis for 7.6% of patients (5.2% Grade 1/2), including two Grade 5 events.[35]

FUTURE PROSPECTS AND CONCLUSIONS

According to Cortés, efficacious drugs always move to earlier lines of therapy and, as T-DXd has been shown to be superior to T-DM1 in DESTINY-Breast03,[13-15] he predicts that this drug will move to earlier lines. He also expects T-DXd to enter the early breast cancer treatment setting. Cortés emphasised that clinicians need to think carefully about not just giving more drugs to all patients, but to devise strategies to determine how and when to provide treatment in an individualised way. Many patients will experience disease progression or die while on treatment for metastatic disease; therefore, it is vital to optimise the drug, which will require an understanding of its mechanism of action. Cortés claimed that the results with T-DXd are the best seen in MBC and may represent a new standard of care. However, further research is needed in drug development, and additional clinical trials are required to evaluate emerging drugs and drug combinations as, "unfortunately, the future is still written in the number of deaths." Cortés indicated that he does not expect results as impressive as those in DESTINY-Breast03[13-15] in future trials, apart from perhaps in DESTINY-Breast02,[19] but thought that other trials would show incremental improvements.

Curigliano identified three key considerations for the future. Firstly, it is important to determine whether the combination of T-DM1 plus tucatinib is more effective than T-DM1 alone in the second-line setting. Secondly, when and how to move T-DXd to a first-line treatment, with clinical studies to compare it with pertuzumab, trastuzumab, and taxane. Finally, there is a need to ascertain the efficacy of T-DXd in patients with early breast cancer, possibly in the neoadjuvant setting, because Curigliano considered that a drug with such a high therapeutic index in the neoadjuvant setting may be an opportunity to increase curative rates. Curigliano concluded by stating that pending all the trials currently running or planned, the future for patients with HER2+ MBC is "very bright," and he strongly believes that more patients may be cured even if they have metastatic disease.

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