

Practical consensus recommendations regarding the management of HER2 neu positive metastatic breast cancer

M. Basade, M. Singhal¹, A. K. Rathi², M. Nandi³, S. Minhas⁴, C. Goswami³, S. Shinde⁵, P. M. Parikh⁶, S. Aggarwal⁵

Abstract

Metastatic breast cancer (MBC) is cancer that has spread from the breast to another part of the body or has come back in another distant location. Treatment options for MBC depend on several factors, including where the cancer has spread, the patient's overall health, and the levels of hormone receptors and HER2 in the tumour. Over-expression of HER2 is generally considered to be a negative prognostic feature because it accompanies an increase in breast cancer mortality. However, the development of agents that specifically target HER2 has improved the management of patients with these tumours.^[7-10] This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at these practical consensus recommendations in regards with the use of these agents and the management of HER2 positive MBC for the benefit of community oncologists.

Key words: Capecitabine, combination systemic therapy, docetaxel, lapatinib, personalized modification, pertuzumab, TDMI, trastuzumab

Introduction

The incidence of Her2 positivity in Indian population is between 26% and 50%.^[1-3] In 1998, after the demonstration of significant survival benefit, trastuzumab was approved by the US Food and Drug Administration as first-line treatment in combination with paclitaxel for women with metastatic HER2/neu-positive breast cancer.^[4-14] Since then, many new anti-HER2 agents like lapatinib, pertuzumab and TDM-1 have been developed for the treatment of HER2 positive patients. The treatment of MBC is generally not curative but mainly palliative as these patients are unlikely to be cured of their disease.^[15,16] This manuscript was prepared to help community oncologists better manage HER2 positive MBC and provide guidelines regarding the use of trastuzumab and other agents.

Expert oncologists from all over India met to discuss and reach a consensus statement to provide community oncologists practical guidelines on the management of HER2 positive MBC. The discussion was based on published evidence and practical experience in real life management of such patients. The expert group discussions were moderated by Dr Mehboob Basade and Dr Chanchal Goswami. The core expert group consisted of Dr Stephen C. Malamud and Dr Manish Singhal. Members of the panel were also allowed to share their personal experiences and make comments. This manuscript is the outcome of the expert group discussion and consensus arrived at in 2017.

Defining Clinical Cohort and Practice of Expert Group Panel Members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the participating delegates and expert group panel members – on the basis of which this document was prepared. The experts discussed a case of a 60 year old postmenopausal

lady diagnosed with infiltrating duct carcinoma left breast. She underwent modified radical mastectomy. Histopathology results were – T2N0M0, ER +ve, PR +ve, HER2 neu- 3 +ve. She took adjuvant chemotherapy with TCH-H followed by hormonal therapy with anastrozole. After nine months of stopping trastuzumab, she developed multiple bone metastases (5) with mild backache and few lung metastases. ECOG grade: 1. Based on this case, a series of questions were put up for poll upon which the expert group discussed and aimed to reach a consensus. Each question had multiple choice options from which participants were to select the one most appropriate for their clinical practice setting. The expert group then formed the practical consensus recommendations for the community oncologists.

Treatment Options in HER2 Positive MBC

When asked to give their opinion on what treatment they would prefer in patients developing metastasis 9 months after stopping adjuvant trastuzumab, half of the polled oncologists were in support of recommending trastuzumab and pertuzumab along with chemotherapy while the other half were in support of recommending T-DM-1 [Table 1]. T-DM1 is in a new class of drugs called antibody-drug conjugates.^[17] It is approved by the FDA to treat HER2 positive MBC that has previously been treated with trastuzumab and taxane chemotherapy.^[18,19] The evidence of clinical activity of T-DM1 in HER2 MBC was demonstrated in the phase III EMILIA trial^[20] in which pre-treated patients with one or two lines of trastuzumab-including chemotherapy were assigned to receive lapatinib plus capecitabine or T-DM1 every 3 weeks. The median PFS was found to be 9.6 months in the T-DM1 group versus 6.4 months in the lapatinib plus capecitabine group and the median OS was 31 months for the T-DM1 group and 25 months for the lapatinib plus capecitabine group. Some other studies have also indicated T-DM1 to be an effective option in HER2 positive MBC patients.^[21-23] The panel also discussed about the combination of pertuzumab and trastuzumab as it has also been shown to be very effective because of more

Access this article online

Quick Response Code:



Website: www.sajc.org

DOI: 10.4103/sajc.sajc_123_18

Department of Medical Oncology, Saifee Hospital, ⁶Department of Oncology, Shalby Cancer and Research Institute, Mumbai, Maharashtra, ¹Department of Medical Oncology, Indraprastha Apollo Hospital, ²Department of Radiation Oncology, MAMC, ⁴Department of Medical Oncology, Sir Ganga Ram Hospital, New Delhi, ³Department of Medical Oncology, Jaypee Hospital, Noida, Uttar Pradesh, ⁵Department of Radiation Oncology, Medica Superspecialty Hospital, Kolkata, West Bengal, India
Correspondence to: Dr. Maheboob Basade, E-mail: basade@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Basade M, Singhal M, Rathi AK, Nandi M, Minhas S, Goswami C, *et al.* Practical consensus recommendations regarding the management of HER2 neu positive metastatic breast cancer. South Asian J Cancer 2018;7:146-50.

comprehensive signalling blockade.^[24,25] The CLEOPATRA trial^[26,27] showed a significant improvement in overall survival with pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive MBC, compared with placebo, trastuzumab, and docetaxel. The study showed the big power of adding a second antibody, pertuzumab, to trastuzumab as first-line metastatic therapy. Considering all the existing evidence, the panel were in support of the polled oncologists and concluded that either a combination of trastuzumab, pertuzumab and docetaxel or T-DM1 should be offered to patients who develop metastasis within 12 months of completing adjuvant trastuzumab. The panel added that the financial burden of adding another anti-HER2 agent to the treatment should also be taken into account before making a decision.

Treatment in Patients Not Receiving Adjuvant Trastuzumab

Treatment for HER2 positive early breast cancer patients generally includes trastuzumab. But there might be some patients who don't receive trastuzumab as a part of adjuvant treatment. When asked what will be their preferred treatment for such patients, the majority of the polled oncologists voted for a treatment comprising pertuzumab, trastuzumab and docetaxel as indicated in Table 2. A study by Murthy *et al.*^[28] has indicated that patients with HER2 positive breast cancer without prior exposure to trastuzumab have superior clinical outcomes than those who have had trastuzumab exposure when treated with trastuzumab for metastatic disease. In the study, the clinical benefit (complete response, partial response, or stable disease of ≥6 months) rates were 71% in the group who did not receive prior trastuzumab and 39% in the group previously treated with trastuzumab. The combination of pertuzumab, trastuzumab and docetaxel has been shown to be effective in HER2 positive MBC in the CLEOPATRA trial.^[26,27] The panel concluded that the combination of pertuzumab, trastuzumab and docetaxel should be the standard of care for patients who have not received trastuzumab in the adjuvant setting.

Treatment Options in de novo MBC patients

To the question as to what treatment they would recommend to de novo HER2 positive MBC patients, 50% of the polled oncologists were in support of recommending the standard pertuzumab plus trastuzumab plus docetaxel regimen while the remaining half were divided equally between recommending trastuzumab plus taxane and lapatinib plus taxane regimens [Table 3]. In Asia, up to 25% of breast cancer patients present with de novo MBC.^[29-32] De novo

MBC is metastatic at diagnosis. Despite presenting with more advanced-stage disease and higher tumour burdens, patients with de novo HER2-positive MBC have more favourable clinical outcomes than those with recurrent HER2-positive MBC.^[33] These differences may be due to effects of prior drug exposure in the patients with recurrent HER2 positive MBC. Overall, patients with de novo MBC have been shown to have a better outcome when compared with patients with recurrent MBC.^[34] As de novo patients are not exposed to trastuzumab or any other anti-HER2 agents, their efficacy is not reduced due to resistance. The consensus that was reached was that there is no significant reason to deviate from the standard treatment of pertuzumab plus trastuzumab plus docetaxel in patients with de novo MBC.

Treatment after Progression

Most patients with HER2 positive MBC eventually progress. Lungs are a common site of progression in all MBC patients.^[35] When asked as to what treatment would they prefer when the patient progresses to lungs 9 months after receiving a trastuzumab based treatment, the polled oncologists unanimously voted for T-DM1 [Table 4]. T-DM1 has been shown to be effective in second line therapy in the EMILIA trial^[20] and the TH3RESA trial.^[36] In the EMILIA trial, T-DM1 was compared with lapatinib plus capecitabine and T-DM1 regimen showed significantly improved OS and PFS. The T-DM1 regimen was also accompanied by less toxicity than the lapatinib plus capecitabine regimen. The TH3RESA trial was a randomised, open-label, phase 3 trial which took place in medical centres in 22 countries across Europe, North America, South America, and Asia-Pacific. In the trial, 602 patients with HER2 positive MBC who had been treated with two or more HER2-directed regimens, including trastuzumab and lapatinib, were randomized to receive T-DM1 or treatment of physician's choice. It was observed that the OS was favourable in the T-DM1 regimen. PFS was also significantly improved with T-DM1. The panel discussed about the available evidence on T-DM1's efficacy in the second line of treatment and were in support of the polled oncologists. The panel concluded that T-DM1 should be offered to patients who have progressed to lungs after a trastuzumab based treatment.

The next question that was asked to the oncologists was what treatment they would prefer for the patient who receives whole brain radiation therapy (WBRT) after developing multiple brain metastases while on treatment with T-DM1. The

Table 1: Question 1 - What treatment will you prefer in patients developing metastasis 9 months after stopping adjuvant trastuzumab?

Options	Trastuzumab + chemotherapy	Trastuzumab + chemotherapy + pertuzumab	Lapatinib + capecitabine	T-DM1
Percentage of polled oncologists	0	50	0	50

Expert group consensus: Either trastuzumab+pertuzumab+docetaxel or T-DM1 should be offered to patients who develop metastasis within 12 months of completing adjuvant trastuzumab

Table 2: Question 2 - What would be your preferred treatment option in case the patient would have not received trastuzumab in adjuvant setting?

Options	Trastuzumab + taxane	Lapatinib + taxane	Pertuzumab + trastuzumab + docetaxel	Trastuzumab + paclitaxel + everolimus	T-DM1
Percentage of polled oncologists	33.33	0	66.67	0	0

Expert group consensus: The combination of pertuzumab, trastuzumab and docetaxel should be the standard of care for patients who have not received trastuzumab in the adjuvant setting

polled oncologists were equally divided between preferring lapatinib plus capecitabine regimen and lapatinib plus pertuzumab treatment as indicated by Table 5. Previous studies have identified the subgroups of patients with triple-negative and HER2 positive breast cancer as having an increased risk for the development of brain metastases.^[37-40] Most chemotherapy agents and HER2 targeted therapies do not cross the intact blood brain barrier (BBB) or are pumped out of the central nervous system (CNS) by P-glycoproteins present in the BBB, therefore they may not reach sufficient therapeutic levels to eradicate metastatic cells.^[41] Lapatinib, a small molecule with potential ability to cross the BBB, has been extensively tested in the treatment of HER2-positive brain metastases. As a single agent, lapatinib has shown response rates in the brain ranging from 2.6 to 6% in heavily pre-treated patients.^[42,43] However, when added to capecitabine, response rates increase to 20 to 33%.^[43-47] The panel also discussed about the LANDSCAPE trial^[48] in which the combination of lapatinib and capecitabine was shown to be active as first-line treatment of brain metastases from HER2 positive breast cancer. Although the patients included in that study were not previously treated with WBRT, the panel thought that the combination of lapatinib and capecitabine indicated good efficacy in the patients with brain metastases. The panel concluded that the combination of lapatinib and capecitabine should be offered to patients who progress in the brain after receiving T-DM1.

Management of LVEF Drop in Patients on Dual HER2 Blockade Treatment

When asked as to how will they manage a LVEF drop >15% in a patient on dual HER2 blockade treatment (trastuzumab, pertuzumab and docetaxel) who recovers in one month, the majority of the oncologists were in support of recommending the continuation of only one anti-HER2 drug [Table 6].

Asymptomatic decreased LVEF can lead to a markedly increased risk of the development of congestive heart failure and death.^[49] Due to the known cardio-toxicity of trastuzumab, the package insert recommends baseline LVEF assessment and reassessment every 3 months during and upon completion of this therapy.^[50] Trastuzumab interruption is recommended for patients who develop treatment-induced cardio-toxicity and can lead to an incomplete course of treatment. However, trastuzumab is a highly effective targeted treatment that improves survival for patients with HER2-positive breast cancer and increasing efforts are needed to ensure that patients complete the full course of treatment without interruption. A retrospective study was done by Anthony Yu *et al.*^[51] to study the cardiac safety of continuous trastuzumab therapy among patients with asymptomatic declines in LVEF. They evaluated 573 patients out of which 92 developed treatment induced cardio-toxicity. Treatment induced cardio-toxicity was defined as an absolute decrease from baseline in LVEF of > or = 16%. Trastuzumab was continued without interruption in 31 of those 92 patients. None developed symptoms of heart failure despite continuous trastuzumab treatment. The study concluded that among patients who develop asymptomatic treatment-induced cardio-toxicity with LVEF of ≥50%, continuous trastuzumab therapy appears to be safe. Other studies evaluating the cardio-toxicity of trastuzumab plus pertuzumab treatment did not indicate increased risk of cardio-toxicity in neo-adjuvant as well as metastatic settings.^[52,53] The panel was slightly divided regarding the continuation of both the anti-HER2 agents. Cardio-toxicity is the most common reason for patients with HER2-positive breast cancer to receive an incomplete course of life-saving trastuzumab therapy. The panel concluded that given the life-saving benefit of anti-HER2 therapy, efforts should be made to avoid unnecessary interruption or discontinuation of treatment.

Table 3: Question 3 - What would be your preferred treatment option in case of de novo metastatic breast cancer patient?

Options	Trastuzumab + taxane	Lapatinib + taxane	Pertuzumab + trastuzumab + docetaxel	Trastuzumab + paclitaxel + everolimus	T-DM1
Percentage of polled oncologists	25	25	50	0	0

Expert group consensus: Patients with de novo MBC should also receive pertuzumab, trastuzumab and docetaxel as standard therapy. MBC=Metastatic breast cancer

Table 4: Question 4 - What would be your preferred treatment option when the patient progresses to lungs, 9 months after receiving a trastuzumab based treatment?

Options	Trastuzumab with different chemotherapy	Trastuzumab + pertuzumab + different chemotherapy	Lapatinib + capecitabine	T-DM1
Percentage of polled oncologists	0	0	0	100

Expert group consensus: T-DM1 should be offered to patients who have progressed after a trastuzumab based treatment

Table 5: Question 5 - What would be your preferred treatment option for the patient who receives whole brain radiation therapy after developing multiple brain metastases while on treatment with T-DM1?

Options	Trastuzumab + lapatinib	Lapatinib + capecitabine	Lapatinib + pertuzumab	Any other
Percentage of polled oncologists	0	50	50	0

Expert group consensus: WBRT followed by lapatinib and capecitabine should be offered to patients who progress in the brain. WBRT=Whole brain radiation therapy

Table 6: Question 6 - How would you manage a left ventricular ejection fraction drop >15% in a patient on dual human epidermal growth factor receptor 2 blockade treatment (trastuzumab, pertuzumab and docetaxel) who recovers in 1 month?

Options	No anti-HER 2 therapy	Continue single anti-HER 2 drug	Continue both anti-HER 2 drugs
Percentage of polled oncologists	0	66.67	33.3

Expert group consensus: Treatment plan should be modified on a personalized basis for each patient. In the metastatic setting where treatment is with palliative intent, further cardiac toxicity should be minimized as far as possible. HER 2=Human epidermal growth factor receptor 2

Take Home Message

1. Trastuzumab + pertuzumab + docetaxel or T-DM1 should be offered to patients who develop metastasis within 12 months of completing adjuvant trastuzumab. The financial burden of adding another anti-HER2 agent to the treatment should also be taken into account before making a decision.
2. The combination of pertuzumab, trastuzumab and docetaxel should be the standard of care for patients who have not received trastuzumab in the adjuvant setting.
3. Patients with de novo MBC have been shown to have a better outcome when compared with patients with recurrent MBC. No reason to deviate from standard therapy of pertuzumab, trastuzumab and docetaxel.
4. T-DM1 should be offered to patients who have progressed to lungs after a trastuzumab based treatment.
5. The combination of lapatinib and capecitabine has shown good results in patients progressing in brain. Lapatinib and capecitabine should be offered to patients who progress in the brain after receiving T-DM1.
6. Treatment plan should be modified on a personalized basis for each patient. If being given with curative intent, maintaining dose intensity (avoiding unnecessary interruption or discontinuation of treatment) is important. In the metastatic setting where treatment is with palliative intent, further cardiac toxicity should be minimized as far as possible.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Dykins R, Corbett IP, Henry JA, Wright C, Yuan J, Hennessy C, et al. Long-term survival in breast cancer related to overexpression of the c-erbB-2 oncoprotein: An immunohistochemical study using monoclonal antibody NCL-CB11. *J Pathol* 1991;163:105-10.
2. Andrulis IL, Bull SB, Blackstein ME, Sutherland D, Mak C, Sidlofsky S, et al. Neu/erbB-2 amplification identifies a poor-prognosis group of women with node-negative breast cancer. Toronto breast cancer study group. *J Clin Oncol* 1998;16:1340-9.
3. Hartmann LC, Ingle JN, Wold LE, Farr GH Jr., Grill JP, Su JQ, et al. Prognostic value of c-erbB2 overexpression in axillary lymph node positive breast cancer. Results from a randomized adjuvant treatment protocol. *Cancer* 1994;74:2956-63.
4. Press MF, Pike MC, Chazin VR, Hung G, Udove JA, Markowicz M, et al. Her-2/neu expression in node-negative breast cancer: Direct tissue quantitation by computerized image analysis and association of overexpression with increased risk of recurrent disease. *Cancer Res* 1993;53:4960-70.
5. Seshadri R, Firgaira FA, Horsfall DJ, McCaul K, Setlur V, Kitchen P, et al. Clinical significance of HER-2/neu oncogene amplification in primary breast cancer. The South Australian Breast Cancer Study Group. *J Clin Oncol* 1993;11:1936-42.
6. Têtu B, Brisson J. Prognostic significance of HER-2/neu oncoprotein expression in node-positive breast cancer. The influence of the pattern of immunostaining and adjuvant therapy. *Cancer* 1994;73:2359-65.
7. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr., Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673-84.
8. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659-72.
9. Slamon D, Eiermann W, Robert N. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. *Breast Cancer Res Treat* 2005;94 Suppl 1:S5a.
10. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Solola R, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006;354:809-20.
11. Vaidyanathan K, Kumar P, Reddy CO, Deshmone V, Somasundaram K, Mukherjee G, et al. ErbB-2 expression and its association with other biological parameters of breast cancer among Indian women. *Indian J Cancer* 2010;47:8-15.
12. Nihra P, Patel S, Taviad D, Chaudhary S. Study of ER (Estrogen Receptor), PR (Progesterone Receptor) and HER-2/NEU (Human Epidermal Growth Factor Receptor) expression by immunohistochemistry in breast carcinoma. *Int J Biomed Adv Res* 2014;5:275-8.
13. Zubeda S, Kaipa PR, Shaik NA, Mohiuddin MK, Vaidya S, Pavani B, et al. Her-2/neu status: A neglected marker of prognostication and management of breast cancer patients in India. *Asian Pac J Cancer Prev* 2013;14:2231-5.
14. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-92.
15. Falkson G, Gelman RS, Leone L, Falkson CI. Survival of premenopausal women with metastatic breast cancer. Long-term follow-up of Eastern Cooperative Group and Cancer and Leukemia Group B studies. *Cancer* 1990;66:1621-9.
16. Greenberg PA, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU, et al. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996;14:2197-205.
17. Leach B. T-DM1 Approved for HER2-Positive Metastatic Breast Cancer. Available from: <http://www.onclive.com/web-exclusives/t-dm1-approved-for-her2-positive-metastatic-breast-cancer>.
18. T-DM1 (Kadcyla) Wins FDA Approval. Available from: <http://www.breastcancer.org/research-news/20130222-5>.
19. Amiri-Kordestani L, Blumenthal GM, Xu QC, Zhang L, Tang SW, Ha L, et al. FDA approval: Ado-trastuzumab emtansine for the treatment of patients with HER2-positive metastatic breast cancer. *Clin Cancer Res* 2014;20:4436-41.
20. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367:1783-91.
21. Hurvitz SA, Dirix L, Kocsis J, Bianchi GV, Lu J, Vinholes J, et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2013;31:1157-63.
22. Yardley DA, Krop IE, LoRusso PM, Mayer M, Barnett B, Yoo B, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer previously treated with chemotherapy and 2 or more HER2-targeted agents: Results from the T-PAS expanded access study. *Cancer J* 2015;21:357-64.
23. Jacot W, Jean-Sébastien Frenel EP, Guiu S, Levy C. Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases. *Breast Cancer Research and Treatment* 2016;157:307-18.
24. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res* 2004;64:2343-6.
25. Scheuer W, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M, et al. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res* 2009;69:9330-6.
26. Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2013;14:461-71.
27. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015;372:724-34.
28. Murthy RK, Varma A, Mishra P, Hess KR, Young E, Murray JL, et al. Effect of adjuvant/neoadjuvant trastuzumab on clinical outcomes in patients with HER2-positive metastatic breast cancer. *Cancer* 2014;120:1932-8.
29. Yip CH, Taib NA, Mohamed I. Epidemiology of breast cancer in Malaysia. *Asian Pac J Cancer Prev* 2006;7:369-74.
30. Tan EY, Wong HB, Ang BK, Chan MY. Locally advanced and metastatic breast cancer in a tertiary hospital. *Ann Acad Med Singapore* 2005;34:595-601.
31. Lim SE, Back M, Quek E, Iau P, Putti T, Wong JE, et al. Clinical observations from a breast cancer registry in Asian women. *World J Surg* 2007;31:1387-92.
32. Chopra R. The Indian scene. *J Clin Oncol* 2001;19:106S-111S.
33. Yardley DA, Kaufman PA, Brufsky A, Yood MU, Rugo H, Mayer M, et al. Treatment patterns and clinical outcomes for patients with *de novo* versus

- recurrent HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2014;145:725-34.
34. Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, *et al.* Prognosis of metastatic breast cancer: Are there differences between patients with *de novo* and recurrent metastatic breast cancer? *Br J Cancer* 2015;112:1445-51.
 35. Wu Q, Li J, Zhu S, Wu J, Chen C, Liu Q, *et al.* Breast cancer subtypes predict the preferential site of distant metastases: A SEER based study. *Oncotarget* 2017;8:27990-6.
 36. Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, *et al.* Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): A randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:689-99.
 37. Gabos Z, Sinha R, Hanson J, Chauhan N, Hugh J, Mackey JR, *et al.* Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. *J Clin Oncol* 2006;24:5658-63.
 38. Tham YL, Sexton K, Kramer R, Hilsenbeck S, Elledge R. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. *Cancer* 2006;107:696-704.
 39. Pestalozzi BC, Zahrieh D, Price KN, Holmberg SB, Lindtner J, Collins J, *et al.* Identifying breast cancer patients at risk for central nervous system (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). *Ann Oncol* 2006;17:935-44.
 40. Nam BH, Kim SY, Han HS, Kwon Y, Lee KS, Kim TH, *et al.* Breast cancer subtypes and survival in patients with brain metastases. *Breast Cancer Res* 2008;10:R20.
 41. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin Oncol* 2004;22:3608-17.
 42. Lin NU, Carey LA, Liu MC, Younger J, Come SE, Ewend M, *et al.* Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2008;26:1993-9.
 43. Lin NU, Diéras V, Paul D, Lossignol D, Christodoulou C, Stemmler HJ, *et al.* Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res* 2009;15:1452-9.
 44. Sutherland S, Ashley S, Miles D, Chan S, Wardley A, Davidson N, *et al.* Treatment of HER2-positive metastatic breast cancer with lapatinib and capecitabine in the lapatinib expanded access programme, including efficacy in brain metastases – the UK experience. *Br J Cancer* 2010;102:995-1002.
 45. Metro G, Foglietta J, Russillo M, Stocchi L, Vidiri A, Giannarelli D, *et al.* Clinical outcome of patients with brain metastases from HER2-positive breast cancer treated with lapatinib and capecitabine. *Ann Oncol* 2011;22:625-30.
 46. Iwata H, Narabayashi M, Ito Y, Saji S, Fujiwara Y, Usami S, *et al.* A phase II study of lapatinib for brain metastases in patients with HER2-overexpressing breast cancer following trastuzumab based systemic therapy and cranial radiotherapy: Subset analysis of Japanese patients. *Int J Clin Oncol* 2013;18:621-8.
 47. Ro J, Park S, Kim S, Kim TY, Im YH, Rha SY, *et al.* Clinical outcomes of HER2-positive metastatic breast cancer patients with brain metastasis treated with lapatinib and capecitabine: An open-label expanded access study in Korea. *BMC Cancer* 2012;12:322.
 48. Bachelot T, Romieu G, Campone M, Diéras V, Cropet C, Dalenc F, *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;14:64-71.
 49. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS, *et al.* Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation* 2003;108:977-82.
 50. Herceptin (Trastuzumab) Package Insert. South San Francisco, CA: Genentech, Incorporated; 2009.
 51. Yu AF, Yadav NU, Eaton AA, Lung BY, Thaler HT, Liu JE, *et al.* Continuous trastuzumab therapy in breast cancer patients with asymptomatic left ventricular dysfunction. *Oncologist* 2015;20:1105-10.
 52. Yu AF, Singh JC, Wang R, Liu JE, Eaton A, Oeffinger KC, *et al.* Cardiac safety of dual anti-HER2 therapy in the neoadjuvant setting for treatment of HER2-positive breast cancer. *Oncologist* 2017;22:642-7.
 53. Yu AF, Manrique C, Pun S, Liu JE, Mara E, Fleisher M, *et al.* Cardiac safety of paclitaxel plus trastuzumab and pertuzumab in patients with HER2-positive metastatic breast cancer. *Oncologist* 2016;21:418-24.

Best of ASCO India

6-8 July 2018, Coimbatore

Dr R Bharath - bharath37@gmail.com

www.BestOfASCO.in

Conference Organizer : Kashish Parikh

+91-98190-25850 and kashishparikh@gmail.com

4th AMMO Conference

11-12 August 2018, Nashik

Dr Shailesh Bondarde - shaileshbondarde@yahoo.com

www.medintelservices.com

Conference Organizer : Kashish Parikh

+91-98190-25850 and kashishparikh@gmail.com

ICON

39th ICON Conference

8-9 Sept 2018, Indore

Dr PM Parikh - purvish1@gmail.com

www.OncologyIndia.org

Conference Organizer : Kashish Parikh

+91-98190-25850 and kashishparikh@gmail.com