Prognostic and predictive factors in metastatic breast cancer

AUTHOR: Stephen Chia, MD, FRCPC
SECTION EDITOR: Harold J Burstein, MD, PhD
DEPUTY EDITOR: Sadhna R Vora, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Apr 05, 2022.**

INTRODUCTION

Although metastatic breast cancer (MBC) is unlikely to be cured, meaningful improvements in survival have been seen, coincident with the introduction of newer systemic therapies [1-3]. Median overall survival approaches two years, although this can range from a few months to many years, dependent on molecular subtype and treatments received [4]. As greater knowledge is generated regarding the specific molecular alterations associated with individual breast cancers, it will be of paramount importance to distinguish the differences between the multitudes of prognostic factors likely expressed versus the few predictive factors that will help select specific therapy(s).

This topic reviews prognostic and predictive factors for patients with MBC. A further discussion of prognostic and predictive factors utilized in primary breast cancer (for patients with non-metastatic disease) is covered separately. (See "Prognostic and predictive factors in early, non-metastatic breast cancer".)

PROGNOSTIC VERSUS PREDICTIVE FACTORS

By definition, a **prognostic** factor is capable of providing information on clinical outcome at the time of diagnosis, or at various times during the patient's course with metastatic disease, independent of therapy. Such markers are usually indicators of rate of growth, sites of invasion,

and tumor burden [5,6]. By contrast, a **predictive** factor is capable of providing information on the likelihood of response to a given therapeutic modality. Such markers are either within the target of the treatment, the surrounding stroma, or serve as modulators or epiphenomena related to expression and/or function of the target. Although they can be separately classified, several factors in breast cancer are both prognostic and predictive (eg, the presence of over-expression of the human epidermal growth factor receptor 2).

PROGNOSTIC FACTORS

The most useful prognostic factors are clinically based. While quantification of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) are also prognostic, their role in the clinical management of patients with MBC is not clear and requires further elucidation.

Clinical factors — The effect of clinical factors on prognosis is summarized below:

- Relapse-free interval of ≥2 years from primary breast cancer is more favorable than a shorter time to relapse [7-10].

- Patients with metastases involving the chest wall, bones, or lymph nodes may have prolonged progression-free survival (PFS), while those with hepatic and/or lymphangitic pulmonary disease tend to have shorter PFS and overall survival (OS) [7,8,11]. Patients with symptomatic lymphangitic lung metastases, bone marrow replacement with associated cytopenias, leptomeningeal carcinomatous, or significant liver metastases with associated liver dysfunction are described as having visceral crisis [12]. Patients without visceral crisis but with poor prognostic features represent an intermediate phenotype.

- Patients with hormone receptor positivity generally have a more favorable prognosis, and patients with hormone receptor-positive tumors for both estrogen receptor (ER) and progesterone receptor (PR) have significantly longer survival than single hormone receptor-positive tumors (ER-positive/PR-negative or ER-negative/PR-positive) [13]. Patients with either human epidermal growth factor receptor 2 (HER2) overexpression or triple (ER, PR, HER2)-negative MBC have a shorter median survival, in particular, in the era without targeted therapy (eg, anti-HER2 therapy) [9,14,15]. The prognosis associated with particular molecular phenotypes is discussed separately. (See "Prognostic and predictive factors in early, non-metastatic breast cancer", section on 'Global genomic profiling'.)

- Other adverse prognostic features include significant weight loss, poor performance status (table 1), and elevated serum lactic dehydrogenase [7,16]. Age less than 35 years old is a poor prognostic factor for women with early-stage breast cancer, but the effect of

age on survival after recurrence has not been clearly established [9,17]. Similarly, the initial stage at diagnosis does not reliably indicate prognosis after relapse.

Circulating tumor cells — CTCs appear to be of prognostic value for patients with MBC. However, their role to guide management of these patients is not well defined. Therefore, we do not recommend routinely assessing for CTCs in these patients.

The presence of CTCs (typically defined as ≥5/7.5 mL whole blood) in the peripheral blood of women with breast cancer has been associated with a poorer prognosis in patients with MBC (versus undetectable or <5 cells/7.5 mL whole blood) [18-25]. This was shown in a pooled analysis of over 1900 patients who participated in 1 of 20 studies in MBC, all of whom underwent quantification for CTCs [26]. The main findings were as follows:

- Compared with patients without elevated CTCs, those with elevated CTCs at baseline (47 percent) had shortened PFS (hazard ratio [HR] 1.92, 95% CI 1.73-2.14) and OS (HR 2.78, 95% CI 2.42-3.19).

- Patients with increasing CTCs three to five weeks after the start of a new line of therapy had worse PFS (HR 1.85, 95% CI 1.48-2.32) and OS (HR 2.26, 95% CI 1.68-3.03) compared with those whose CTCs did not rise. A similar association between rising CTCs and survival outcomes was noted at weeks 6 to 8.

In addition, the role of CTCs to guide treatment decisions for women with MBC was prospectively evaluated in the SWOG 0500 trial [24]. For this trial, 595 women with MBC who underwent chemotherapy had evaluation for CTCs at baseline and then after one cycle. Women whose CTCs remained elevated after the first cycle of therapy were randomly assigned to either continue their initial treatment plan or to change of chemotherapy. The main findings of this trial are as follows:

- Of 126 women with persistently elevated CTCs after their first cycle of chemotherapy, changing to an alternate regimen had no difference in OS compared with continuation of the initial regimen (median 12.5 versus 10.7 months, respectively).

- There is an overall prognostic value of elevated CTCs. The median OS was 35, 23, and 13 months in those without a baseline elevation of CTCs, those who had a decline in their CTCs after the first cycle (but elevated CTCs at baseline), and those with persistently elevated CTCs, respectively.

In summary, these studies support the prognostic value of CTCs. However, their role in the monitoring of patients remains controversial. We agree with the 2015 American Society of

Clinical Oncology expert panel update, which concluded that measurement of CTCs should not be used to influence treatment decisions in metastatic disease at this time [27].

Circulating tumor DNA — A significant proportion of MBC patients have fragments of tumor DNA that are potentially detectable and able to be analyzed circulating in blood. ctDNA assays at present, however, do not have a validated clinical role in breast cancer.

Evidence suggests that early dynamic changes in ctDNA relative to treatment may predict PFS outcomes to palbociclib and fulvestrant, according to an analysis of plasma samples from PALOMA-3 [28]. The investigators utilized plasma samples from baseline with detectable phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) mutation in ctDNA with matched plasma samples after two weeks of treatment and found a quantitative amount above the median on palbociclib, and fulvestrant had an inferior PFS compared with those below the median on day 15 (HR 3.94, 95% CI 1.61-9.64). A separate study suggests that patients with high levels in both ctDNA and CTCs have a more than 17-fold increase in risk of death compared with patients with low levels of each [25]. However, a guideline from the American Society of Clinical Oncology notes that, while some ctDNA assays may have utility in certain contexts, there is insufficient evidence of clinical validity and utility for the majority of ctDNA assays in advanced cancer [29].

Gene expression analyses — While the Oncotype Dx 21-gene recurrence score (RS) and Predictor Analysis of Microarray 50 (PAM50) intrinsic subtype have an established prognostic and predictive role in non-metastatic breast cancer, early evidence suggests that they may be useful in the metastatic disease as well. However, we await further data before recommending their use in this setting, particularly to address if there is any predictive capacity to the assays in selection of optimal therapy for MBC. Use in non-metastatic breast cancer is discussed elsewhere. (See "Prognostic and predictive factors in early, non-metastatic breast cancer", section on 'Receptor status' and "Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer".)

In a retrospective analysis of 821 tumor samples from postmenopausal women with hormone receptor-positive MBC, intrinsic subtype as determined by the PAM50 assay was the strongest prognostic factor, with a luminal A subtype correlating with improved progression-free and overall survival (OS) relative to other subtypes [30]. Progression-free and overall survival were as follows, respectively, according to subtype: luminal A, 16.9 and 45 months; luminal B, 11 and 37 months; HER2-enriched, 4.7 and 16 months; and basal-like, 4.1 and 23 months.

Similarly, the Recurrence Score (RS by Oncotype DX) has shown promising results in the metastatic setting, though prospective randomized data are still needed [31]. In a registry study

of 101 MBC patients, RS was associated with time to tumor progression and OS, and on multivariate analysis was independently prognostic for these outcomes among the 69 patients who had hormone-positive, HER2-negative disease.

PREDICTIVE FACTORS

Tests done on metastatic tissue — An attempt should be made to biopsy the tumor of all patients with MBC in order to re-examine the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Data suggest that discordance of these markers between the primary and MBC may be clinically meaningful, with discordance rates of approximately 13 and 30 percent for ER and PR, respectively, and ranging from 3 to 5 percent for HER2 [32,33]. Alterations in either the hormone receptor status and/or the HER2 status are both prognostic but also significantly predictive (would significantly alter treatment options to be considered and attempted). (See "Overview of the approach to metastatic breast cancer", section on 'Biopsy of metastatic lesion'.)

Hormone receptors — Assay of hormone receptors is a routine part of the evaluation of breast cancers, since the results predict the potential for a clinical response (or benefit) to hormone therapy, both in the adjuvant setting and for those with metastatic disease. The predictive and prognostic implications of hormone receptor expression are discussed elsewhere. (See "Hormone receptors in breast cancer: Clinical utility and guideline recommendations to improve test accuracy" and "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer" and "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

HER2 overexpression — As with hormone receptors, assay for human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification is a routine part of the evaluation of breast cancers (both primary and metastatic) because it is predictive of who might benefit from HER2-directed therapies, such as trastuzumab, ado-trastuzumab emtansine, pertuzumab, and lapatinib [34]. Guidelines for HER2 testing from a joint American Society of Clinical Oncology/College of American Pathologists consensus panel [34], the data on HER2 status and treatment as well as recommendations for optimal performance, interpretation, and reporting of individual assays are discussed in detail elsewhere. (See "HER2 and predicting response to therapy in breast cancer", section on 'Testing for HER2 expression'.)

PD-L1 expression — Expression of programmed cell death-ligand 1 (PD-L1) with a clinical predictive score (greater than or equal to 10) within the KEYNOTE 355 study has been shown, in subset analyses, to predict benefit for the addition of the programmed cell death 1 (PD-1)

antibody pembrolizumab to first-line chemotherapy in triple-negative breast cancer. These data are discussed elsewhere. (See "ER/PR negative, HER2-negative (triple-negative) breast cancer", section on 'PD-L1 combined positive score of at least 10'.)

PIK3CA mutations — Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) mutations are found in 30 to 40 percent of breast cancers and are associated with a poorer prognosis in advanced breast cancers.

In a phase 3 trial (SOLAR-1), *PIK3CA* mutation-positive status (either in tumor tissue or in circulating tumor DNA) has been shown to predict clinical benefit in improving progression-free survival (PFS) for the addition of an alpha-specific PIK3CA inhibitor, alpelisib, to fulvestrant in ER-positive/HER2-negative metastatic breast cancers. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

It is important in consideration of this therapeutic regimen to ensure the testing for *PIK3CA* "hot-spot" mutations is aligned with those tested on SOLAR-1 (exons 7, 9, and 20).

Other tests — Early evidence suggests that the Predictor Analysis of Microarray 50 (PAM50) intrinsic subtype may have a predictive role for certain types of anti-HER2 therapies in metastatic disease, though based on available data, we do not recommend its use in this setting. In a retrospective study including 644 tumor samples from patients with hormone receptor-positive/HER2-negative disease, patients with a HER2-enriched profile experienced improved progression-free survival (PFS) with the addition of lapatinib to endocrine therapy, while those with other subtypes did not [30]. Prospective validation is necessary before incorporation of this assay in the management of metastatic disease.

Serum tumor markers — Tumor markers, including CA 15-3 and CA 27.29, are well-characterized assays that detect circulating MUC-1 antigen in peripheral blood and are commonly used to monitor disease status for patients undergoing treatment for MBC. This is particularly true in situations in which there appears to be a correlation of tumor burden in metastatic disease with degree of elevation of these tumor markers, and in which conventional clinical examination and radiological monitoring is either difficult or infrequent.

We support the 2015 American Society of Clinical Oncology updated guidelines, which state that circulating tumor markers can be useful for monitoring selected patients with metastatic disease [27]. However, while prognostic, serum tumor markers are not predictive for treatment outcomes and have no role in the selection of a therapeutic regimen. (See "Overview of the approach to metastatic breast cancer", section on 'Monitoring therapy'.)

Germline BRCA testing — Germline breast cancer susceptibility gene (*BRCA*) testing for patients with metastatic HER2-negative breast cancer may assist in treatment selection. Patients who have a germline *BRCA* mutation may potentially benefit from the oral inhibitors of poly(ADP-ribose) polymerase (PARP) olaparib and talazoparib. Both have both demonstrated clinical activity in phase III trials compared with treatments of clinician choice. These results are discussed elsewhere. (See "Overview of the approach to metastatic breast cancer", section on 'Special considerations'.)

Next-generation sequencing of breast tumors — Understanding the molecular drivers of cancer progression and metastases is an area of ongoing and active research, predominantly driven by the goal of identifying specific genomic aberrations that may ultimately result in individualized cancer treatment. In addition to likely providing prognostic information, the value of next-generation sequencing (NGS) to identify and predict candidates for specific mutation-driven treatment holds promise but is not yet ready for routine clinical use.

Various platforms for NGS of breast cancers are now commercially available. However, the clinician should be clear why the test might be ordered. There are several potential reasons:

- To determine if the metastasis is expressing either estrogen receptor (ER) or HER2 if its primary did not. This is the basis of the recommendation to re-biopsy a metastasis as discussed above, and we recommend that the marker status be determined by a dedicated test, as per the American Society of Clinical Oncology/College of American Pathologists guidelines [35,36].

- To determine if the metastasis has a genetic or phenotypic abnormality that renders the patient potentially eligible for a clinical trial directed against that alteration.

- To determine if the patient has a genetic or phenotypic abnormality that might be a target for an available drug that has been shown to be effective in another type of cancer other than breast. Preferably, this should be performed within the context of a clinical trial.

Although the ability to decipher genomic aberrations in individual breast cancers to the single nucleotide resolution is now possible in both a timely and cost-achievable manner, there is a lack of data to show that this information can guide treatment decisions for patients with MBC.

The tumor and germline DNA from 825 primary breast cancer patients across six different platforms (mRNA expression, whole-exome sequencing, DNA methylation, single-nucleotide polymorphisms, miRNA sequencing, and by reverse-phase protein array) was performed by The Cancer Genome Atlas, and their results published in 2012 [37]. The most frequently observed

somatic mutations by far were in the *p53* gene and the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) gene:

- Mutated p53 was found in 37 percent of samples, but predominantly in basal-like breast cancers (80 percent) and the HER2-enriched subtype (72 percent).

- A mutated *PIK3CA* gene was observed with an overall prevalence of 36 percent; however, it was more so within the ER-positive (luminal) subtypes, with an observed frequency of 45 percent in the luminal A subtype and 29 percent in luminal B breast cancers. The identification of a hot-spot mutation in ER-positive, HER2-negative MBC was used to select the patient population on the SOLAR-1 trial [38].

Other less frequent somatic mutations include:

- Mitogen-activated protein kinase kinase kinase 1 (*MAP3K1*, 8 percent).

- GATA binding protein 3 (*GATA3*, 11 percent).

- Histone-lysine N-methyltransferase *MLL3* (7 percent).

- Cadherin 1, type 1, E-cadherin (*CDH1*, 7 percent).

- Mitogen-activated protein kinase kinase 4 (*MAP2K4*, 4 percent).

- Phosphatase and tensin homolog (*PTEN*, 3 percent).

- RAC-alpha serine/threonine-protein kinase (*AKT1*, 2 percent).

- Neurotrophic tropomyosin-related kinase translocations (*NTRK*, 1 percent). Chromosomal alterations involving NTRK genes (*NTRK1, NTRK2, NTRK3*) leading to fusion chimeric TRK proteins with subsequent oncogenic potential are found exclusively in secretory breast cancers. Phase II basket trials of pan-TRK inhibitors, which included a few breast cancers with *NTRK* translocations, have demonstrated high response rates and prolonged duration of clinical benefit. (See "TRK fusion-positive cancers and TRK inhibitor therapy".)

Another example includes the METABRIC study, which produced an integrated analysis of copy number and gene expression using profiles from 2000 breast tumors [39]. The study discovered 10 novel subgroups (integrated clusters) with individual prognostic effect. However, as the samples were predominantly of early-stage breast tumors, it is not clear whether there is the same prognostic capacity in the metastatic setting. Furthermore, the ability to tailor individual treatments (in either early or advanced stage) with associated improved outcomes was not assessed in the study.

Trials suggest that the use of molecularly targeted agents outside their indications does not necessarily improve outcomes relative to standard of care in heavily pretreated patients with breast cancer. One trial, known as the SAFIR01 trial, aimed to define the proportion of patients in which a targeted therapy could be offered based on the results of the genomic analyses [40]. This trial enrolled 423 patients with MBC, in which biopsies were obtainable in 407. A defined and targetable genomic alteration was identified in 195 (46 percent) patients. However, only 55 patients (13 percent) received personalized therapy on the basis of genomic analyses; of these patients, four had an objective response, and an additional nine patients had no evidence of disease progression for 16 weeks or longer.

Similarly, in the randomized phase II SHIVA trial, among 741 patients with cancer, 293 had a targetable molecular alteration, and 195 were randomly assigned to a molecularly targeted agent or treatment at clinician's choice [41]. Of these, 40 patients had breast cancer. Among all treated patients, the median PFS was 2.3 months with targeted therapy and 2.0 months in the control group.

Taken together, these data suggest that actionable alterations can be identified in a proportion of metastatic breast cancers. However, further evaluation on the predictive ability of these NGS findings is required before they are used in routine clinical practice. In addition, we do not recommend that NGS evaluation be part of standard of care at this time because there is little or no evidence that just because a targeted therapy works in one cancer that it will work in the same manner in another, even if the molecular target is present in both tumor types.

An expert panel has produced a guidance document to rank DNA alterations into tiers of evidence for clinical utility for selecting breast cancer patients for targeted therapies according to ESCAT [42]. Only *HER2* amplification, germline *BRCA1/2* mutations, and *PIK3CA* mutations were given level 1A evidence as molecular targets.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

SUMMARY AND RECOMMENDATIONS

Although metastatic breast cancer (MBC) is unlikely to be cured, meaningful improvements in survival have been seen, coincident with the introduction of newer systemic therapies. Median

overall survival (OS) approaches two years, although this can range from a few months to many years. (See 'Introduction' above.)

- Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) have predictive value for patients with MBC. Because the expression of these receptors may differ between metastatic and primary breast cancer, a repeat biopsy should be obtained in women with MBC. (See 'Tests done on metastatic tissue' above.)

- Tumor markers, including CA 15-3 and CA 27.29, can sometimes correlate with clinical or radiologically defined disease burden. In other patients, they may be useful markers of disease when conventional clinical examination and radiological monitoring is either difficult or infrequent. While prognostic, they do not hold predictive value for selection of and response to treatment. (See 'Serum tumor markers' above.)

- The presence and serial rise of circulating tumor cells (CTCs, typically defined as ≥5/7.5 mL whole blood) and circulating tumor DNA (ctDNA) in the peripheral blood of women with breast cancer has been associated with a poorer prognosis in patients with MBC. However at present, measurement of CTCs or ctDNA should not be used to influence treatment decisions in metastatic disease. (See 'Circulating tumor cells' above.)

- Understanding the molecular drivers of cancer progression and metastases is an area of ongoing and active research. While possibly prognostic, the value of next-generation sequencing to predict candidates for specific mutation-driven treatment is not yet ready for routine clinical use (see 'Next-generation sequencing of breast tumors' above). They should only be considered and used for enrollment onto clinical research trials and programs.

Use of UpToDate is subject to the Terms of Use.

REFERENCES

1. Chia SK, Speers CH, D'yachkova Y, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. Cancer 2007; 110:973.

2. Gennari A, Conte P, Rosso R, et al. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. Cancer 2005; 104:1742.

3. Dafni U, Grimani I, Xyrafas A, et al. Fifteen-year trends in metastatic breast cancer survival

in Greece. Breast Cancer Res Treat 2010; 119:621.

4. Greenberg PA, Hortobagyi GN, Smith TL, et al. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol 1996; 14:2197.

5. Gasparini G, Pozza F, Harris AL. Evaluating the potential usefulness of new prognostic and predictive indicators in node-negative breast cancer patients. J Natl Cancer Inst 1993; 85:1206.

6. Hayes DF, Trock B, Harris AL. Assessing the clinical impact of prognostic factors: when is "statistically significant" clinically useful? Breast Cancer Res Treat 1998; 52:305.

7. Swenerton KD, Legha SS, Smith T, et al. Prognostic factors in metastatic breast cancer treated with combination chemotherapy. Cancer Res 1979; 39:1552.

8. Hortobagyi GN, Smith TL, Legha SS, et al. Multivariate analysis of prognostic factors in metastatic breast cancer. J Clin Oncol 1983; 1:776.

9. Clark GM, Sledge GW Jr, Osborne CK, McGuire WL. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. J Clin Oncol 1987; 5:55.

10. Harris JR, Hellman S. Observations on survival curve analysis with particular reference to breast cancer treatment. Cancer 1986; 57:925.

11. Robertson JF, Dixon AR, Nicholson RI, et al. Confirmation of a prognostic index for patients with metastatic breast cancer treated by endocrine therapy. Breast Cancer Res Treat 1992; 22:221.

12. Barrios CH, Sampaio C, Vinholes J, Caponero R. What is the role of chemotherapy in estrogen receptor-positive, advanced breast cancer? Ann Oncol 2009; 20:1157.

13. Stuart-Harris R, Shadbolt B, Palmqvist C, Chaudri Ross HA. The prognostic significance of single hormone receptor positive metastatic breast cancer: an analysis of three randomised phase III trials of aromatase inhibitors. Breast 2009; 18:351.

14. Emi Y, Kitamura K, Shikada Y, et al. Metastatic breast cancer with HER2/neu-positive cells tends to have a morbid prognosis. Surgery 2002; 131:S217.

15. Ismail-Khan R, Bui MM. A review of triple-negative breast cancer. Cancer Control 2010; 17:173.

16. Yamamoto N, Watanabe T, Katsumata N, et al. Construction and validation of a practical prognostic index for patients with metastatic breast cancer. J Clin Oncol 1998; 16:2401.

17. Leivonen MK, Kalima TV. Prognostic factors associated with survival after breast cancer recurrence. Acta Oncol 1991; 30:583.

18. Cristofanilli M, Hayes DF, Budd GT, et al. Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer. J Clin Oncol 2005; 23:1420.

19. Hayes DF, Cristofanilli M, Budd GT, et al. Circulating tumor cells at each follow-up time point during therapy of metastatic breast cancer patients predict progression-free and overall survival. Clin Cancer Res 2006; 12:4218.

20. Cristofanilli M, Broglio KR, Guarneri V, et al. Circulating tumor cells in metastatic breast cancer: biologic staging beyond tumor burden. Clin Breast Cancer 2007; 7:471.

21. Dawood S, Broglio K, Valero V, et al. Circulating tumor cells in metastatic breast cancer: from prognostic stratification to modification of the staging system? Cancer 2008; 113:2422.

22. Budd GT, Cristofanilli M, Ellis MJ, et al. Circulating tumor cells versus imaging--predicting overall survival in metastatic breast cancer. Clin Cancer Res 2006; 12:6403.

23. Zhang L, Riethdorf S, Wu G, et al. Meta-analysis of the prognostic value of circulating tumor cells in breast cancer. Clin Cancer Res 2012; 18:5701.

24. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol 2014; 32:3483.

25. Ye Z, Wang C, Wan S, et al. Association of clinical outcomes in metastatic breast cancer patients with circulating tumour cell and circulating cell-free DNA. Eur J Cancer 2019; 106:133.

26. Bidard FC, Peeters DJ, Fehm T, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. Lancet Oncol 2014; 15:406.

27. Van Poznak C, Somerfield MR, Bast RC, et al. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2015; 33:2695.

28. O'Leary B, Hrebien S, Morden JP, et al. Early circulating tumor DNA dynamics and clonal selection with palbociclib and fulvestrant for breast cancer. Nat Commun 2018; 9:896.

29. Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol 2018; 36:1631.

30. Prat A, Cheang MC, Galván P, et al. Prognostic Value of Intrinsic Subtypes in Hormone Receptor-Positive Metastatic Breast Cancer Treated With Letrozole With or Without Lapatinib. JAMA Oncol 2016; 2:1287.

31. King TA, Lyman JP, Gonen M, et al. Prognostic Impact of 21-Gene Recurrence Score in Patients With Stage IV Breast Cancer: TBCRC 013. J Clin Oncol 2016; 34:2359.

32. de Dueñas EM, Hernández AL, Zotano AG, et al. Prospective evaluation of the conversion rate in the receptor status between primary breast cancer and metastasis: results from the GEICAM 2009-03 ConvertHER study. Breast Cancer Res Treat 2014; 143:507.

33. Amir E, Clemons M, Purdie CA, et al. Tissue confirmation of disease recurrence in breast cancer patients: pooled analysis of multi-centre, multi-disciplinary prospective studies. Cancer Treat Rev 2012; 38:708.

34. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018; 36:2105.

35. Wolff AC, Hammond ME, Hicks DG, et al. Reply to R. Bhargava et al and K. Lambein et al. J Clin Oncol 2014; 32:1857.

36. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010; 28:2784.

37. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012; 490:61.

38. André F, Ciruelos EM, Rubovszky G, et al. Alpelisib (ALP) + fulvestrant (FUL) for advanced breast cancer (ABC): Results of the phase III SOLAR-1 trial. Ann Oncol 2018; 29 Suppl 8:viii709.

39. Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 2012; 486:346.

40. André F, Bachelot T, Commo F, et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). Lancet Oncol 2014; 15:267.

41. Le Tourneau C, Delord JP, Gonçalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 2015; 16:1324.

42. Condorelli R, Mosele F, Verret B, et al. Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2019; 30:365.

Topic 88415 Version 13.0

GRAPHICS

Karnofsky and Eastern Cooperative Oncology Group (ECOG) performance status measures

Karnofsky	
Score	**Definition**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated, although death is not imminent
20	Hospitalization is necessary, very sick, active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

ECOG	
Score	**Definition**
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair
5	Dead

Graphic 57945 Version 11.0

Contributor Disclosures

Stephen Chia, MD, FRCPC Grant/Research/Clinical Trial Support: AstraZeneca [Targeted therapy in HER 2 low MBC]; Genomic Health [Prognosis and prediction in early-stage breast cancer]; Hoffmann LaRoche [Immunotherapy in metastatic triple-negative breast cancer]; Merck [Targeted therapy in ER+/HER 2 negative stage II-III breast cancer]; Novartis [Targeted therapy in PIK3CA mutated ER+ MBC]. Consultant/Advisory Boards: AztraZeneca [Targeted therapy in HER 2 low MBC]; Eli Lilly [CDK 4/6 inhibitor in high risk ER+/HER 2 negative early stage breast cancer]; Genomic Health [Prognosis in metastatic breast cancer]; Gilead [ADC in metastatic triple negative breast cancer]; Merck [Metastatic triple-negative breast cancer]; Novartis [Targeted therapy in PIK3CA mutated ER+ MBC]. All of the relevant financial relationships listed have been mitigated. **Harold J Burstein, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Sadhna R Vora, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

$\rightarrow$