METASTATIC BREAST CANCER

Executive Summary

Metastatic breast cancer is defined as disease beyond the breast and regional lymph nodes. Although metastatic breast cancer is generally incurable, patients can be treated and palliated with hormonal therapy, chemotherapy, and/or targeted agents.[1,13]

Breast cancer does metastasize to any site in the body, including bones, liver, lung, serosal surfaces, and brain. Though the patterns of metastases can vary with the biologic subtypes described in the next paragraph, any biologic subtype can metastasize to any part of the body. Survival for patients with metastatic breast cancer is highly variable, and treatment is almost always indicated, using hormones, chemotherapy, or other targeted agents.[1]

Breast cancer is no longer viewed as a single disease, but rather as a series of diseases defined by biologic characteristics. Hormone receptor (HR) positive tumors demonstrate positivity for either estrogen receptors, or progesterone receptors. Breast cancer can be viewed as 4 sub-types, as follows: 1) HR positive/HER2 negative, 2) HR positive/HER2 positive, 3)HR negative/HER2 positive, 4) HR negative/HER2 negative. These biologic sub-types help predict which therapies will have potential efficacy. Hormone therapy is beneficial only for patients with HR-positive positive tumors, and trastuzumab and similar HER2 targeted therapies are only helpful in women with HER2 positive cancers.

Therapy recommendations can be influenced by previous treatment for early-stage breast cancer. If, for instance, the patient is receiving tamoxifen as adjuvant therapy, and develops metastatic disease, even though her tumor is estrogen receptor positive, this is an indication that her tumor is no longer responsive to tamoxifen, and other therapies need to be considered.[2]

Public Health Relevance

Breast cancer comprises one-quarter of all new cancer cases worldwide including women and men, with an estimated 1.67 million cases in 2012 alone, according to the International Agency for Research on Cancer's (IARC) database, GLOBOCAN 2012. Although highly treatable with systemic therapy, surgery, and radiation therapy (as described in the present briefing), breast cancer was the cause of death of approximately half a million women worldwide in 2012.[3] In sub-Saharan Africa alone, it is believed that nearly 50,000 women passed away from the disease during that one year. The ratio of incidence to mortality in high-income, middle-income, and low-income countries varies drastically given the disparities in access to resources, clinical knowledge, and medicines, as is true for all cancers. According to one study in 2010, the 5-year survival rate for breast cancer ranged from 12% survival in The Gambia, an extremely poor country, to 79% in South Korea, a high-income country.[4] As El Saghir and colleagues noted in

their 2011 article in *The Breast*, women suffering from breast cancer in the developing world are more likely to present at later stages to a health facility due to structural barriers to care, absence of treatment options, or inadequate information being disseminated to the public.[5] Women who receive treatment for early stage breast cancer (localized disease) have a significantly higher chance of survival than those treated for metastatic disease. Even in less developed regions of the world, such as Costa Rica, India, Philippines, Saudi Arabia, and Thailand, overall survival at 5 years for women treated for localized disease was 73.6% on average, compared to 47.4% with regional disease.[4] There are several major global initiatives focusing on implementation of breast cancer guidelines, including the Breast Health Global Initiative, which has developed a set of guidelines for public sector development of national responses to the disease.[6,7]

Requirements for diagnosis, treatment, and monitoring

Diagnostics:

The treatment of breast cancer should always be determined by pathology evaluation of the primary cancer. It is recommended that biopsy be performed by ultrasound-guided core needle technique which generally will give adequate tissue for histologic and marker studies. Fine needle aspirate can play a role but cannot distinguish between in-site and invasive cancer and often does not give adequate material for immunohistochemistry. Surgical excision should only rarely be required if needle biopsy is technically not feasible. Evaluation of the biopsy by an experienced pathologist will yield the histologic subtype (ductal, lobular, etc) and grade of the cancer. Immunohistochemistry (IHC) analysis for estrogen receptors, and in some cases progesterone receptors is critical since this will determine prognosis and whether the cancer is potentially sensitive to hormone therapy. HER2 can be assessed by either IHC or by fluorescene in situ hybridization (FISH) if IHC is equivocal.

For patients who had pathology evaluation during their initial early-stage presentation, that information can be used to guide treatment. For patients who present with metastatic disease, tissue acquisition from the breast primary, or other easily accessible sites of disease is acceptable. Tissue should be obtained by the easiest and safest method..

Testing:

Staging should be performed to assess the extent of disease. CT scans and bone scans can delineate the extent of metastatic disease. In more resource-constrained settings, a chest x-ray, liver ultrasound, and plain films of bones that are painful, are acceptable.

Administration and Care of Patients:

Hormone therapies are largely oral (tamoxifen and aromatase inhibitors). No special testing or administrative resources are necessary for the utilization of these drugs, though a reliable supply is important.

Cytotoxic chemotherapy requires the ability to administer intravenous chemotherapy, with particular consideration of avoidance of extravasation with doxorubicin, and allergic reactions with taxanes. Chemotherapy can be administered in an out-patient infusion setting, or an in-patient setting, though this is not required. IV fluids and anti-emetics as well as hypersensitivity medications are required. Monitoring of CBC, renal function, electrolytes and liver functions tests are required.

Trastuzumab and similar anti-HER2 targeted therapies are generally administered intravenously. Administration is relatively straightforward, and is usually done in out-patient infusion facilities.

Cardiac monitoring is recommended for patients receiving an anthracycline, or trastuzumab, though the incidence of serious cardiac toxicity is low, especially if anthracycline doses remain below cumulatively toxic levels, the potential benefit in disease control is substantial.

As with all cancer treatment, social support, clean water and adequate nutrition are essential.

Overview of Regimens

The following tables include basic information on administration and dosing for the 4 biologic subtypes of breast cancer, followed by specific regimens.

1) HR- Positive/HER2 Negative tumors

Pre-menopausal patients should be treated initially with hormonal therapy, preferably tamoxifen, unless they were on tamoxifen at the time of the development of metastatic disease. Patients who are tolerating tamoxifen should be treated until clear signs of tumor progression. Stable disease is an indication to continue tamoxifen therapy. Premenopausal women should undergo either oophorectomy or ovarian suppression with an LHRH agonist.

For postmenopausal women (either natural, surgical, or chemical) can be treated with either tamoxifen or an aromatase inhibitor. If they were on one of these agents at the time of development of metastatic disease, they should be treated with the other agent. Treatment should continue until there is clear evidence of tumor progression, at which time the patient should be converted to the other agent (from tamoxifen to and aromatase inhibitor or visa versa. The 3 available aromatase inhibitors have equal efficacy. Stable disease is an indication to continue hormone therapy.

At the time of tumor progression, single agent chemotherapy should be utilized, unless there is rapidly progressive disease or high disease burden that requires a rapid response in which case combination chemotherapy can be used.[13] The choice of chemotherapeutic agents , and there are no data to suggest that initial treatment with one versus another is more efficacious. The only exception is that patients who were treated in the adjuvant setting with chemotherapy 12 months or less from the time of developing metastatic disease, should be treated with chemotherapy agents other than those received in the adjuvant setting.

2) HR Positive/HER2 Positive tumors

As above, hormone therapy should always be a component of the therapy for these patients and factors determining choice are the same as above in #1. Chemotherapy and trastuzumab should be initiated concurrently with hormone therapy?. Typically trastuzumab is given concurrently with a taxane, and not administered concurrently with an anthracycline. However, trastuzumab can be given concurrently with other cytotoxic agents, such as vinorelbine.

Studies presented in abstract form but not yet published suggest that the addition of pertuzumab to trastuzumab and a taxane significantly improve survival. The addition of pertuzumab adds substantially to the cost of an already costly regimen (trastuzumab and a taxane), and since the results have not yet been published in a peer-reviewed journal this cannot be recommended as standard of care at this time.

3) HR Negative/HER2 Positive tumors

Hormone therapy is not indicated. Trastuzumab chemotherapy combinations as described in #2 are indicated.

4) HR Negative/HER2 Negative tumors

Hormone therapies, and trastuzumab containing regimens are not indicated for these patients. Single agent chemotherapy should be utilized, unless there is need for rapid control of disease due to visceral crisis or very high tumor burden.[13] The choice of chemotherapeutic agents is arbitrary, and there are no data to suggest that initial treatment with one versus another is more efficacious. The only exception is that patients who were treated in the adjuvant setting with chemotherapy 12 months or less from the time of developing metastatic disease, should be treated with chemotherapy agents other than those received in the adjuvant setting.

Standard Chemotherapy Regimens (non-trastuzumab regimens)

Doxorubicin (for sub-types 1, 4 – and 2, 3 if trastuzumab not available)

Doxorubicin	*IV*	*60 mg/m2 q 3 weeks*	

Paclitaxel (for sub-types 1, 4 – and 2, 3 if trastuzumab not available)

Paclitaxel	*IV*	*175 mg/m2*	*q 3 weeks**
Or			
Paclitaxel	*IV*	*80 mg/m2*	*q weekly**

**Weekly paclitaxel is the more efficacious option but requires more frequent visits*

Note: cumulative dose of doxorubicin should not exceed 450 mg/m2 due to increased likelihood of severe cardiomyopathy with increasing dose.

Standard Regimens Including Trastuzumab, for HER2 Positive disease

Paclitaxel and trastuzumab (for sub-types 2,3)			
Paclitaxel	*IV*	*80 mg/m2*	*weekly*
*Trastuzumab**	*IV*	*2 mg/kg*	*weekly*
**loading dose first week of therapy trastuzumab 4 mg/kg*			

Docetaxel and Trastuzumab (for sub-types 2,3)			
Docetaxel	*IV*	*60-75 mg/m2*	
*Trastuzumab**	*IV*	*6 mg/kg*	*q 3 wks*
**First dose of trastuzumab loading dose 8 mg/kg*			

Note: Capecitabine, vinorelbine, and gemcitabine have all been shown to have activity for patients with metastatic breast cancer, and can be supported to be given as single agents for patients with HER2 negative breast cancer. For patients with HER2 positive breast cancer trastuzumab has also been given with vinorelbine, successfully. These regimens have been listed below.

Single Agent Chemotherapy Regimens, for HER2 Negative disease

Capecitabine (single agent)			
Capecitabine	*PO*	*2000 mg/m2/day**	*days 1-14 of 21 day cycle*
**Dose to be given in 2 divided doses per day*			

Vinorelbine (single agent)			
Vinorelbine	*IV*	*25 mg/m2*	*q 1 wk*

Gemcitabine (single agent)			
Gemcitabine	*IV*	*1000 mg/m2*	*days 1, 8 of 21 day cycle*

Cyclophosphamide (single agent)			
Cyclophosphamide	*IV*	*1000 mg/m2*	*day 1 of a 21 day cycle*

Single Agent Chemotherapy Regimens, for HER2 Positive disease

Vinorelbine (with trastuzumab)			
Vinorelbine	*IV*	*25 mg/m2*	*q 1 wk*
WITH EITHER			
*Trastuzumab**	*IV*	*2 mg/kg*	*weekly*
**loading dose first week of therapy trastuzumab 4 mg/kg*			
OR			
*Trastuzumab**	*IV*	*6 mg/kg*	*q 3 wks*
**Loading dose for first dose of trastuzumab 8 mg/kg*			

Standard Hormone Regimens

Tamoxifen	Oral	20 mg/day	until tumor progression

Aromatase Inhibitors (all of equal efficacy) – only for use in postmenopausal women (natural or surgical) or premenopausal women who are receiving ovarian suppression. Anastrozole is recommended to be included on the EML as a class example of aromatase inhibitors, which should also include letrozole and exemestane.

Anastrozole	Oral	1 mg/day	until tumor progression

Premenopausal women should receive tamoxifen, in addition to ovarian ablation (surgical) or ovarian suppression, until tumor progression. .

Postmenopausal women can be treated with either tamoxifen, or an aromatase inhibitor, but not both concurrently. If there is tumor progression on one of these agents, and that should be stopped, and the other initiated. Sequential use of these agents results in increased survival and improved quality of life since delay in time to tumor progression results in increased time until use of chemotherapy.[15]

Review of Benefits and Harms

Benefits

Hormone therapy will yield clinical benefit for approximately 1/2 of the patients who have tumors that are estrogen and/or progesterone receptor positive. Clinical benefit as defined by either reduction in tumor size, or stable disease for at least several months. Patients who have clinical benefit generally have a reduction in symptoms, improved quality of life, and prolongation of survival.

For patients who have had progressive disease on hormone therapy, or those with estrogen and/or progesterone receptor negative disease, chemotherapy can lead to a reduction in tumor burden in about one third of patients. Patients who benefit from chemotherapy have a decrease in her symptoms, improvement in quality of life, and modest prolongation in survival.

For patients with HER2 positive disease, the addition of trastuzumab to chemotherapy dramatically increases the response rate and overall survival. Typically trastuzumab is given concurrently with a taxane. However, patients may be treated with trastuzumab and vinorelbine, or capecitabine. Treatment options should be discussed with patients.[13]

Harms and Toxicity Considerations

Common
Risks of treatment include common short-term toxicities such as alopecia, neutropenia, fever and infection, and neuropathy (ranging 15-60%) from taxanes. Paclitaxel and trastuzumab are both associated with infusion reactions in up to 30-40% of patients. Most infusion reactions are mild and easily managed.[8,9]

Tamoxifen can cause hot flashes, mood changes, and rarely thromboembolic disease and endometrial cancer. Tamoxifen generally has a positive effect on bone density. Aromatase inhibitors can cause hot flashes, mood changes, musculoskeletal complaints and bone loss.

Vinorelbine often causes severe neutropenia and granulocytopenia, which increases patients' risk of infection. Like other vinca alkaloids, vinorelbine also frequently causes constipation. Vinorelbine is a strong vesicant, care must be taken to avoid extravasation and associated tissue damage.[16]

Palmar-plantar erythrodysesthesia (hand-foot) syndrome is associated with capecitabine, with an increased incidence of up to 60% for patients treated with capecitabine. This adverse effect typically resolves following treatment interruption.[17]

Gemcitabine frequently causes myelosuppression with dose-limiting thrombocytopenia and leukopenia with associated risk of infection. Gemcitabine is also associated with increased

hepatic transaminases which may lead to more severe hepatotoxicity in up to 10% of patients. Many patients experience edema and dyspnea. [18]

Serious

Cardiac muscle suppression or cardiac damage can occur after therapy with anthracyclines and trastuzumab, and administration of both agents together increases the risk. For the regimens described above, the risk of congestive heart failure is small and reversible upon discontinuation in most cases.[10,11,12] Rare incidences of bone marrow damage, myelodysplastic syndrome and acute leukemia can occur after therapy with doxorubicin. Diarrhea occurs in up to 50% of patients treated with capecitabine. Diarrhea can be severe and may require hospital admission for IV fluid replacement, it is often dose-limiting. [19]

Systematic Reviews

The following reviews and analyses summarize the literature supporting the treatment regimens for metastatic breast cancer.

Balduzzi, S., Mantarro, S., Guarneri, V., Tagliabue, L., Pistotti, V., Moja, L., & D'Amico, R. (2014). Trastuzumab‐containing regimens for metastatic breast cancer. *The Cochrane Library*.

Main Results

"The review found seven trials, involving 1497 patients, which met the criteria to be included. The trials were generally of moderate methodological quality; two studies have not published their results on overall survival so the presence of selective outcome reporting bias cannot be ruled out. None of the studies used blinding to treatment allocation, though this is unlikely to have biased the results for overall survival. Studies varied in terms of co-administered regimen and in terms of treatment line. In four studies, trastuzumabwas administered with a chemotherapy, such as a taxane-containing, anthracycline-containing or capecitabine-containing regimen. Two studies considered postmenopausal women and administered trastuzumab with hormone-blocking medications, such as an aromatase inhibitor. One study administered trastuzumab in addition to lapatinib. Five studies out of seven included women treated with trastuzumab administered until progression as first-line treatment and two studies considered trastuzumab beyond progression. The combined HRs for overall survival and progression-free survival favoured the trastuzumab-containing regimens (HR 0.82, 95% confidence interval (CI) 0.71 to 0.94, P = 0.004; and HR 0.61, 95% CI 0.54 to 0.70, P < 0.00001, respectively; moderate-quality evidence). Trastuzumab increased the risk of congestive heart failure (RR 3.49, 90% CI 1.88 to 6.47, P = 0.0009; moderate-quality evidence) and left ventricular ejection fraction (LVEF) decline (RR 2.65, 90% CI 1.48 to 4.74, P = 0.006). For haematological toxicities, such as neutropenic fever and anaemia, there was no clear evidence that risks differed between groups, while trastuzumab seemed to raise the risk of neutropenia. The overall survival improvement was maintained when considering patients treated as first-line or patients receiving taxane-based regimens. The progression-free survival improvement was maintained when considering patients receiving taxane-based regimens, and patients

treated as first-line or subsequent lines. Few data were collected on central nervous system progression. Similarly, few studies reported on quality of life and treatment-related deaths."

Authors' conclusions

"Trastuzumab improved overall survival and progression-free survival in HER2-positive women with metastatic breast cancer, but it also increased the risk of cardiac toxicities, such as congestive heart failure and LVEF decline. The available subgroup analyses are limited by the small number of studies. Studies that administered trastuzumab as first-line treatment, or along with a taxane-based regimen, improved mortality outcomes. The evidence to support the use of trastuzumab beyond progression is limited. The recruitment in three out of seven studies was stopped early and in three trials more than 50% of patients in the control groups were permitted to switch to the trastuzumab arms at progression, making it more difficult to understand the real net benefit of trastuzumab. Trastuzumab is generally used for women with HER2-positive early breast cancer in clinical practice, while women enrolled in most of the trials in the metastatic setting were naive to trastuzumab. The effectiveness of trastuzumab for women relapsing after adjuvant trastuzumab is therefore still an open issue, although it is likely that the majority are being offered it again."

From Balduzzi et al 2014: Summary of Findings for the Main Comparison

Summary of findings for the main comparison.

Summary of findings for the main comparison. Overview: efficacy and safety outcomes for patient groups at different risks

Patient or population: patients with HER2-positive metastatic breast cancer
Settings: metastatic breast cancer
Intervention: trastuzumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Trastuzumab				
Overall survival Follow-up: median 2 years	**Moderate**[1]		**HR 0.82** (0.71 to 0.94)	1309 (5 studies)	⊕⊕⊕⊖ **moderate**[2]	
	700 per 1000	**627 per 1000** (575 to 678)				
	High[1]					
	800 per 1000	**733 per 1000** (681 to 780)				
Progression-free survival Follow-up: median 2 years	**Moderate**		**HR 0.61** (0.54 to 0.70)	1489 (7 studies)	⊕⊕⊕⊖ **moderate**[3]	
	700 per 1000	**520 per 1000** (478 to 569)				
	High					
	800 per 1000	**625 per 1000** (581 to 676)				
Congestive heart failure	**Low**		**RR 3.49** (1.88 to 6.47)[4]	1459 (7 studies)	⊕⊕⊕⊖ **moderate**[3]	
	10 per 1000	**35 per 1000** (19 to 65)				
	Moderate					
	20 per 1000	**70 per 1000** (38 to 129)				
	High					
	50 per 1000	**175 per 1000** (94 to 323)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Moderate risk derived from Slamon 2001 first-line treatment. High risk: estimated from moderate risk increased by 10% absolute risk.

[2]Gasparini 2006, Huober 2012 and von Minckwitz 2009 did not report the overall survival data stratified by arm.

[3]All the studies were open-label.

[4]Confidence interval 90%.

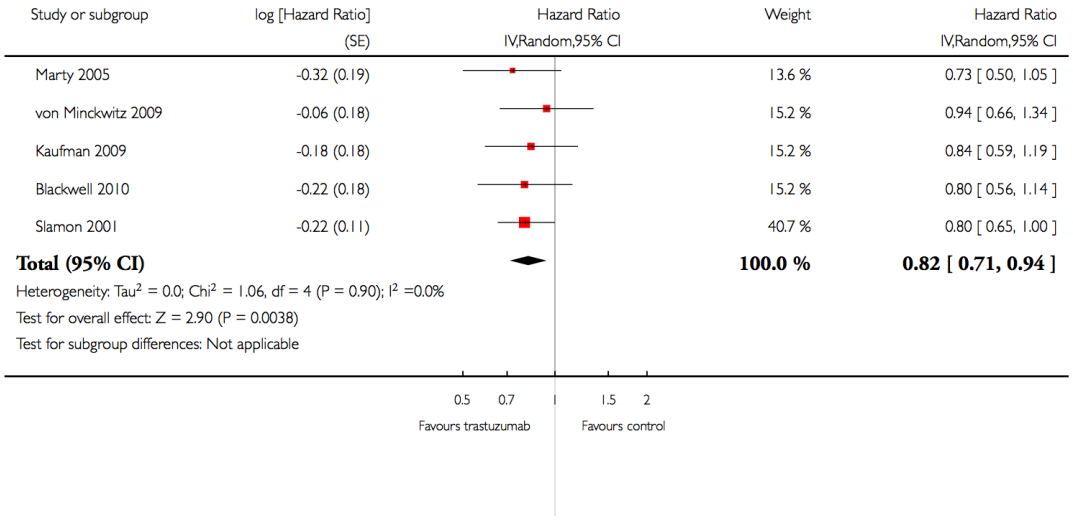
From Balduzzi et al 2014: Analysis I.I

Analysis 1.1. Comparison 1 Efficacy of trastuzumab, Outcome 1 Overall survival - all studies.

Review: Trastuzumab-containing regimens for metastatic breast cancer

Comparison: 1 Efficacy of trastuzumab

Outcome: 1 Overall survival - all studies



Gennari, A., *et al*. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. *Journal of Clinical Oncology* **29**(16): 2144-2149 (2011).

Purpose: To evaluate the effect of different first-line chemotherapy durations in patients with metastatic breast cancer (MBC) on overall survival (OS) and progression-free survival (PFS). **Methods:** We searched literature databases to identify randomized controlled trials that compared different chemotherapy durations in the first-line treatment of MBC. Only trials with unconfounded comparisons of additional cycles of chemotherapy were included. The main outcome measures for this analysis were OS and PFS. Published data from retrieved studies were analyzed according to standard meta-analytic techniques. **Results:** We found 11 randomized clinical trials including 2,269 patients. Longer first-line chemotherapy duration resulted into a significantly improved OS (hazard ratio [HR], 0.91; 95% CI, 0.84 to 0.99; P = .046) and PFS (HR, 0.64; 95% CI, 0.55 to 0.76; P < .001). There were no differences in effects on either OS or PFS between subgroups defined by time of random assignment, study design, number of chemotherapy cycles in the control arm or concomitant endocrine therapy. **Conclusion:** Longer first-line chemotherapy duration is associated with marginally longer OS and a substantially longer PFS.

Additional reviews and analyses:

- Swain, S. 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. *The Lancet Oncology* **14**(6): 461-471 (2013).
- Wilcken, N., *et al*. Systemic treatment of HER2-positive metastatic breast cancer: A systematic review." *Asia-Pacific Journal of Clinical Oncology* **10**(S4):1-14 (2014).
- Partridge, A.H., *et al*. "Chemotherapy and Targeted Therapy for Women With Human Epidermal Growth Factor Receptor 2–Negative (or unknown) Advanced Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline." *Journal of Clinical Oncology*. JCO-2014 (2014).
- Stage IIIB, Inoperable IIIC, IV, Recurrent, and Metastatic Breast Cancer. *United States National Cancer Institute.* Accessed online: 9 September 2014 http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page6
- Giordano, S. H., *et al*. Systemic therapy for patients with advanced human epidermal growth factor receptor 2–positive breast cancer: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology* JCO-2013 (2014).

Recommendations

The reviewers recommend the incorporation of metastatic breast cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that trastuzumab, vinorelbine, capecitabine, gemcitabine, and anastrozole (as a class of agent for aromatase inhibitors), be added to the core Essential Medicines List.

Standard Regimen

• Chemotherapy regimens utilizing cyclophosphamide, doxorubicin, paclitaxel or, docetaxel, vinorelbine, capecitabine, and gemcitabine administered as single-agents, sequentially, for patients with HER2 negative disease
• For patients with HER2 positive disease trastuzumab should be used in combination with a taxane, vinorelbine or capecitabine.
• Hormone therapies utilizing tamoxifen and anastrozole sequentially

Additions proposed for Section 8.2 of the EML

Vinorelbine
Capecitabine
Gemcitabine
Trastuzumab
Anastrozole (as a class agent including other aromatase inhibitors – letrozole and exemestane)

References

[1] Stage IIIB, Inoperable IIIC, IV, Recurrent, and Metastatic Breast Cancer. *United States National Cancer Institute.* Accessed online: 9 September 2014 http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page6

[2] Mouridsen H, Gershanovich M, Sun Y, et al.: Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 21 (11): 2101-9, 2003.

[3] Ferlay J, *et al*. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; (2013). Available from: http://globocan.iarc.fr, accessed on day/month/year.

[4] Sankaranarayanan, R., *et al*. Cancer survival in Africa, Asia, and Central America: a population-based study." *The Lancet Oncology* .**11**(2): 165-173 (2010).

[5] El Saghir, N. S., *et al*. Breast cancer management in low resource countries (LRCs): consensus statement from the Breast Health Global Initiative. *The Breast.* **20**:S3-S11 (2011).

[6] Anderson, B. O., *et al*. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010." *The Lancet Oncology.* **12**(4):387-398 (2011).

[7] Anderson, B. O., *et al*. Guideline implementation for breast healthcare in low-income and middle-income countries. *Cancer.* **113**(S8):2221-2243 (2008).

[8] Castells MC, Matulonis UA. Infusion reactions to systemic chemotherapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.

[9] LaCasce AS, Castells MC, Burnstein H, Meyerhardt JA. Infusion reactions to therapeutic monoclonal antibodies used for cancer therapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.

[10] Floyd J, Morgan JP. Cardiotoxicity of anthracycline-like chemotherapy agents. Post TW (Ed), UpToDate, Waltham, MA, 2014.

[11] Perez EA, Morgan JP. Cardiotoxicity of trastuzumab and other HER2-targeted agents. Post TW (Ed), UpToDate, Waltham, MA, 2014.

[12] Perez, E. A., and Rodeheffer, R. Clinical cardiac tolerability of trastuzumab. Journal of Clinical Oncology 22(2):322-329 (2004).

[13] Cardoso F. et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). The Breast. 23(5):489-502, 2014.

[14] El Saghir N.S. et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Critical Reviews in Oncology/Hematology. 80(3):433-449.

[15] Mouridsen, H., Gershanovich, M., Sun, Y., Pérez-Carrión, R., Boni, C., Monnier, A., ... & Bhatnagar, A. (2003). Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *Journal of Clinical Oncology*, *21*(11), 2101-2109.

[16] Vinorelbine. DrugPoints Summary. Micromedex 2.0. Truven Health Analytics, Inc. Greenwood Village, CO

[17] Payne AS, Savarese DMF. Cutaneous complications of conventional chemotherapy agents. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014

[18] Gemcitabine. DrugPoints Summary. Micromedex 2.0. Truven Health Analytics, Inc. Greenwood Village, CO

[19] Krishnamurthi SS. Enterotoxicity of chemotherapeutic agents. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.