

# Cancer Association of South Africa (CANSA)

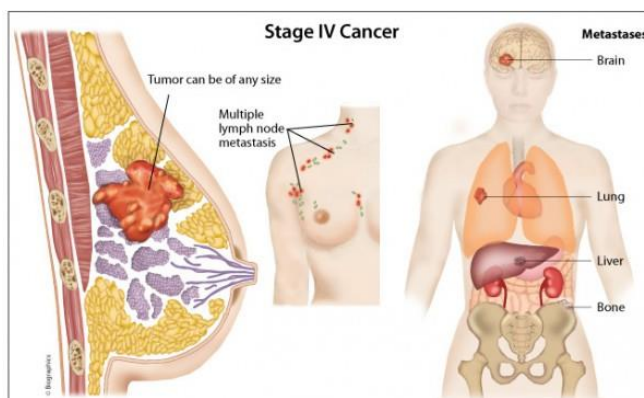


## CANSA Fact Sheet on Metastatic Breast Cancer

### Introduction

Metastatic breast cancer is cancer that has spread beyond the breast and lymph nodes under the arm. It occurs in both men and women. The most common sites where breast cancer spreads to are the bones, lungs, liver and brain.

[Picture Credit: Stage IV]



Cancer cells can break away from the original tumour in the breast and travel to other parts of the body through the bloodstream or the lymphatic system, which is a large network of nodes and vessels that works to remove bacteria, viruses, and cellular waste products from the body.

The metastatic tumour in a different part of the body is made up of cells from the breast cancer. For instance, if breast cancer spreads to the bone, the metastatic tumour in the bone is made up of breast cancer cells, not bone cells.

Breast cancer can be "metastatic at diagnosis". This means that the cancer in the breast was not detected before it spread to another part of the body. It is also known as cancer of unknown primary (CUP).

No one dies from breast cancer that remains in the breast. The lump itself is not what kills. The spread of cancerous cells to a vital organ is what kills. This is called metastasis. Metastasis refers to the spread of the cancer to distant organs. When the cancer does so, it is known as metastatic, or stage IV, disease.

Research shows that in about 6 -10 % of all breast cancer patients, the cancer has spread to distant organs and is classified as Stage IV at the time of the first diagnosis. In the majority of patients with metastatic breast cancer, the metastasis is diagnosed after a cancer has already been treated at an earlier stage.

Metastatic breast cancer is also known as 'MBC', stage IV or Advanced Breast Cancer.

### **Tumour Grade and Tumour Stage**

Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

### What are the cancer stages?

Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

### TNM staging

Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

### What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical “grade” to most cancers.

Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

### **Incidence of Metastatic Breast Cancer in South Africa**

According to the outdated National Cancer Registry (2019), known for under reporting, the following number of breast cancer cases in women was histologically diagnosed during 2019:

Group	Actual Number of Cases	Estimated Lifetime Risk	Percentage of All Cancers
2019			
All females	10 174	1 : 27	23,22%
Asian females	528	1 : 18	38,63%
Black females	4 412	1 : 47	21,90%
Coloured females	1 398	1 : 20	28,43%
White females	3 836	1 : 11	21,14%

### **Frequency of Histologically Diagnosed Cases of Breast Cancer**

According to the National Cancer Registry (2019), the frequency of histologically diagnosed cases of breast cancer in women in South Africa is as follow:

Group 2019	0 to 19 Years	20 to 29 Years	30 to 39 Years	40 to 49 Years	50 to 59 Years	60 to 69 Years	70 to 79 Years	80 + Years
All females	1	154	965	2 055	2 420	2 358	1 579	642
Asian females	0	5	36	101	125	137	101	23
Black females	0	107	615	1 122	1 089	829	436	214
Coloured females	1	16	116	259	386	348	203	69
White females	0	26	198	573	820	1 044	839	336

### Diagnosis of Metastatic Breast Cancer

A metastatic tumour is always caused by cancer cells from another part of the body.

In most cases, when a metastatic tumour is found first, the primary cancer can also be found. The search for the primary cancer may involve laboratory tests, X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans, and other procedures.

However, in some patients, a metastatic tumour is diagnosed but the primary tumour cannot be found, despite extensive tests, because it either is too small or has completely regressed. The pathologist knows that the diagnosed tumour is a metastasis because the cells do not look like those of the organ or tissue in which the tumour was found. Doctors refer to the primary cancer as unknown or occult (hidden), and the patient is said to have cancer of unknown primary (CUP).

Some women have metastatic breast cancer when they are first diagnosed, but this is not common (approximately five percent of diagnoses). More commonly, metastatic breast cancer arises months or years after a person has completed treatment for early or locally advanced (stage I, II or III) breast cancer. This is sometimes called distant recurrence.

Some people with metastatic tumours do not have symptoms. Their metastases are found by X-rays or other tests.

When symptoms of metastatic cancer occur, the type and frequency of the symptoms will depend on the size and location of the metastasis. For example, cancer that spreads to the bone is likely to cause pain and can lead to bone fractures. Cancer that spreads to the brain can cause a variety of symptoms, including headaches, seizures, and unsteadiness. Shortness of breath may be a sign of lung metastasis. Abdominal swelling or jaundice (yellowing of the skin) can indicate that cancer has spread to the liver.

Sometimes a person's original cancer is discovered only after a metastatic tumour causes symptoms.

**Dieci, M.V., Miglietta, F., Grifuolo, G. & Guarneri, V. 2020.**

"The overexpression of human epidermal growth factor receptor-2 (HER2) results in a biologically and clinically aggressive breast cancer (BC) subtype. Since the introduction of anti-HER2 targeted agents, survival rates of patients with HER2-positive metastatic BC have dramatically improved. Currently, although the treatment decision process in metastatic BC is primarily based on HER2 and hormone-receptor (HR) status, a rapidly growing body of data suggests that several other sources of biological heterogeneity may characterize HER2-positive metastatic BC. Moreover, pivotal clinical trials of new anti-HER2 antibody-drug conjugates showed encouraging results in HER2-low metastatic BC, thus leading to the possibility, in the near future, to expand the pool of patients

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suitable for HER2-targeted treatments. The present review summarizes and puts in perspective available evidence on biomarkers that hold the greatest promise to become potentially useful tools for optimizing HER2-positive metastatic BC patients' prognostic stratification and treatment in the next future. These biomarkers include HER2 levels and heterogeneity, HER3, intrinsic molecular subtypes by PAM50 analysis, DNA mutations, and immune-related factors. Molecular discordance between primary and metastatic tumors is also discussed."

### **Treatment of Metastatic Breast Cancer**

Treatments for metastatic and earlier-stage breast cancer are very different. For earlier-stage breast cancer - particularly for women who are relatively young and healthy - doctors will often advise a very aggressive, rigorous course of treatment aimed at getting rid of the cancer completely. The side effects can be difficult, but there is a finish line in sight: initial breast cancer treatment usually lasts no more than six to nine months.

With metastatic cancer, some form of treatment will be a fact of life, more or less, as from the date of commencement of treatment. This means the treatment philosophy changes. The aim of treatment changes to gain maximal control of the tumour at the lowest possible cost in terms of toxicity.

Research shows that Metastatic Breast Cancer is best treated by a team of specialists. The medical team may include:

- surgeon: performs biopsies and other procedures and removes single metastatic cancers
- medical oncologist: specialises in chemotherapy, hormonal therapy, targeted therapies, pain medications, and nutritional support
- radiation oncologist: specialises in radiation therapy
- radiologist: takes and interprets mammograms, ultrasounds, bone scans, CT scans, MRIs, PET scans, and other tests to determine the location and size of the cancer and to help determine how the cancer is responding to treatment
- pathologist: examines the biopsy sample and conducts special tests on cancer tissue to determine the "personality" of the cancer (characteristics such as hormone-receptor status and HER2 status)

**Exman, P. & Tolaney, S.M.** 2021.

"Cases of human epidermal growth factor receptor 2 (HER2)-positive breast cancer represent approximately 15% to 20% of all breast cancers. Historically, this subtype of breast cancer was associated with an increased risk for the development of systemic and brain metastases and poor overall survival. The introduction of trastuzumab dramatically changed the outcomes of patients with HER2-positive disease, with many demonstrating outcomes similar to those of patients with luminal tumors. Currently, the first-line standard of care for patients with HER2-positive metastatic breast cancer is dual HER2 antibody therapy with pertuzumab/trastuzumab plus a taxane. After progression, the standard of care is trastuzumab emtansine (T-DM1). Although the treatment choices for patients whose disease has progressed on these agents are more limited, promising new drugs have emerged as effective options, including tucatinib and trastuzumab deruxtecan, which were recently approved by the US Food and Drug Administration. Finding the best treatment sequencing for each patient, developing reliable predictive biomarkers, and understanding the

mechanisms of resistance to these drugs are necessary to maximize patient outcomes and quality of life. In this review, we analyze the management strategies for metastatic HER2-positive breast cancer, address specific situations, such as the treatment of patients with brain metastases, and discuss future directions in the treatment of this subtype.”

**Marks, C.E., Thomas, S.M., Fayanju, O.M., DiLalla, G., Sammons, S., Hwang, E.S. & Plichta, J.K.** 2021.

**Background:** We sought to identify characteristics of metastatic breast cancer (MBC) patients who may benefit most from primary tumor resection.

**Methods:** Recursive partitioning analysis (RPA) was used to categorize non-surgical patients with de novo MBC in the NCDB (2010-2015) into 3 groups (I/II/III) based on 3-year overall survival (OS). After bootstrapping (BS), group-level profiles were applied, and the association of surgery with OS was estimated using Cox proportional hazards models.

**Results:** All patients benefitted from surgery (median OS, surgery vs no surgery): 72.7 vs 42.9 months, 47.3 vs 30.4 months, 23.8 vs 14.4 months (all  $p < 0.001$ ) in BS-groups I, II, and III, respectively. After adjustment, surgery remained associated with improved OS (HR 0.52, 95% CI 0.50-0.55). The effect of surgery on OS differed quantitatively across groups.

**Conclusion:** Prognostic groups may inform the degree of benefit from surgery, with the greatest benefit seen in those with the most favorable survival.

It may seem logical to assume that metastatic breast cancer has the same hormone-receptor status and HER2 status as the original cancer. Research has shown that the "personality" of the recurrent or metastatic cancer may be different than the original cancer. For example, the hormone-receptor status may change from hormone-receptor-positive to hormone-receptor-negative or *vice versa*. The HER2 status also may be different than the original breast cancer. If either of these factors have changed, they can affect the treatment plan.

A mutation in the oestrogen receptor 1 (*ESR1*) gene portends a worse prognosis among patients with oestrogen receptor (ER)-positive, metastatic breast cancer. A mutation in this gene may confer resistance to aromatase inhibitor (AI) therapy.

**Saura, C., Oliveira, M., Feng, Y.H., Dai, M.S., Chen, S.W., Hurvitz, S.A., Kim, S.B., Moy, B., Delaloge, S., Gradishar, W., Masuda, N., Palacova, M., Trudeau, M.E., Mattson, J., Yap, Y.S., Hou, M.F., De Laurentiis, M., Yeh, Y.M., Chang, H.T., Yau, T., Wildiers, H., Haley, B., Fagnani, D., Lu, Y.S., Crown, J., Lin, J., Takahashi, M., Takano, T., Yamaguchi, M., Fujii, T., Yao, B., Bebchuk, J., Keyvanjah, K., Bryce, R., Brufsky, A. & NALA Investigators.** 2020.

**Purpose:** NALA (ClinicalTrials.gov identifier: [NCT01808573](https://clinicaltrials.gov/ct2/show/study/NCT01808573)) is a randomized, active-controlled, phase III trial comparing neratinib, an irreversible pan-HER tyrosine kinase inhibitor (TKI), plus capecitabine (N+C) against lapatinib, a reversible dual TKI, plus capecitabine (L+C) in patients with centrally confirmed HER2-positive, metastatic breast cancer (MBC) with  $\geq 2$  previous HER2-directed MBC regimens.

**Methods:** Patients, including those with stable, asymptomatic CNS disease, were randomly assigned 1:1 to neratinib (240 mg once every day) plus capecitabine (750 mg/m<sup>2</sup> twice a day 14 d/21 d) with loperamide prophylaxis, or to lapatinib (1,250 mg once every day) plus capecitabine (1,000 mg/m<sup>2</sup> twice a day 14 d/21 d). Coprimary end points were centrally confirmed progression-free

survival (PFS) and overall survival (OS). NALA was considered positive if either primary end point was met ( $\alpha$  split between end points). Secondary end points were time to CNS disease intervention, investigator-assessed PFS, objective response rate (ORR), duration of response (DoR), clinical benefit rate, safety, and health-related quality of life (HRQoL).

**Results:** A total of 621 patients from 28 countries were randomly assigned (N+C, n = 307; L+C, n = 314). Centrally reviewed PFS was improved with N+C (hazard ratio [HR], 0.76; 95% CI, 0.63 to 0.93; stratified log-rank  $P = .0059$ ). The OS HR was 0.88 (95% CI, 0.72 to 1.07;  $P = .2098$ ). Fewer interventions for CNS disease occurred with N+C versus L+C (cumulative incidence, 22.8% v 29.2%;  $P = .043$ ). ORRs were N+C 32.8% (95% CI, 27.1 to 38.9) and L+C 26.7% (95% CI, 21.5 to 32.4;  $P = .1201$ ); median DoR was 8.5 versus 5.6 months, respectively (HR, 0.50; 95% CI, 0.33 to 0.74;  $P = .0004$ ). The most common all-grade adverse events were diarrhea (N+C 83% v L+C 66%) and nausea (53% v 42%). Discontinuation rates and HRQoL were similar between groups.

**Conclusion:** N+C significantly improved PFS and time to intervention for CNS disease versus L+C. No new N+C safety signals were observed.

**Bredit, P., Walshe, J.M. & Denduluri, N. 2020.**

“The human epidermal growth factor receptor 2 (HER2), is amplified and/or overexpressed in approximately 15%-20% of breast cancers. Targeting of the HER2 receptor with the humanized monoclonal antibody trastuzumab in combination with chemotherapy has become the backbone of treatment for both early stage and metastatic breast cancer for the last 2 decades. Relapsed or de novo metastatic HER2-positive breast cancer essentially remains an incurable disease. Nonetheless, with advances in therapeutics, survival rates in this group continue to increase with median survival now in excess of 57 months. First line systemic therapy for HER2-positive metastatic breast cancer using taxane chemotherapy combined with trastuzumab and pertuzumab, and second line therapy with trastuzumab emtansine, are well established. Recent studies of small molecule oral tyrosine kinase inhibitors such as tucatinib and neratinib, and antibody drug conjugates such as trastuzumab deruxtecan further improve outcomes. Major treatment challenges remain in the areas of brain metastases and development of drug resistance. This review details an up to date analysis of current and emerging treatments of metastatic HER2-positive breast cancer.”

**McAndrew, N.P. & Finn, R.S. 2020.**

“There are over 2 million cases a year of breast cancer, leading to over 600,000 deaths globally [1]. Despite these large numbers, increasingly more women are being cured with early stage disease and women with advanced disease are living longer [2]. The appreciation for molecular subtypes of the disease has led to significant therapeutic advances and estrogen receptor positive (ER+) breast cancer represents the largest of these subgroups. An appreciation for the importance of estrogen signaling in ER+ dates back to 1896 when Dr. George Thomas Beatson observed impressive disease responses after performing bilateral oophorectomy in 3 women at Glasgow Cancer Hospital [3]. The evolution of treatment for advanced disease from progestins, to the selective estrogen receptor modulator tamoxifen, and subsequently the aromatase inhibitors and the selective estrogen receptor degrader fulvestrant, has been accompanied by improved efficacy and decreased side effects. While the use of these drugs has changed the natural history of both early and advanced disease, it has been long recognized that many patients will develop resistance to this approach. After many years of trying to improve on single-agent endocrine treatment, since 2012 there has been an explosion of new drugs that have shown improved efficacy in combination with endocrine approaches. The first of these to receive FDA approval was the mTOR inhibitor everolimus (2012) [4], followed by the approval of 3 cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors [palbociclib (2015) [5], ribociclib (2018) [6], and abemaciclib (2018) [7]], and more recently the PI3-kinase inhibitor alpelisib (2019) [8]. In addition, chemotherapy is still used frequently when endocrine

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manipulations have been exhausted. Like other incurable malignancies, the goal in advanced ER+ breast cancer is to prolong survival and maintain quality of life. Currently, we have more tools available to achieve this than ever before and we will review the efficacy and side effect data with these agents that are driving physician choices for individual patients.”

### **Pain Control and Palliation for Metastatic Breast Cancer**

With metastatic breast cancer, pain can be related to treatment or the cancer itself. Pain is not the same for everyone. Even among people at a similar stage of disease, pain can vary. Some people have more intense and more frequent pain than others.

One should never feel pain is simply a part of one’s treatment or that one should be strong and endure it. Even when pain is mild, it can interfere with daily life and make other side effects, such as fatigue, seem worse. Let the health care provider(s) know about any pain or discomfort that may be experienced.

Pain is usually easier to treat when one first has it. Waiting until the pain is severe before getting relief can make it harder to control and may require more medication. That is why it is so important to talk with one’s health care provider about pain. Sometimes, treatment plans can be changed to reduce painful side effects.

Every visit with one’s health care provider should include a discussion of pain. The health care provider can change the type and dose of pain medication throughout one’s care in response to specific needs.

A health care provider may also suggest other types of pain control as needs change. This ensures one is getting the most benefit from available therapies and is as comfortable as possible.

Palliative care and pain specialists (physicians, nurse practitioners and nurses) treat pain from cancer or other causes. They can treat people with early breast cancer as well as those with metastatic cancer.

Palliative medicine is a medical specialty, just like oncology. Palliative care specialists give extra care to help people maintain the best quality of life possible. They have special training in pain management and symptom management.

Be sure to ask the oncologist for a referral if pain is not controlled or in the event of having side effects from the pain medications. The provider should be able to follow the specialist’s recommendations and carry out the pain management. If the treatment is effective, one should not need to see the specialist again.

### **About Clinical Trials**

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:



- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The **South African National Clinical Trials Register** provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: [www.sanctr.gov.za/](http://www.sanctr.gov.za/)

### Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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**Stage IV**

<http://wendy-nielsen.com/tag/metastatic-breast-cancer/>

**Susan G Komen**

<http://ww5.komen.org/BreastCancer/ManagingPainRelatedToMetastaticBreastCancer.html>  
<http://ww5.komen.org/BreastCancer/MetastaticBreastCancerIntroduction.html>

**Tumour Grade and Tumour Stage**

[https://www.medicinenet.com/cancer\\_101\\_pictures\\_slideshow/article.htm](https://www.medicinenet.com/cancer_101_pictures_slideshow/article.htm)

**WebMD**

<http://www.webmd.com/breast-cancer/features/metastatic-breast-cancer-chronic-condition>