Advanced Breast Cancer Backgrounder

Facts and Figures

Breast cancer is the most common cancer in women. In 2012, there were an estimated 1.67 million new cases worldwide – one in four of all cancer cases.[1]

In 2012, an estimated 458,337 women were diagnosed with breast cancer in Europe[2] and, in the US, about 246,660 women are expected to be diagnosed with breast cancer in 2016.[3]

Breast cancer is the fifth most common cause of death from cancer, and an estimated 522,000 women died worldwide from the disease in 2012.[1] In 2012, an estimated 131,259 women died of breast cancer in Europe[2] and, in the US, about 40,450 women are expected to die from the disease in 2016.[3]

Over the last 30-40 years, breast cancer mortality has declined in both Europe and the US, thanks to earlier diagnosis and better treatment.[4,5]

Approximately 30% of women who are diagnosed with early breast cancer will go on to develop advanced disease.[6] The number of people living with metastatic breast cancer in the US is estimated to be over 155,000.[7] In Europe the estimated 5-year prevalence of breast cancer in 2012 was 1,814,572 cases[2] and the median overall survival for women with advanced breast cancer is two to three years.[8]

Types of Breast Cancer

Breast cancer may be non-invasive/pre-invasive or invasive:[9]

- Non-invasive/pre-invasive breast cancer is limited to cells that line the milk ducts (ductal carcinoma *in situ*) or milk producing glands (lobular carcinoma *in situ*) and has not spread into surrounding breast tissue.[9]
- Invasive breast cancer starts in the milk ducts (8/10 cases) or in milk-producing glands (1/10 cases) and is spread to surrounding breast tissue or other parts of the body to form metastases (secondary or advanced tumours).[9]

When breast tumours are examined in the laboratory, they are divided into three broad categories:

- **Hormone receptor (HR) positive**: tumour cells that have oestrogen or progesterone receptors (ER+ or PR+) and have a tendency to grow more slowly than tumours without these receptors. These are more common in post-menopausal women.[10] Approximately 75% of breast tumours have ERs on their cells.[11,12]

- **HER2 positive**: tumours that have extra copies of the HER2 gene or possess excessive levels of HER2 protein. About 20% of breast tumours are HER2+.[10]

- **Triple negative:** tumours that are not ER+ or PR+ and do not have too much HER2, are called triple-negative breast cancer (TNBC). These cancers are more common in younger women and grow and spread more quickly than most other types of breast cancer.[10]

Stages of Breast Cancer[13]

Breast cancer is staged according to the size of the tumour (T), whether it has reached nearby lymph nodes (N) and whether it has formed metastases (M) in other parts of the body:

- Stage 0: the tumour is non-invasive (e.g. ductal or lobular carcinoma *in situ*)
- Stage I: the tumour is invasive but small (2cm or less) and limited to the breast or one to three lymph nodes under the arm, with no metastases
- Stage II: the tumour is invasive and may be larger than 2cm and may have spread to lymph nodes under the arm or near the breastbone, but not into the chest wall or other areas
- Stage III: the tumour is invasive and larger (5cm or more), may affect many lymph nodes under the arm or near the breastbone, and may have spread into the chest wall or skin, but there are no metastases
- Stage IV: the tumour is invasive and may have spread to lymph nodes and other parts of the body with metastases. These occur most commonly in the bones, brain, liver and lungs

About Advanced Breast Cancer

Advanced breast cancer refers to Stages III and IV breast cancer. Stage III disease may be referred to as locally advanced breast cancer.

Breast cancer survival is generally better for women with early stage than advanced breast cancer. The five-year survival rate for women with Stage 0 or Stage I breast cancer is nearly 100% and, for women with Stage II disease, it is about 93%. For Stage III breast cancer, the five-year survival is about 72% and, for women with Stage IV disease it is about 22%.[14]

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Treatment of Advanced Breast Cancer

Advanced breast cancer (Stage III/IV) is generally incurable, however it is still treatable. Current goals are to optimise patient outcomes in respect to both the length, as well as the quality of life.[8]

Treatment of advanced breast cancer depends on whether the tumour is HR+, HER2+ or TNBC, how it has been previously treated and whether there is a need for symptomatic therapy.

Hormone (endocrine) therapy (e.g. tamoxifen or an aromatase inhibitor) is commonly used to treat women with advanced HR+ breast cancer.[15,16] Post-menopausal women may receive 1st line treatment with palbociclib and letrozole, while those who are pre-menopausal are often treated first with tamoxifen.[15] If advanced HR+ breast cancer becomes resistant to tamoxifen or AIs, fulvestrant may be prescribed as 2nd line therapy.[16]

HER2 targeted therapy (e.g. trastuzumab) is typically given with chemotherapy to women with HER2+ Stage IV breast cancer. It can also be given with letrozole. Other combination options include ado-trastuzumab emtansine or pertuzumab with chemotherapy and trastuzumab.[15]

Chemotherapy is typically given to women with advanced TNBC, or in combination with targeted therapy for women with HER2+ disease. A number of different drugs are used to treat advanced TNBC – usually with single agents, though some combinations include carboplatin or cisplatin plus gemcitabine.[17]

Radiotherapy or ***surgery*** may be used to slow the spread of advanced breast cancer or to help prevent or relieve symptoms. For example, they may be used if[15];

- The breast tumour is causing an open wound in the breast or chest
- To treat a small number of metastases in a specific area such as the brain or liver
- To provide relief of pain or other symptoms.

What the Guidelines Say

Both the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) recommend endocrine therapy as standard 1st line treatment for HR+ advanced breast cancer.[8,18]

Date of preparation: 28 November 2016 **Date of expiry: 28 November 2017** **GLOBAL ATLAS ID: 1022571.011**

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For postmenopausal women with HR+ disease, they recommend an aromatase inhibitor, tamoxifen[8,18] or high dose fulvestrant, either as monotherapy[8] or in combination with a nonsteroidal aromatase inhibitor [18] depending on previous exposure to adjuvant endocrine therapy[a]. Premenopausal women should have ovarian suppression/ablation[b] combined with tamoxifen.[8,18]

Optimal 2nd line treatment for HR+ advanced breast is uncertain, but options include tamoxifen or another AI with a different mechanism of action, or fulvestrant 500mg.[8,18] Combination treatment with a nonsteroidal aromatase inhibitor and palbociclib, exemestane and everolimus or fulvestrant and palbociclib may be considered, depending on previous treatment.[18]

For women with HER2+ advanced breast cancer, ESMO recommends anti-HER2 therapy with taxane or anthracycline-based chemotherapy. They also suggest that, for women with HER2+, ER+ advanced disease, combination treatment with anti-HER2 and endocrine therapy should be considered.[8]

Anthracycline- and taxane-based chemotherapy is recommended for women with TNBC who have not received these agents as adjuvant treatment.[8]

Future treatment

Treatment of advanced breast cancer is moving towards a more personalised approach, with therapy tailored towards the molecular profile of each woman's tumour.

In addition to the three broad categories of invasive breast cancer (HR+, HER2+ and TNBC), molecular profiling can identify additional sub-groups against which treatment may be targeted in the future (e.g. PI3K, FGFR1, AKT and PTEN).[19]

Research is also investigating the potential of immunotherapy (e.g. checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4) in the treatment of advanced breast cancer.[20]

[a]additional treatment given after primary treatment
[b]removal or destruction of a body part or tissue or its function

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Date of preparation: 28 November 2016 **Date of expiry: 28 November 2017** **GLOBAL ATLAS ID: 1022571.011**

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