HER2 LOW

Breast Cancer

In the past, breast cancers with low presence of cell surface HER2 protein would not have received any form HER2 targeted treatment given the lack of clinical evidence. Since 5th June 2022, there is now good clinical evidence as published in the New England Journal of Medicine from the DESTINY-Breast04 study that the new ADC drug T-Dxd can significantly improve these patients' cancer free and overall survival. This is a landmark study that offers a completely new treatment option for those who would have otherwise just relied on further anti-hormone-based therapies or standard chemotherapies.

TRIPLE NEGATIVE

Breast Cancer

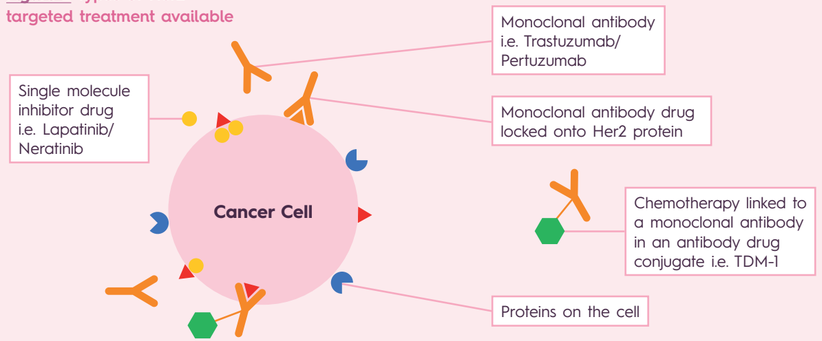
Sacituzumab Govitecan

Sacituzumab govitecan is a new generation ADC that targets the Trop 2 protein on the surface of breast cancer cells. It is a drug that attaches to the Trop 2 protein specifically and delivers a small amount of chemotherapy to the attached breast cancer cells. It was shown in the ASCENT study, as published in the New England Journal of Medicine on the 22nd April 2021 to improve patients' cancer free and overall survival when compared to the standard chemotherapy options. All of these women would have previously been treated with a taxane chemotherapy. The common side effects related to sacituzumab govitecan are diarrhoea and reduction in bone marrow function leading to lower red cell, white cell and platelet counts. This new drug is now available on PBS as a treatment option for women with metastatic triple negative BC.

Pembrolizumab

At the 2021 San Antonio Breast Cancer Symposium, the final study results of the KEYNOTE 355 trial which randomly allocated patients with metastatic triple negative breast cancer to either upfront chemotherapy alone or chemotherapy with pembrolizumab were presented. Pembrolizumab is an immunotherapy drug, designed to amplify the individual's immune response towards attacking cancer cells and is not a form of chemotherapy. The addition of pembrolizumab had improved both cancer free and overall survival in women especially if their cancer cells and immune cells have a high presence of PDL-1 protein. The combined positive score (CPS) was designed to measure the level of presence of the PDL-1 protein and a cutoff of at least 10 is considered reasonable to expect treatment benefit. This treatment is not currently available on PBS and we hope that it might be made available in future.

Figure 2 Types of Her2 targeted treatment available



Summary

As shown in Table 1, we have seen great discoveries and achievements in new drug developments in treating metastatic breast cancer which would offer women better treatments to improve their cancer free and overall lifespan and time with family. Developments in breast cancer treatments are changing rapidly and we are hopeful that all of these aforementioned new drugs will be made available to the Australian public in the near future.

Table 1 Summary of new efficacious treatments in BC

Subtype	New Drug	Standard comparison	Cancer outcomes
Hormone positive BC with PIK3CA protein change	Alpelisib & Fulvestrant	Fulvestrant	↑ Cancer free survival
Her2 positive BC	Trastuzumab Deruxtecan (T-Dxd)	Trastuzumab emtansine (T-DM1)	↑ Cancer free & overall survival
Her2 positive BC	Tucatinib & trastuzumab & capecitabine	Trastuzumab & capecitabine	↑ Cancer free & overall survival
Her2 low BC	T-Dxd	Physician's choice chemotherapy	↑ Cancer free & overall survival
Triple negative BC	Sacituzumab Govitecan	Physician's choice chemotherapy	↑ Cancer free & overall survival
Triple negative BC	Pembrolizumab + chemotherapy	chemotherapy	↑ Cancer free & overall survival

breast cancer research centre-wa
Incorporating Perth Breast Cancer Institute

Hollywood Consulting
Centre Suite 404-405, Level 4
91 Monash Avenue, Nedlands 6009

(08) 6500 5576 reception@bcrc-wa.com.au

Published by Breast Cancer Research Centre-WA August 2022

PYNKS

Breast Cancer Updates 2022

PYNKS
A group for women living with Metastatic Breast Cancer

breast cancer research centre-wa
Incorporating Perth Breast Cancer Institute

HORMONE POSITIVE

Breast Cancer

Fulvestrant and Ribociclib

Fulvestrant is a monthly injectable endocrine treatment that destroys the breast cancer cell surface proteins that accept oestrogen. Ribociclib is an oral drug that blocks the cell cycle CDK 4/6 protein which drives the breast cancer cells to rapidly divide and grow. Study updates from the MONALEESA-3 trial have reported that when used upfront, Fulvestrant and Ribociclib in combination have improved the overall lifespan in women with metastatic hormone positive breast cancer. If we line up all the women on this study from those with the shortest to the longest lifespans, the person in the middle would have lived 16 months longer with the combination therapy than just being on Fulvestrant alone, a significant improvement from 52 months to 68 months. At present, Ribociclib remains the only CDK 4/6 protein blocker drug that can be combined with Fulvestrant for upfront use in Australia. The other CDK 4/6 protein blocker drugs (Palbociclib and Abemaciclib) are currently only used in combination with aromatase inhibitors (Letrozole and Anastrozole) in the upfront setting. Aromatase inhibitors are oral drugs that block the function of aromatase, a hormone in the body that switches testosterone into oestrogen.

Alpelisib

Alpelisib, an oral drug that targets the PIK3CA protein, although currently not commercially available or PBS funded in Australia, has been shown great promise in breast cancers that have genetic changes responsible for making the PIK3CA protein. These genetic changes are not inheritable and are only detected in the breast cancer tumour tissue and not in the rest of the healthy tissues. Up to 40% of hormone positive breast cancers can be found to have this PIK3CA protein-related change. Occasionally, when breast cancers die, cancer-related genetic material will be released into the bloodstream. These changes can be detected in the bloodstream through non-invasive blood sampling, also known as a 'liquid biopsy'. The SOLAR-1 study has shown that in patients where such cancer genetic material containing the PIK3CA protein-related changes are picked up through blood sampling, Alpelisib and Fulvestrant combination have improved treatment outcomes when compared to Fulvestrant alone. Liquid biopsy is a promising non-invasive test in cases where tumour tissue biopsies are technically difficult or unsafe. Unfortunately, this test is not currently available in Australia. We look forward to such targeted drug therapy and 'liquid biopsy' being made available through clinical trials in the near future.

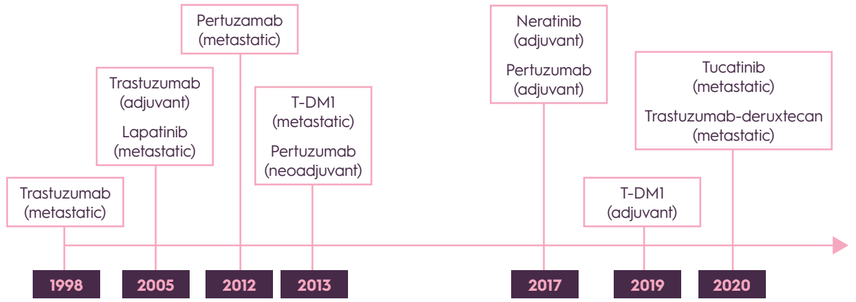
HER2 POSITIVE

Breast Cancer

As shown in Figure 1 below, 6 HER2-targeted therapies have been approved by the European and American drug agencies to treat metastatic HER2 positive breast cancer since 1998. At present, both trastuzumab and pertuzumab are approved to be used upfront with chemotherapy in women with metastatic HER2 positive breast cancers in Australia. When such women were followed-up by the original Cleopatra trial designed to test this treatment combination, 37% of these women remain alive at 8 years after starting treatment. This is a remarkable achievement in the history of breast cancer treatment.

If metastatic breast cancers become resistant to these initial treatments (trastuzumab, pertuzumab and chemotherapy) and no longer work, patients are usually switched to T-DM1, otherwise known as "trastuzumab emtansine". As shown in Figure 2 below, T-DM1 is an antibody drug conjugate (ADC) with a small amount of chemotherapy attached to the monoclonal antibody that targets the HER2 protein. Because the small molecule of chemotherapy is only released within the HER2 positive breast cancer cell, this is called targeted treatment and not referred to as "chemotherapy". When TDM-1 no longer works, the small molecule inhibitor drug lapatinib can then be used.

Figure 1 Timeline of Her2 targeted therapies approved by the EMA & FDA



Her2 targeted therapies approved by both European Medicines Agency (EMA) and US Food and Drug Administration (FDA)

Trastuzumab Deruxtecan (T-Dxd)

As reported in the New England Journal of Medicine on the 24th March 2022, the phase 3 DESTINY-Breast03 study has confirmed that the new drug trastuzumab deruxtecan (T-Dxd) had improved important cancer outcomes when compared with the current standard treatment T-DM1. Among the 524 patients who have previously been treated with trastuzumab and a taxane chemotherapy, more patients are alive and with lower chances of cancer progression (34% vs 76%) within 12 months of treatment. Key side effect of the new T-Dxd drug is mainly with higher probability of drug-induced lung inflammation (10.5% vs 1.9%) when compared to the current standard treatment T-DM1. Women on the new drug will be monitored closely for these changes. We anticipate and hope that this new drug will be made available to the Australian public on PBS.

Tucatinib

Like Lapatinib or Neratinib, Tucatinib is a new small molecule inhibitor drug that can be taken in tablet form and also targets the HER2 protein. When used in combination with standard treatment trastuzumab and capecitabine chemotherapy, this drug was reported as part of the HER2CLIMB study in the New England Journal of Medicine on the 13th Feb 2020 to outperform standard treatment. Treated patients on this study had been previously treated with many lines of treatment and had evidence of HER2 positive breast cancer spreading to their brain and spinal cord. This important study finding represents another new treatment option for women who had cancer progression after many standard lines of HER2-based therapy. Women treated with this drug were observed to have higher chances of diarrhoea and changes in their liver enzyme activity.