Cancer Association of South Africa (CANSA)

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Fact Sheet on Herceptin (Trastuzumab)

Introduction

Herceptin is approved for the treatment of early-stage breast cancer that is **H**uman **E**pidermal growth factor **R**eceptor **2**-positive (**HER2**+) and has spread into the lymph nodes, or is HER2-positive and has not spread into the lymph nodes. If it has not spread into the lymph nodes, the cancer needs to be oestrogen receptor/progesterone receptor (ER/PR)-negative or have one high-risk* feature.

[Picture Credit: Herceptin Image]

Herceptin can be used in several different ways:

- As part of a treatment course including the chemotherapy drugs doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. This treatment course is known as "**AC→TH**"
- With the chemotherapy drugs docetaxel and carboplatin. This treatment course is known as "**TCH**"
- Alone after treatment with multiple other therapies, including an anthracycline (doxorubicin) based therapy (a type of chemotherapy)

Patients are selected for therapy based on an FDA-approved test for Herceptin

*High risk is defined as ER/PR-positive with one of the following features: tumour size >2 cm, age <35 years, or tumour grade 2 or 3.

Metastatic Breast Cancer - Herceptin has 2 approved uses in metastatic breast cancer:

- Herceptin in combination with the chemotherapy drug paclitaxel is approved for the first line treatment of **H**uman **E**pidermal growth factor **R**eceptor **2**-positive (**HER2**+) metastatic breast cancer
- Herceptin alone is approved for the treatment of HER2-positive breast cancer in patients who have received one or more chemotherapy courses for metastatic disease

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Patients are selected for therapy based on an FDA-approved test for Herceptin

Murthy, R.K., Loi, S., Okines, A., Paplomata, E., Hamilton, E., Hurvitz, S.A., Lin, N.U., Borges, V., Abramson, V., Anders, C., Bedard, P.L., Oliveira, M., Jakobsen, E., Bachelot, T., Shachar, S.S., Müller, V., Braga, S., Duhoux, F.P., Greil, R., Cameron, D., Carey, L.A., Curigliano, G., Gelmon, K., Hortobagyi, G., Krop, I., Loibl, S., Pegram, M., Slamon, D., Palanca-Wessels, M.C., Walker, L., Feng, W. & Winer, E.P. 2020.

Background: Patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer who have disease progression after therapy with multiple HER2-targeted agents have limited treatment options. Tucatinib is an investigational, oral, highly selective inhibitor of the HER2 tyrosine kinase.

Methods: We randomly assigned patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine, who had or did not have brain metastases, to receive either tucatinib or placebo, in combination with trastuzumab and capecitabine. The primary end point was progression-free survival among the first 480 patients who underwent randomization. Secondary end points, assessed in the total population (612 patients), included overall survival, progression-free survival among patients with brain metastases, confirmed objective response rate, and safety.

Results: Progression-free survival at 1 year was 33.1% in the tucatinib-combination group and 12.3% in the placebo-combination group (hazard ratio for disease progression or death, 0.54; 95% confidence interval [CI], 0.42 to 0.71; P<0.001), and the median duration of progression-free survival was 7.8 months and 5.6 months, respectively. Overall survival at 2 years was 44.9% in the tucatinib-combination group and 26.6% in the placebo-combination group (hazard ratio for death, 0.66; 95% CI, 0.50 to 0.88; P = 0.005), and the median overall survival was 21.9 months and 17.4 months, respectively. Among the patients with brain metastases, progression-free survival at 1 year was 24.9% in the tucatinib-combination group and 0% in the placebo-combination group (hazard ratio, 0.48; 95% CI, 0.34 to 0.69; P<0.001), and the median progression-free survival was 7.6 months and 5.4 months, respectively. Common adverse events in the tucatinib group included diarrhea, palmar-plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Diarrhea and elevated aminotransferase levels of grade 3 or higher were more common in the tucatinib-combination group than in the placebo-combination group.

Conclusions: In heavily pretreated patients with HER2-positive metastatic breast cancer, including those with brain metastases, adding tucatinib to trastuzumab and capecitabine resulted in better progression-free survival and overall survival outcomes than adding placebo; the risks of diarrhea and elevated aminotransferase levels were higher with tucatinib. (Funded by Seattle Genetics; HER2CLIMB ClinicalTrials.gov number, NCT02614794.).

Gastric Cancer - Herceptin is approved, in combination with chemotherapy (cisplatin and either capecitabine or 5-fluorouracil), for the treatment of HER2-positive metastatic cancer of the stomach or gastroesophageal junction (where the oesophagus meets the stomach) in patients who have not received prior treatment for their metastatic disease.

Oh, D-Y. & Bang, Y-J. 2020.

"HER2 is an established therapeutic target in a large subset of women with breast cancer; a variety of agents including trastuzumab, pertuzumab, lapatinib, neratinib and trastuzumab emtansine (T-DM1) have been approved for the treatment of HER2-positive breast cancer. HER2 is also overexpressed in subsets of patients with other solid tumours. Notably, the addition of trastuzumab to first-line chemotherapy has improved the overall survival of patients with HER2-positive gastric

cancer, and has become the standard-of-care treatment for this group of patients. However, trials involving pertuzumab, lapatinib and T-DM1 have failed to provide significant improvements in the outcomes of patients with HER2-positive gastric cancer. HER2-targeted therapies are also being tested in patients with other solid tumours harbouring HER2 overexpression, and/or amplifications or other mutations of the gene encoding HER2 (ERBB2), including biliary tract, colorectal, non-small-cell lung and bladder cancers. The experience with gastric cancer suggests that the successes observed in HER2-positive breast cancer might not be replicated in these other tumour types, owing to differences in the level of HER2 overexpression and other aspects of disease biology. In this Review, we describe the current role of HER2-targeted therapies beyond breast cancer and also highlight the potential of novel HER2-targeted agents that are currently in clinical development."

How Herceptin Works

Herceptin works on the surface of the cancer cells that grow in an uncontrolled fashion by blocking the chemical signals that can stimulate this uncontrolled growth.

Genes are like instruction manuals that tell each cell of our body how to grow, what kind of cell to become, and how to behave. Genes do this by ordering the cell to make special proteins that cause a certain activity - like cell growth, rest, or repair.

Some cancer cells have abnormalities in genes that tell the cell how much and how fast to grow. Sometimes the cancer cells have too many copies of these genes with abnormalities. When there are too many copies of these genes, doctors refer to it as "overexpression." With some forms of gene overexpression, cancer cells will make too many of the proteins that control cell growth and division, causing the cancer to grow and spread.

Some breast cancer cells make (overexpress) too many copies of a particular gene known as *HER2*. The *HER2* gene makes a protein known as a HER2 receptor. HER2 receptors are like ears, or antennae, on the surface of all cells. These HER2 receptors receive signals that stimulate the cell to grow and multiply. But breast cancer cells with too many HER2 receptors can pick up too many growth signals and so start growing and multiplying too much and too fast. Breast cancer cells that overexpress the *HER2* gene are said to be HER2-positive.

Herceptin works by attaching itself to the HER2 receptors on the surface of breast cancer cells and blocking them from receiving growth signals. By blocking the signals, Herceptin can slow or stop the growth of the breast cancer. Herceptin is an example of an immune targeted therapy. In addition to blocking HER2 receptors, Herceptin can also help fight breast cancer by alerting the immune system to destroy cancer cells onto which it is attached.

Wilson, F.R., Coombes, M.E., Wylie, Q., Yurchenko, M., Brezden-Maslely, D., Hutton, B., Skidmore, B. & Cameron, C. 2017.

BACKGROUND: Human epidermal growth factor receptor 2-positive (HER2+) breast cancer is an aggressive disease that makes up about 20% of all invasive breast cancers. HER2+ breast cancer is associated with poor prognosis and high mortality rates, but the development of HER2-targeted therapies, such as originator trastuzumab (Herceptin®), has substantially improved patient survival. Numerous clinical trials and reviews have investigated the efficacy of HER2-targeted therapies over the past few decades; however, no study has specifically investigated the vast body of evidence on trastuzumab in comparison to chemotherapy regimens, endocrine therapies, and other targeted

therapies. This systematic review and cumulative network meta-analysis (NMA) will synthesize available evidence to evaluate the survival benefit conferred by the addition of originator trastuzumab to standard chemotherapy and to compare the most widely used trastuzumab regimens in patients with HER2+ early breast cancer, based on results from randomized controlled trials (RCTs) and comparative observational studies.
METHODS/DESIGN: A systematic search of Embase, MEDLINE®, and the Cochrane Library has been designed by an experienced medical information specialist and peer reviewed by another senior information specialist. RCTs and comparative observational studies of patients with HER2+ early breast cancer indexed from 1990 onwards will be eligible for inclusion. Two investigators will independently assess studies for inclusion and use standardized data extraction templates to collect data on study and patient characteristics. The primary outcome of interest is overall survival. Bayesian cumulative NMA methods will be used to quantify the evolution of publicly available evidence using both fixed and random effects models.
DISCUSSION: This study will evaluate survival trends associated with originator trastuzumab in patients with HER2+ early breast cancer. As originator trastuzumab has been researched in both clinical and real-world settings for close to 20 years, a cumulative NMA is likely to show improved precision around the parameter estimates for trastuzumab now compared with when the drug was initially launched in the USA in 1998. A better understanding of the evolution of publicly available comparative evidence for originator trastuzumab will further inform treatment for patients with HER2+ early breast cancer, providing benefit to patients, health professionals, and researchers.

What to Know Before Having Treatment with Herceptin
Sometimes people can have a serious reaction to Herceptin, mainly after the first treatment is given. This might involve a severe allergic reaction (anaphylaxis), swelling of face and lips (angioedema), breathing difficulties, abnormal heart rhythms, itchy rash, fever, shivering or a drop in blood pressure. Patients should be monitored during all treatments so that any reactions can be treated. Patients should also be monitored for at least six hours after their first treatment, and for two hours after subsequent treatments. On very rare occasions, a reaction may occur more than six hours after the treatment. It is important to tell one's doctor or nurse if one thinks one is having a reaction.
Herceptin has been associated with causing heart failure, particularly when used following anthracycline (doxorubicin or epirubicin) containing chemotherapy. Heart function should be checked before starting and regularly during treatment with Herceptin. Tests to check one's heart function might include an electrocardiogram (ECG) and Magnetic Resonance Imaging (MRI) scan.

Nemeth, B.T., Varga, Z.V., Wu, W.J. & Pacher, P. 2017.
"Epidermal growth factor receptor-2 (HER-2) is overexpressed in 20 to 25% of human breast cancers, which is associated with aggressive tumour growth and poor prognosis. Trastuzumab (Herceptin®) is a humanized monoclonal antibody directed against HER-2, the first highly selective form of therapy targeting HER-2 overexpressing tumours. Although initial trials indicated high efficacy and a favourable safety profile of the drug, the first large, randomized trial prompted a retrospective analysis of cardiac dysfunction in earlier trials utilizing trastuzumab. There has been ongoing debate on the cardiac safety of trastuzumab ever since, initiating numerous clinical and preclinical investigations to better understand the background of trastuzumabcardiotoxicity and evaluate its effects on patient morbidity. Here, we have given a comprehensive overview of our current

knowledge on the cardiotoxicity of trastuzumab, primarily focusing on data from clinical trials and highlighting the main molecular mechanisms proposed."

It is important to avoid getting pregnant while having treatment with Herceptin and for seven months after the last dose. If one could get pregnant one should preferably use an effective method of contraception to prevent pregnancy. Ask the treating physician for further advice.

Herceptin should not be used in the following individuals:

- People with severe breathing difficulties at rest due to complications of advanced cancer.
- People who need oxygen treatment.
- Children and adolescents under 18 years of age.
- People with an allergy to mouse protein.

Herceptin should also not be used if one is allergic to any of its ingredients. If feeling as if experiencing an allergic reaction, inform the treating doctor or pharmacist immediately.

Herceptin should be used with caution in:

- People with heart failure
- People with coronary heart disease
- People with a history of high blood pressure (hypertension)

Herceptin, Pregnancy, and Breastfeeding - Herceptin could be harmful to a developing baby if used during pregnancy. Herceptin is not recommended for use in pregnancy unless considered essential by a doctor. The potential benefits must outweigh any risks to the developing baby.

It is important to use contraception to avoid getting pregnant during treatment and for seven months after the last dose. If one thinks that one could be pregnant at any point in this time one should get medical advice from one's doctor straight away.

It is not known if Herceptin passes into breast milk. Women should not breastfeed during treatment with Herceptin, or for seven months after the last dose. Speak to the treating physician for further advice.

Concurrent Herceptin Use - one should tell one's doctor or pharmacist if taking any other medicines, including those bought without a prescription, herbal medicines, vitamins, minerals and supplements before treatment with Herceptin is started. Similarly, one should also check with one's doctor or pharmacist before taking any new medicines while on treatment with Herceptin, so they can check that the combination is safe.

There is a higher risk of side effects on the heart if Herceptin is used in combination with chemotherapy medicines called anthracyclines. These include doxorubicin, epirubicin and idarubicin. These medicines should not be used in combination with Herceptin or for seven months after Herceptin treatment is finished, unless there are facilities for heart monitoring.

People who had treatment with an anthracycline medicine before starting treatment with Herceptin also have a higher risk of side effects on the heart, but the risk is lower than if these medicines are used at the same time.

How Herceptin is Administered

Herceptin is injected into a vein through an IV. The patient will receive this injection in a clinic or hospital setting. Herceptin must be given slowly, and the IV infusion can take up to 90 minutes to complete.

Herceptin is usually given once every week or every 3 weeks. The doctor's dosing instructions must be followed very carefully.

Patients may need frequent medical tests to be sure this medicine is not causing harmful effects. Cancer treatments may be delayed based on the results of these tests.

Herceptin Dosing Information – the usual adult dose of Herceptin in the treatment of metastatic Breast Cancer:

- Administer trastuzumab, alone or in combination with paclitaxel
- Initial dose: 4 mg/kg IV infusion over 90 minutes
- Subsequent therapy: 2 mg/kg IV infusion over 30 minutes once weekly until disease progression

The usual adult dose of Herceptin for Breast Cancer - adjuvant: administer according to one of the following doses and schedules:

Initiate trastuzumab during and following paclitaxel, docetaxel, or docetaxel/carboplatin: Initial dose: 4 mg/kg IV infusion over 90 minutes then 2 mg/kg IV infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).

Subsequent therapy: one week after the last weekly dose of trastuzumab, give trastuzumab as 6 mg/kg IV infusion over 30 to 90 minutes every 3 weeks for a total of 52 weeks of therapy.

or

Initiate trastuzumab as a single agent within 3 weeks following completion of all chemotherapy.

Initial dose: 8 mg/kg IV infusion over 90 minutes

Subsequent therapy: 6 mg/kg IV infusion over 30 to 90 minutes every 3 weeks for a total of 17 doses (52 weeks of therapy)

Usual adult dose of Herceptin for Oesophageal Carcinoma - for use in the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma:

Administer trastuzumab in combination with cisplatin and capecitabine or 5-fluorouracil. Initial dose: 8 mg/kg IV infusion over 90 minutes

Subsequent therapy: 6 mg/kg IV infusion over 30 to 90 minutes every 3 weeks until disease progression

Usual adult dose of Herceptin for Gastric Cancer - for use in the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma:

Administer trastuzumab in combination with cisplatin and capecitabine or 5-fluorouracil.

Initial dose: 8 mg/kg IV infusion over 90 minutes

Subsequent therapy: 6 mg/kg IV infusion over 30 to 90 minutes every 3 weeks until disease progression

Endo, S., Kurokawa, Y., Gamoh, M., Kimura, Y., Matsuyama, J., Taniguchi, H., Takeno, A., Kawabata, R., Kawada, J., Masuzawa, T., Yamamoto, K., Kobayashi, K., Sakai, D., Shimokawa, T. & Satoh, T. 2019.
BACKGROUND/AIM: Trastuzumab with S-1 plus cisplatin was proved to be effective for human epidermal growth factor receptor type 2 (HER2)-positive advanced gastric cancer with measurable lesions. However, the efficacy and safety of this regimen in the absence of measurable lesions are unknown.
PATIENTS AND METHODS: Patients with HER2-positive gastric cancer without measurable lesions received cisplatin plus trastuzumab intravenously on day 1 and oral S-1 on days 1-14 of a 21-day cycle. The primary end-point was overall survival, and 40 patients were planned to be enrolled.
RESULTS: Fifteen patients were enrolled. The median overall survival was 14.4 months. The 1- and 3-year overall survival rates were 66.7 % and 26.7 %, respectively. Major grade 3-4 adverse events included neutropenia (47%), anemia (40%), diarrhea (20%), nausea (20%), and anorexia (20%).
CONCLUSION: Trastuzumab with S-1 plus cisplatin might be effective and tolerable for HER2-positive advanced gastric cancer without measurable lesions.

What to do should one miss a dose - call the treating doctor for instructions if an appointment for Herceptin injection is missed.

What to do in case of an overdose - seek emergency medical attention.

Possible Herceptin side effects - some side effects may occur during the injection. Tell your caregiver right away if you feel dizzy, nauseated, light-headed, weak, short of breath, or if you have a headache, fever, chills, sudden chest pain, wheezing, dry cough, hives, or swelling of your face, lips, tongue, or throat.

Get emergency medical help if experiencing any **signs of an allergic reaction to Herceptin**: hives; difficult breathing; swelling of the face, lips, tongue, or throat.

Call the treating doctor at once if experiencing:

- shortness of breath (even with mild exertion or while lying down);
- rapid or shallow breathing, grunting, gasping for breath, pain when you breathe;
- blue-coloured skin or lips;
- sudden chest pain or discomfort, wheezing, new or worsening cough;
- pounding heartbeats or fluttering in your chest;
- swelling, rapid weight gain;
- fever, swollen gums, painful mouth sores, pain when swallowing, skin sores, cold or flu symptoms; or
- heart attack symptoms--chest pain or pressure, pain spreading to your jaw or shoulder, nausea, sweating.

Common Herceptin side effects may include:

- nausea, diarrhoea, weight loss;
- headache, sleep problems (insomnia), tiredness;
- mouth sores;
- fever, chills, cough, or other signs of infection;
- skin rash, bruising, pale skin;
- altered sense of taste; or
- cold symptoms such as stuffy nose, sinus pain, sore throat.

Barish, R., Gates, E. & Barac, A. 2019.
"Trastuzumab targets the human epidermal growth factor receptor 2 (HER2). Its overexpression occurs in 25% of breast cancers and is associated with aggressive tumor characteristics and poor prognosis in absence of targeted therapy. Trastuzumab dramatically improves HER2-positive breast cancer outcomes; however, its clinical use is associated with left ventricular dysfunction and heart failure. Patients receiving trastuzumab or other HER2-targeted therapies undergo routine cardiac function assessment. Holding and/or stopping trastuzumab treatment in the setting of left ventricular dysfunction is recommended. This article summarizes the role of trastuzumab in cancer treatment, the mechanisms of trastuzumab-induced cardiotoxicity, recent clinical investigations, and current controversies."

Availability of Herceptin in South Africa

Breast cancer is the leading form of cancer affecting women in South Africa. Between 20-30% of breast cancer patients are HER2 positive, which is a particularly aggressive strain of cancer. Treatment consisting of 12 months of Herceptin (trastuzumab), in combination with other therapies, has been shown to be highly effective for treating HER2 positive breast cancer – improving overall survival rates by 37%.

Herceptin (trastuzumab) is recommended as an essential medicine by the World Health Organisation for HER2 positive breast cancer, yet its high cost means the majority of women in South Africa who need it will never access it. In South Africa, only pharmaceutical company Roche's branded versions of Herceptin (trastuzumab) are available, sold under the brand names Herceptin and Herclon.

In the Private Sector - a 12-month course of Herceptin costs approximately R485,800, or more if higher dosing is required.

In the Public Sector - Adjuvant biological therapy - due to the high risk of micro-metastatic disease associated with HER2+ tumours (even small, node negative tumours), adjuvant trastuzumab based therapy should be considered in all HER2+ tumours.

Roche has been in negotiations with the National Department of Health over the past year to improve equitable access to trastuzumab in the public sector. We have offered the National Department of Health a significantly reduced and cost-effective treatment option. This option supports the testing of breast cancer patients in the public sector, and if positive for the HER2 gene, makes trastuzumab available for the treatment of these patients.

A final agreement has however not yet been concluded. We reiterate our commitment to ensuring access to this life-saving medicine and we will continue to engage with the National Department of Health. Our proposal to the National Department of Health is on par with collaborative options adopted in low income countries such as India. We sincerely hope that we can reach a final agreement soon so that together we can ensure South African women benefit from this breast cancer treatment.

While price is certainly a factor, other enablers are necessary to ensure access to medicines, such as:

- Awareness of the disease
- Access to the services needed for diagnosis
- Funding
- Treatment

Roche is working with a number of stakeholders, including patient groups, to ensure broad access for cancer patients and to find collaborative solutions to healthcare challenges.

Roche has met with the Fix the Patent Laws Alliance on more than one occasion over the past year, where we have shared with them the steps Roche has taken to achieve access to trastuzumab. We remain fully committed to working with patient groups, the National Department of Health and others to urgently reach a solution which improves the care and outcomes of women with HER2-positive breast cancer in South Africa. We believe that together we can do more for women suffering from breast cancer.

Adjuvant trastuzumab is not recommended in either low-risk, negative patients or patients who have not received adjuvant chemotherapy.

Trastuzumab (given every three weeks) for one year in the adjuvant setting is the current, international, standard of care.

Due to overlapping cardiotoxicities of anthracyclines and trastuzumab, the benefit of trastuzumab is greater if given concurrently with adjuvant chemotherapy (as opposed to sequentially).
(ROCHE South Africa; Breast Cancer Prevention and Control Policy).

Medical Disclaimer

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