BREAST CANCER and HER2+ BREAST CANCER
WITH A LOOK AT TRASTUZUMAB ACCESS IN SOUTH AFRICA

August 2018
INCIDENCE

Breast cancer is the most common cancer in South Africa and the second most common cancer globally. It is the most common cancer faced by women worldwide.\(^i\) Breast cancer is the leading cause of cancer death faced by women in developing countries and the 5th leading cause of cancer death globally.\(^ii\)

In South Africa, breast cancer is the second leading cause of cancer death after cervical cancer.\(^iii\) In 2014, 8230 cases of breast cancer were diagnosed accounting for 21% of all cancers diagnosed in South African women. Approximately 1 in 27 SA women will experience breast cancer in their lifetime\(^iv\) The age standardized incidence rate for breast cancer for all women was 33/100 000 varying from 87/100 000 in white women to 18/100 000 in black women. Since 2011, there has been an increase in certain cancer incidence rates for the white population. This is attributed to increased reporting of cancers from the private laboratories due to cancer becoming a reportable disease. Rates for black women, who are overrepresented among public health care users, have remained fairly stable over many years. However, concerns about under-reporting and under-diagnosis in the public sector may contribute.

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\(^iii\) http://www.who.int/cancer/country-profiles/zaf_en.pdf?ua=1

\(^iv\) Cancer Incidence in South Africa 2014. The National Cancer Registry. www.ncr.ac.za
While Africa generally experiences lower rates of breast cancer than other regions, numbers of cancers diagnosed are increasing in the continent as well as in South Africa⁵.  

⁵ http://www.who.int/cancer/country-profiles/zaf_en.pdf?ua=1
AETIOLOGY

Cancer occurs as a result of mutations, or abnormal changes, in the genes responsible for regulating the growth of cells and keeping them healthy.

The genes are in each cell’s nucleus, which acts as the “control room” of each cell. Normally, the cells in our bodies replace themselves through an orderly process of cell growth: healthy new cells take over as old ones die out. Breast cancer however arises due to uncontrolled growth of breast cells. These cells usually form a tumor that can often be seen on an x-ray or felt as a lump. The tumor is malignant (cancer) if the cells grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. Breast cancer occurs mostly in women, but men can also get breast cancer.

Breast cancer is always caused by a genetic abnormality (a “mistake” in the genetic material). However, only 5-10% of cancers are due to an abnormality inherited from your mother or father. 85-90% of breast cancers are due to somatic genetic abnormalities that happen as a result of the aging process and the “wear and tear” of life in general.

Both genetic or environmental factors, or in most cases, a combination of the two, lead to these changes (mutations) in the breast cells’ genetic material (DNA) which result in uncontrolled growth. However, most patients will never know exactly what caused their cancer, although, there are certain established risk factors that are associated with breast cancer:
GENETIC FACTORS

• **Gender:** Breast cancer occurs nearly 100 times more often in women than in men.

• **Age:** Two out of three women with invasive cancer are diagnosed after age 55.

• **Race:** Breast cancer is diagnosed more often in Caucasian women than women of other races.

• **Family History and Genetic Factors:** A person with a family history (mother, sister, father or child) of breast or ovarian cancer have a higher risk of being diagnosed with breast cancer in the future. The risk increases if the relative was diagnosed before the age of 50.

• **Personal Health History:** People with breast cancer in one breast have an increased risk of being diagnosed with breast cancer in the other breast in the future. Also, the risk increases if abnormal breast cells have been detected before (such as atypical hyperplasia, lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS)).

• **Menstrual and Reproductive History:** Early menstruation (before age 12), late menopause (after 55), having a first child at an older age, or never having given birth can also increase the risk for breast cancer.

• **Certain Genetic Changes:** Mutations in certain genes, such as BRCA1 and BRCA2, can increase the risk for breast cancer. This is determined through a genetic test, which is considered if a person with breast cancer has a significant family history of breast cancer especially at a young age. Individuals with these gene mutations can pass the gene mutation onto their children.

• **Dense Breast Tissue:** Having dense breast tissue can increase your risk for breast cancer and make lumps harder to detect.
ENVIRONMENTAL AND LIFESTYLE RISK FACTORS

- **Lack of Physical Activity**: A sedentary lifestyle with little physical activity can increase the risk for breast cancer.

- **Poor Diet**: A diet high in saturated fat and high fibre lacking fruits and vegetables can increase the risk for breast cancer.

- **Being Overweight or Obese**: Being overweight or obese can increase the risk for breast cancer. The risk is increased after menopause.

- **Drinking Alcohol**: Frequent consumption of alcohol can increase the risk for breast cancer. The more alcohol consumed, the greater the risk.

- **Radiation to the Chest**: Having radiation therapy to the chest before the age of 30 can increase the risk for breast cancer.

- **Combined Hormone Replacement Therapy (HRT)**: Taking combined hormone replacement therapy, as prescribed for menopause, can increase the risk for breast cancer and increases the risk that the cancer will be detected at a more advanced stage.

Usually breast cancer either begins in the cells of the lobules, which are the milk-producing glands, or the ducts, the passages that drain milk from the lobules to the nipple. Less commonly, breast cancer can begin in other tissues in the breast. These cancers are called sarcomas and lymphomas and are not really thought of as breast cancers.
SYMPTOMS

Many breast cancers are found on screening mammograms and ultrasounds which can detect cancers at an earlier stage, often before they can be felt, and before symptoms develop.

The most common symptom of breast cancer is a new lump or mass in the breast or armpit. A painless, hard mass that has irregular edges is more likely to be cancer, but breast cancers can be tender, soft, or rounded.

Other possible symptoms of breast cancer include:
- Swelling of all or part of a breast (even if no distinct lump is felt)
- Skin irritation or dimpling (sometimes looking like an orange peel)
- Breast or nipple pain
- Nipple retraction (turning inward)
- Redness, scaliness, or thickening of the nipple or breast skin
- Bloody nipple discharge

If you have any of these symptoms, consult your health care professional immediately.
THE SPREAD OF BREAST CANCER

Breast cancer can spread when the cancer cells get into the blood or lymph system and are carried to other parts of the body.

The lymph system is a network of vessels found throughout the body that connects lymph nodes (small bean-shaped collections of immune system cells). The clear fluid inside the lymph vessels, called lymph, contains tissue by-products and waste material, as well as immune system cells. The lymph vessels carry lymph fluid away from the breast. In the case of breast cancer, cancer cells can enter those lymph vessels and start to grow in lymph nodes. Most of the lymph vessels of the breast drain into:

- Lymph nodes under the arm (axillary nodes)
- Lymph nodes around the collar bone (supraclavicular [above the collar bone] and infraclavicular [below the collar bone] lymph nodes)
- Lymph nodes inside the chest near the breast bone (internal mammary lymph nodes)
TREATMENT

LOCAL TREATMENTS

Some treatments are local, meaning they treat the tumor without affecting the rest of the body. Most women with breast cancer will have some type of surgery to remove the tumor. Depending on the type of breast cancer and how advanced it is, radiotherapy might be necessary after surgery.

SYSTEMIC TREATMENTS

Drugs used to treat breast cancer are considered systemic therapies because they can reach cancer cells almost anywhere in the body. They can be given by mouth or put directly into the bloodstream. Depending on the type of breast cancer, different types of drug treatment might be used, including:

- Chemotherapy for Breast Cancer
- Hormone Therapy for Breast Cancer
- Targeted Therapy for Breast Cancer
MOLECULAR TYPES OF BREAST CANCER

There are five main intrinsic or molecular subtypes of breast cancer that are based on the genes that a cancer expresses:

- **Luminal A** breast cancer is hormone-receptor positive (oestrogen-receptor and/or progesterone-receptor positive), HER2 negative, and has low levels of the protein Ki-67 (less than 15%), which helps control how fast cancer cells grow. Luminal A cancers are low-grade, tend to grow slowly and have the best prognosis.

- **Luminal B** breast cancer is hormone-receptor positive (oestrogen-receptor and/or progesterone-receptor positive), and either HER2 positive or HER2 negative with high levels of Ki-67 (greater than 15%). Luminal B cancers generally grow faster than luminal A cancers and their prognosis is worse.

- **Triple-negative/basal-like** breast cancer is hormone-receptor negative (oestrogen-receptor and progesterone-receptor negative) and HER2 negative. This type of cancer is more common in women with BRCA1 gene mutations.

- **Normal-like** breast cancer is similar to luminal A disease: hormone-receptor positive (oestrogen-receptor and/or progesterone-receptor positive), HER2 negative, and has low levels of the protein Ki-67, which helps control how fast cancer cells grow. Still, while normal-like breast cancer has a good prognosis, its prognosis is slightly worse than luminal A cancer’s prognosis.

- **HER2-enriched** breast cancer is hormone-receptor negative (oestrogen-receptor and progesterone-receptor negative) and HER2 positive. HER2-enriched cancers tend to grow faster than luminal cancers and can have a worse prognosis, but they are often successfully treated with targeted therapies aimed at the HER2 protein.
HER2-POSITIVE BREAST CANCER

The HER2 gene makes HER2 proteins. They live on the outside of breast cells and send signals to the cell nucleus. These signals can tell cells to grow, multiply or repair damage. But in about 20% of breast cancers, the HER2 gene doesn’t work correctly and makes too many copies of itself (known as HER2 gene amplification). All these extra HER2 genes tell breast cells to make too many HER2 receptors (HER2 protein overexpression). This makes breast cells grow and divide in an uncontrolled way.
Breast cancers with HER2 gene amplification or HER2 protein overexpression are called HER2-positive in the pathology report. The gene mutations that cause HER2-positive breast cancer are sporadic, meaning they happen at some point during our lives. They are not inherited from parents or passed on to children.

Approximately 1 in 5 women diagnosed with breast cancer are HER2 positive. HER2 overexpression is associated with more aggressive disease, higher rates of recurrence and higher mortality rates than HER2 negative tumors. International evidence has demonstrated that HER2 overexpression is generally more common among younger women with breast cancer than older women.

Evidence from South Africa indicates that young black women may be more at risk for developing breast cancer at a younger age and HER2-enriched breast cancer than other races. A study of black women diagnosed with breast cancer at Chris Hani Baragwanath between October 2006 to July 2012, showed that 26% (of the 942 for whom data was available on molecular subtype was available) were HER2 positive.

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A study comparing breast cancer receptor status with race in Namibia and South Africa considered diagnostic results of 10,047 women (with known receptor status) diagnosed between 2009–2011 in South Africa’s public sector or between 2011-2013 in Namibia. The study found that overall 25.2% of tumours were HER2 positive. The study also demonstrated that black women are more likely to be diagnosed with HER2 enriched breast cancer\textsuperscript{xii} - a subtype of HER2 breast cancer that is more responsive to trastuzumab therapy.\textsuperscript{xiii}

A study at the Mammogram Clinic of the Universitas Hospital, Bloemfontein compared the demographic status of women who consented to participate in the study, with their breast cancer profiles. While the study found that breast cancer was most common amongst women between 50 and 60, breast cancer under the age of 40 occurred more frequently in black women than other racial groups. The authors concluded that “[t]his may suggest that pregnancy and parity were risk factors in this racial group.”\textsuperscript{xiv}

\textsuperscript{xiii} Montemurro et al. Potential biomarkers of long-term benefit from single-agent trastuzumab or lapatinib in HER2-positive metastatic breast cancer. Volume 8, Issue 1, February 2014, Pages 20–26
\textsuperscript{xiv} Matatiele PR & Van den Heever WMJ. Breast cancer profiles of women presenting with newly diagnosed breast cancer at Universitas Hospital (Bloemfontein, South Africa). SA Fam Pract 2008, Volume 50 No 6
TREATMENT OF HER2-POSITIVE BREAST CANCERS

The local treatment of HER2-positive cancers is no different from other breast cancers. The systemic therapy will still combine chemotherapy and hormonal therapy as appropriate but other very specific targeted or molecular therapies may be indicated in HER2-positive breast cancers.

Treatments registered for use in South Africa include:

- Trastuzumab (Herceptin): used in early or metastatic disease.
- Lapatinib (Tykerb): used in metastatic disease especially in the brain.

For women with HER2-positive breast cancers, the drug trastuzumab has been shown to reduce the risk of the cancer coming back. Trastuzumab is a type of drug called a monoclonal antibody. Monoclonal antibodies are sometimes called targeted therapies because they work by ‘targeting’ specific proteins (receptors) on the surface of cells. Trastuzumab locks on to the HER2 protein. This blocks the receptor and stops the cells from dividing and growing.xv

Trastuzumab is usually given following surgery and chemotherapy for primary breast cancer to reduce the risk of the cancer coming back in cancers that have spread to lymph nodes or are larger than 2cm in size. This is known as adjuvant therapy.

Trastuzumab is usually given in combination with all after a course of chemotherapy. Trastuzumab may sometimes be given with chemotherapy before surgery and then continued after surgery. This is known as neoadjuvant therapy.

Common side effects include fever or chills, muscle aches, nausea, skin reactions at the site of injection if given under the skin, a low white blood cell count and diarrhoea. A rare but serious side effect is heart failure due to the effect of trastuzumab on the heart muscle.

Taking account of efficacy and safety evidence, the World Health Organisation added trastuzumab to its Essential Medicines Lists for Cancer in the treatment of early and metastatic HER2 positive breast cancer in 2015. “The [WHO’s] list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed”.

Scientists are still studying how long women should take this medication for the greatest benefit. One year of trastuzumab, in addition to chemotherapy, is recommended as standard care in a number of countries for women with early HER2 positive breast cancer. However the high price of trastuzumab remains a barrier to access and completion of trastuzumab in countries where its cost is not fully covered by governments or insurers.

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ACCESS TO TRASTUZUMAB IN SOUTH AFRICA

South Africa has a dual and highly inequitable health care system. The vast majority of people living in South Africa, for whom private medical insurance is unaffordable and inaccessible, are dependent on the government-funded public sector for healthcare services.

Only 15% of people living in South Africa have private insurance enabling them to access private sector care, which they purchase personally or receive via their employer or family members. Private sector expenditure on medical scheme members is approximately 5.25 times greater than per capita spending on individuals that are dependent on the public sector.\textsuperscript{xx} Demographic data demonstrates a racial disparity in access to private sector care, with black South Africans being the least likely to have private insurance coverage.\textsuperscript{xxi}

Trastuzumab is included on South Africa’s essential medicines list (EML) for the treatment of early breast cancer since June 2017 and has been approved by Treasury for supply at public sector cancer treatment centres where breast cancer is treated.

Breast cancer is also a Prescribed Minimum Benefit for the private sector. PMB regulations specify that the diagnosis, treatment and care of the PMB conditions must be funded in full providing that a designated servicer provider is used and that the treatment is not less than what would have been provided in the state sector.\textsuperscript{xxii}

\hspace{1cm} xxi. StatsSA. Use of health facilities and levels of selected health conditions in South Africa: Findings from the General Household Survey, 2011. Available at: Use of health facilities and levels of selected health conditions in South Africa: Findings from the General Household Survey, 2011
OPPORTUNITIES AND CHALLENGES TO ACHIEVING EQUITABLE TRASTUZUMAB ACCESS IN SOUTH AFRICA

The Cancer Alliance launched its campaign for access to trastuzumab in South Africa on World Cancer Day (4 February) 2016. At this time trastuzumab was unavailable in the public sector where 84% of the people living in South Africa access care, and not fully covered for members of private medical schemes.

Since the campaign was launched, South Africa’s Department of Health has taken important steps to ensure trastuzumab access for women with HER2 positive early breast cancer. However, the medicine’s high cost and ongoing patent barriers held by Roche still remain a challenge to ensuring broad, equitable and affordable access to trastuzumab.

Below is a timeline of the Tobeka Daki Campaign for Access to Trastuzumab and a discussion of its achievements to date, as well as ongoing challenges to access.
TIMELINE OF THE TOBEKA DAKI CAMPAIGN FOR ACCESS TO TRASTUZUMAB

4 February 2016  Cancer Alliance and Fix the Patent Laws launch campaign for access to trastuzumab on World Cancer Day and release a video featuring Tobeka Daki, a mother of two with HER2+ breast cancer who is unable to access trastuzumab due to its high cost. Tobeka was told by her oncologist that she needed trastuzumab in 2014. At the time, Tobeka had private health insurance, but her medical scheme told her she wasn’t covered to receive this treatment. While coping with cancer, Tobeka wasn’t able to work and subsequently lost her medical aid. Thereafter she sought treatment from a public sector facility where trastuzumab was unavailable.

17 March 2016  Tobeka Daki gives testimony on her inability to access trastuzumab given its excessive price at the United Nations High-Level Panel on Access to Medicines.

Tobeka Daki protests the unaffordability of trastuzumab at the annual AIDS conference in Durban in 2016. A few months later Daki died because she was never able to access the medicine.
31 March 2016  Led by Tobeka Daki, the Cancer Alliance and Fix the Patent Laws picket outside of Roche South Africa calling for the company to drop the price of trastuzumab and confirm it will not seek to assert secondary patents to block the entry of competitor products in the country.

10 May 2016  South Africa’s Health Minister Aaron Motsoaledi calls for strong action and solidarity in combating price gouging by pharmaceutical companies, including for trastuzumab. During the health budget vote, the Minister states:

“You are aware of the exploding prevalence of Cancer around the world and in our own country. We have just moved in a circle. Just as the price of ARVs were unaffordable then, Cancer drugs are devilishly unaffordable today. If no drastic action is taken today, we are going to be counting body bags like we are at war. Two years ago, I was regarded as exaggerating or outright insane by some, when I spoke openly against Pharmaceutical companies that were planning a price onslaught against us. Today, that onslaught which I had foreseen is here with us.

If you have breast cancer and you need treatment with Trastuzumab, known commonly as Herceptin you must part with close to R500 000.00 for a year’s treatment.”

– Health Minister Aaron Motsoaledi

21 July 2016  Led by Tobeka Daki, women at the International Aids Conference in Durban protest the unaffordable cost of trastuzumab.

27 September 2016  Led by Tobeka Daki, around 1,000 activists march to the offices of the Department of Trade and Industry to demand reform of South Africa’s patent laws to improve affordability and accessibility of medicines in the country, including trastuzumab.
November 2016 The Cancer Alliance makes a submission to the Department of Health motivating for the provision of trastuzumab in South Africa and responding to the Department’s cost concerns.

14 November 2016 Tobeka Daki dies in her home after never being able to access trastuzumab treatment.

7 February 2017 Activists around the world march against lives lost due to pharmaceutical companies’ greed and Fix the Patent Laws relaunches its campaign for trastuzumab access the Tobeka Daki Campaign for Access to Trastuzumab.

14 March 2017 eNCA airs a documentary exploring access challenges for trastuzumab in South Africa.

29 June 2017 South Africa’s National Essential Medicines List Committee approves the inclusion of trastuzumab on the country’s Tertiary and Quaternary Essential Medicines List.

August 2017 South Africa’s Department of Health launches a Breast Cancer Control Policy recommending the provision of one-year of adjuvant trastuzumab treatment for women with HER2+ breast cancer.
WHAT IS TRASTUZUMAB?

Trastuzumab is a biologic therapy that is recommended as an adjuvant therapy (a therapy that is given in addition to local surgical treatment) in combination with chemotherapy for the treatment of early HER2+ breast cancer.

Trastuzumab is a monoclonal antibody that binds to the human epidermal growth factor receptor (HER2) that is overexpressed in individuals with HER2 positive breast cancer – inhibiting the growth of tumour cells. Trastuzumab thereby reduces the risk of tumour recurrence and death in patients with HER2+ early breast cancer.

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ii. https://www.herceptin.com/breast/metastatic
POLICY UPDATE

During 2017, the Department of Health launched a Breast Cancer Control Policy recommending the provision of one-year of trastuzumab treatment in addition to chemotherapy for individuals with HER2+ breast cancer.

In the same year, the Department of Health added trastuzumab to the country's Tertiary and Quaternary Essential Medicines List. These important commitments to provide trastuzumab in the public sector were in part due to the tireless advocacy of the late Tobeka Daki as a member of the Cancer Alliance and Fix the Patent Laws coalition.

In this policy brief, we provide an update on the status of government’s policy commitment to roll-out trastuzumab in the public sector, as well as challenges and opportunities to securing affordable treatment options.
Currently only Roche’s trastuzumab products, Herceptin® and its clone, Herclon®, are registered in South Africa.

Mylan has submitted a dossier for registration of its trastuzumab biosimilar product with the South African Health Products Regulatory Authority (SAHPRA), previously known as the Medicines Control Council (MCC). Mylan received regulatory approval for marketing of its trastuzumab biosimilar from the U.S. Food and Drug Administration (FDA) in October 2017. In Europe, Celtrion, Amgen and Samsung Bioepis have received authorisation to market their trastuzumab products from the European Medicines Agency.

Expanded competition for trastuzumab is expected to lead to a significant price decreases - as generally seen when monopoly patent periods end and competitor products enter the market. However, in South Africa ongoing secondary patents combined with regulatory delays could prevent South Africans from benefitting from price decreases seen globally.

vi. https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm
Table 1. A snapshot of trastuzumab products available globally

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PATENTS ON TRASTUZUMAB IN SOUTH AFRICA

While the initial 20-year patent on trastuzumab in South Africa expired in 2016, an additional eight secondary patents related to trastuzumab could block the entry of competitor products, excluding Mylan’s product (see below), in South Africa until 2026.

In cross-checking the status of patents granted in South Africa with other jurisdictions using WIPO’s Patentscope database, we found that matching applications (or divisional applications thereof) were withdrawn or revoked in Europe for seven of the eight granted secondary patents in South Africa. In other words, patent granted in South Africa were withdrawn or rejected in Europe or granted on a smaller scope of protection following examination.

See full patent data in an annexure to this document.
While Roche may seek to assert its ongoing secondary patents to prevent competitor products from being sold in South Africa, this does not apply the Mylan’s product. Mylan has received a global licence from Roche that allows it to market its trastuzumab product in South Africa. The global license was granted as part of a settlement agreement in which Mylan agreed to withdraw its legal challenges on Roche’s U.S. held trastuzumab patents.\textsuperscript{vii}

While the Mylan license should allow for some cost-saving following the introduction of Mylan’s trastuzumab product in South Africa, its introduction may not lead to significant cost savings. Research has demonstrated that when one competitor product enters the market it is generally priced close to the cost of the originator product. Whereas, when multiple competitor products enter the market prices fall significantly.\textsuperscript{viii} It therefore remains important for Roche to clarify that it will not seek to block additional competitor products from entering the market through asserting secondary patent claims in South Africa.

\textsuperscript{viii} https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm

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In South Africa, only Roche’s trastuzumab products are available sold under the brand names Herceptin® and Herclon®.

The Department of Health recently finalised a tender to make trastuzumab available in the public sector under the new Breast Cancer Control Policy and updated essential medicines lists.

Under the tender, the Department of Health will procure Herclon® from Roche at R6,531.61 for a 440mg vial – or around R130,632 for a year’s treatment.

Herclon® has not yet been made available in the private sector and private sector users are only able to access Herceptin®. Herceptin® is sold by Roche at R23,769 for a 440mg vial. At standard doses, the cost of a year of Herceptin® treatment in South Africa is around R475,380.

As breast cancer is a prescribed minimum benefit identified condition and trastuzumab is now the standard of care in the state sector, private medical insurers should fully cover the cost of trastuzumab. Patients denied full coverage of adjuvant trastuzumab by their medical aid should challenge this rejection at the Council for Medical Schemes.

Finally, analyses by health economists in the UK have estimated that trastuzumab can be profitably marketed at a fraction of its current cost in South Africa at around $240 for a year’s treatment.\textsuperscript{x} To combat price gauging by pharmaceutical companies and ensure fair medicine pricing, the Department of Health should urgently explore options to require full disclosure of R&D expenditure (including public expenditure) and production costs for medicines, as recently recommended by the United Nations High-Level Panel on Access to Medicines.

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<td>Refused (1020157003191) and withdrawn in South Korea (1020087009383, 1020127002495) Revoked in the EU (EP1282443)</td>
</tr>
<tr>
<td>HER-2 ANTIBODY COMPOSITION</td>
<td>Genentech Inc.</td>
<td>2007/01234</td>
<td>PCT/US05/025084</td>
<td>15-Jul-2005</td>
<td>12-Feb-2007</td>
<td>15-Jul-2025</td>
<td>Granted (Renewal payments up to date)</td>
<td>Withdrawn (1020077004108, 1020127000415, 1020107019485, 1020157009058, 1020137015103, 1020117009515, 1020177012110) and refused (1020157034266) in South Korea</td>
</tr>
<tr>
<td>EXTENDING TIME TO DISEASE PROGRESSION OR SURVIVAL IN CANCER PATIENTS</td>
<td>Genentech Inc.</td>
<td>2007/07078</td>
<td>PCT/US06/006334</td>
<td>21-Feb-2006</td>
<td>22-Aug-2007</td>
<td>21-Feb-2026</td>
<td>Granted (Renewal payments up to date)</td>
<td>Revoked (EP1850874) and withdrawn in the EU (EP2399605)</td>
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<tr>
<td>PATENT TITLE</td>
<td>PATENT HOLDER</td>
<td>CIPC NUMBER</td>
<td>PCT NUMBER</td>
<td>INTERNATIONAL FILING DATE</td>
<td>LODGING DATE</td>
<td>EXPIRY DATE</td>
<td>STATUS</td>
<td>ACTIONS ON MATCHING APPLICATIONS OR DIVISIONAL PATENTS THEREOF IN OTHER JURISDICTIONS</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
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<tr>
<td>CANCER TREATMENT COMBINATION THERAPY COMPRISING VINFLUNINE AND TRASTUZUMAB</td>
<td>Hoffman- La Roche Ltd</td>
<td>2009/08247</td>
<td>PCT/EP08/056620</td>
<td>29-May-2008</td>
<td>23-Nov-2009</td>
<td>29-May-2028</td>
<td>Lapsed</td>
<td>Withdrawn in the EU (EP2164573) and South Korea (1020097025793) Refused in Ukraine (a200913837)</td>
</tr>
<tr>
<td>TREATMENT OF HER-2-POSITIVE CANCER WITH PACLITAXEL AND TRASTUZUMAB-MCC-DM1</td>
<td>Genentech Inc.</td>
<td>2013/03611</td>
<td>PCT/US11/063764</td>
<td>7-Dec-2011</td>
<td>17-May-2013</td>
<td>7-Dec-2031</td>
<td>Granted (Renewal payments up to 2016)</td>
<td>Withdrawn in South Korea (1020137016922) and the EU (EP2648719)</td>
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Data updated 29 May 2018