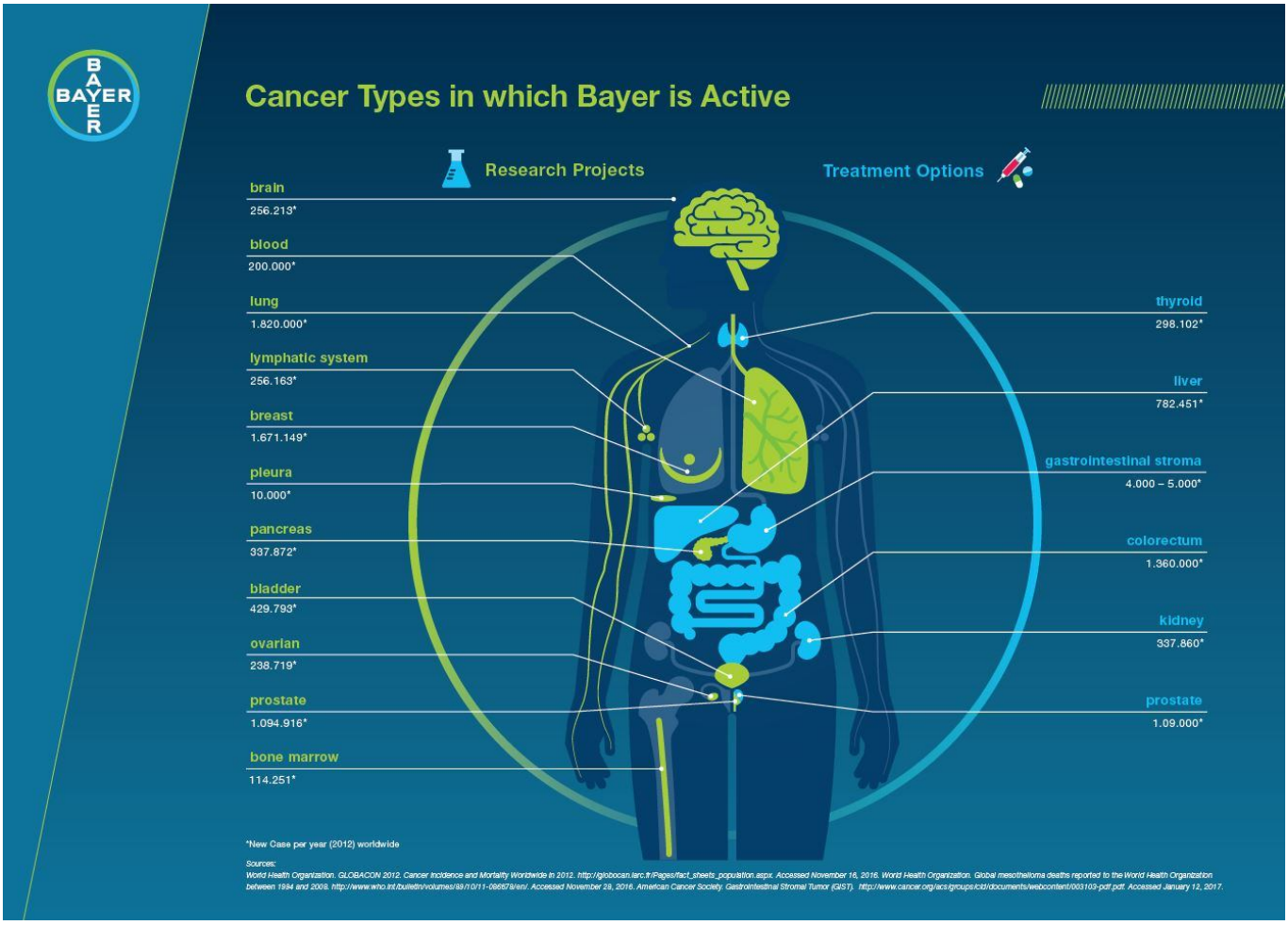
INNOVATION + PARTNERING

The future of cancer therapy is now

Twenty years ago, Bayer was starting research into what would become its very first cancer drug. Fast forward to today, we now have four cancer drugs on the market and several compounds in various stages of development that we hope will go on to benefit patients in the future. So far our drugs have already treated over 600,000 people, but as long as there are patients who are suffering from cancer we won't rest. We will continue to develop new drugs that could change the course of cancer.



*New cases per year (2012) worldwide

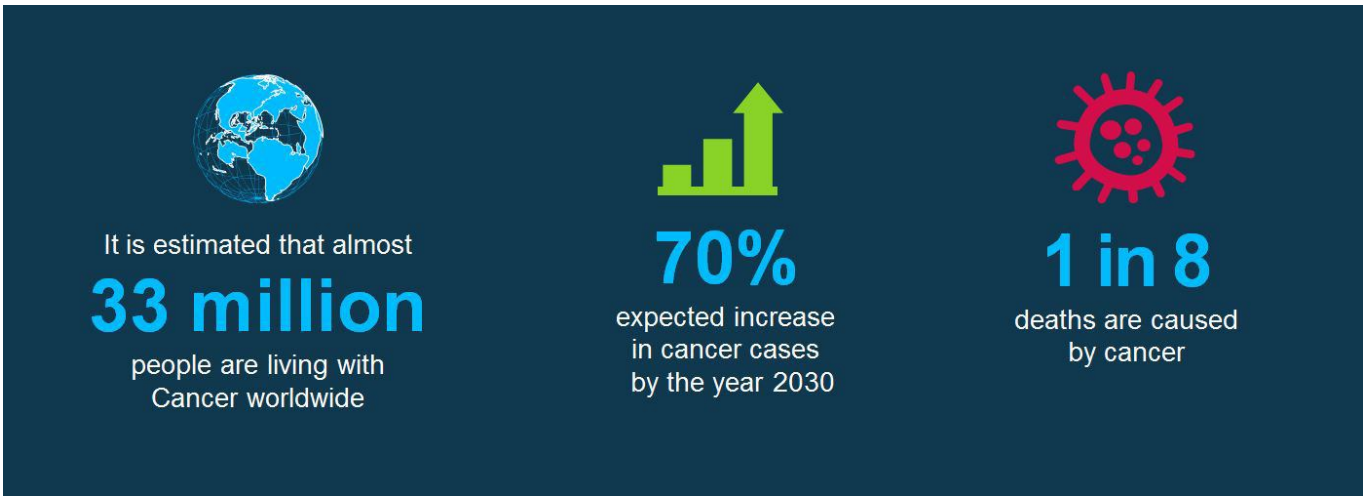
Why we need to move on from the “one-size fits all” approach

For many years, chemotherapy and radiation were the standard cancer treatments available. They caused strong side effects which could often diminish the patient’s quality of life and there was a need for alternatives.

Twenty years ago, Rituximab, the first monoclonal antibody was approved for cancer treatment alongside the first targeted therapy named Trastuzumab. These treatments heralded the dawn of more targeted treatments with fewer side effects for patients.

After further research, cancer was found to be a disease of great complexity that required more

targeted treatments for patients. A glance at the oncology landscape today shows a wealth of new possibilities for earlier cancer diagnosis and treatment, resulting in lower death rates and enabling some cancers to be managed as chronic diseases. However, people are still dying of cancer. New research is vital to further our understanding of this complex disease and Bayer is fully committed and prepared for this challenge.



1. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. // 2. World Health Organization. Cancer. // 3. Global Oncology Trend Report: A Review of 2015 and Outlook to 2020

We have come a long way from our first cancer drug 20 years ago and we're proud to show our progress at the American Association of Cancer Research (AACR) annual meeting. We understand that people are waiting today for the cancer treatment of the future – we're talking precision medicine, targeted treatments and more personalized approaches. We're working on it, so let us tell you more:

Researching new and targeted ways to treat cancer and improve patients' lives

Immuno-Oncology: Using the immune system to fight cancer

It is every oncologist's dream to be able to successfully activate the immune system to fight cancer. Decades of research have uncovered "immune checkpoints" which cancer cells activate to reduce the efficiency of the immune system. There is already a first generation of antibodies that can block these checkpoints and reactivate the immune system to find and

destroy cancer cells. These antibodies are called immune checkpoints inhibitors (ICIs). However, around 70 per cent of patients have not responded to the first generation of ICIs, so we are looking into how new therapies can be developed for these patients.

We have joined forces with the renowned German Cancer Research Center (DKFZ) and with the drug discovery company Compugen to find out how cancer cells evade the immune system so that we can create the next generation of immunotherapies.

At the AACR meeting this year, we will present our work so far with both partners. With the DKFZ, we present a new antibody that blocks a specific immune checkpoint and is showing promising preclinical anti-cancer results. We hope that the first trials with patients will go ahead this year, in 2018. Our collaboration with Compugen has also proved fruitful – another antibody also shows the capability of blocking the immunosuppressive activity of a different checkpoint and is also planned to go into clinical studies this year.

> *"Immuno-Oncology has fundamentally changed the way cancer is being treated today. Utilizing the power of the immune system has proven to be a very efficacious therapeutic approach in a growing number of cancer indications. The remarkable and durable responses observed have certainly made a real difference to the lives of many patients."*
>
> Bertolt Kreft, Head of Immuno-Oncology Research at Bayer

DHODH: Small molecules offering big possibilities for new treatment approaches in acute myeloid leukemia?

In 2015, 20,000 patients developed acute myeloid leukemia (AML). The current chemotherapy treatment available is often too toxic for patients, especially for older people, as the treatment does not completely distinguish between healthy or cancerous cells and destroys both of them. For many patients the current treatments provide no hope for a full recovery. Together with our partner, the Broad Institute of MIT and Harvard, we are researching small molecules

that selectively target cancer genome alterations in cancerous cells to stop the spread of cancer in the body.

In the case of AML, we identified a substance that blocks the enzyme Dihydroorotate dehydrogenase (DHODH). This enzyme is involved in the production of DNA building blocks that cells need for cell division. DHODH plays a central role in certain types of leukemia. This project is now advancing into clinical development, potentially offering future AML patients a new treatment option.

> *“Our partnership with the Broad Institute brings together their world-class expertise in disease genomics with Bayer’s experience in drug discovery and development. Our goal is to advance innovative treatments for patients who previously had few or no therapeutic options.”*
>
> Andrea Haegebarth, Head of Oncogenic Signaling Research at Bayer

PSMA-TTC: Finding new ways to tackle prostate cancer

Prostate cancer is one of the most common cancers in men and it is estimated that by 2030, 1.7 million new cases will be diagnosed annually. Prostate cancer is driven, in many cases, by the male hormone testosterone and the usual first lines of treatment for this cancer are castration and anti-hormone therapies. However, in advanced stages of prostate cancer, patients have often shown resistance to conventional chemotherapy treatment methods. Our scientists have developed a method that could help directly target prostate cancer cells via the prostate-specific membrane antigen (PSMA).

The method uses a targeted thorium conjugate (TTC) which is made up of a targeting antibody and the alpha-particle emitting Thorium-227. The antibody carries the thorium specifically to cancer cells, binds to the surface of the cancer cell and the thorium fires high-energy alpha particles into the cancer cell, causing cell death. By using a specific antibody that targets PSMA, the intention of our new, investigational PSMA-TTC is to seek out prostate cancer cells and kill them while sparing as much healthy tissue as possible. We hope that this new

approach could help those patients suffering from prostate cancer, giving them a new treatment option.

> *“The TTC approach is a nascent technology and is unique to Bayer. We are really excited by the results from our preclinical trials as we have observed strong anti-tumor activity in cancers that were resistant to chemotherapy. These results give us hope that TTCs may benefit patients with tumors that have failed to respond to other treatments.”*
>
> Alan Cuthbertson, Head of Thorium Research at Bayer

Testing for genetic alterations to find the right treatment for patients

Tropomyosin receptor kinase (TRK) fusion cancer is a disease that affects adults and children and there is currently no standard of care. The rate of TRK fusion cancers tends to be higher in cancers that occur in children and the current treatments often involve amputation or chemotherapy; the side effects are difficult to cope with and the treatments are life-changing. Together with our partner Loxo Oncology, we are developing two novel agents that could fulfill the promise of precision medicine where tumor genetics, instead of the site of the tumor, helps doctors to select a specific treatment for their patients.

In TRK fusion cancer, the disease develops when a certain genetic alteration called a “gene fusion” occurs. Chromosomes, which carry genetic information, break up and the wrong pieces fuse back together causing a gene fusion which can lead to activation of otherwise normal proteins. In this case the Neurotrophic tyrosine receptor kinase (NTRK) gene fuses to other genes and activates oncogenic signaling pathways in a cancer cell and causes uncontrolled tumor growth. NTRK gene fusions occur rarely but broadly across tumor types, and patients with this gene mutation can be identified through appropriate testing. The results of this comprehensive gene testing can determine the most appropriate treatment for patients.

adults and children. Since they are the primary driver of tumor growth in some cancers, it is crucial to test for an NTRK gene fusion in order to select the most appropriate treatment for the patient."

Svetlana Kobina, Head of Medical Affairs Oncology at Bayer

Supporting the scientific community to further important research

We collaborate with renowned partners who complement our in-house expertise to bring new treatments to patients as quickly as possible.

You've read about some of our partnerships in research above, but did you know that we are also sharing results of our internal research programs with the wider scientific community? For example, we donate chemical probes, four of which will be presented at this year's AACR meeting. And, for the third year running, we will team up with the AACR to give ten grants to scientists working on ground-breaking cancer research. These activities are part of our commitment to patients: ensuring they have access to the latest treatments that could improve their quality of life. Read more about our commitment to open science and innovation here.

Sources:

Cancer Research UK, Monoclonal Antibodies: http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy/types/monoclonal-antibodies, Last accessed: March 2018

National Cancer Institute, Dictionary of Cancer Terms: https://www.cancer.gov/publications/dictionaries/cancer-terms/ Last accessed: March 2018