

TARGETED THERAPIES FOR CANCER

1. What are targeted therapies?
 2. How do targeted therapies work?
 3. What are some of the different types of targeted therapy?
 4. What are the potential benefits compared to conventional chemotherapy?
 5. What targeted therapies is Boehringer Ingelheim developing?
-

1. What are targeted therapies?

The emergence of effective cancer chemotherapy is one of the major medical advances of the second half of the 20th century. In certain cancers, such as childhood acute lymphoblastic leukaemia and subgroups of Hodgkin's disease and non-Hodgkin's lymphoma, chemotherapy is often curative; and the promise of long-term survival makes therapy well worth the risk of adverse effects and the financial costs. However, traditional chemotherapy is indiscriminate and will affect normal healthy cells as well as rapidly proliferating cancer cells. These 'toxic' chemotherapeutic agents are being supplemented by a new generation of therapies that recognise specific targets in or on cancer cells. These therapies hold the promise of improved efficacy and fewer side effects.

The term 'targeted therapies' refers to a group of agents that includes:

- Angiogenesis inhibitors
- Signal-transduction inhibitors
- Apoptosis-inducing therapies such as cell-cycle kinase inhibitors
- Monoclonal antibodies
- Gene therapy

2. How do targeted therapies work?

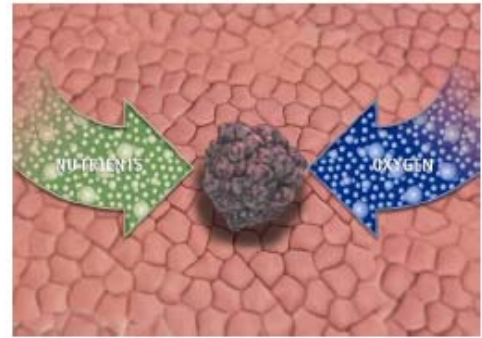
Targeted cancer therapies interfere with cancer cell growth and division in different ways and at various points during the development, growth and spread of cancer. Rather than having broad cytotoxic effects, many of these therapies focus on specific proteins that are involved in the signalling process. By blocking the signals that tell cancer cells to grow and divide uncontrollably, targeted cancer therapies can help to stop the growth and division of cancer cells.

3. What are some of the different types of targeted therapy?

Angiogenesis inhibitors

Angiogenesis, or the growth of new blood vessels, is an important natural process occurring in the body, both in health and in disease. In a healthy body, angiogenesis occurs in wound healing and to restore blood flow to damaged tissues. However, excessive angiogenesis occurs in diseases such as cancer,¹ in which the new blood vessels feed diseased tissues with oxygen and nutrients, encouraging tumour growth, and allowing tumour cells to escape into the circulation, leading to growth of secondary tumours or metastases.²

Angiogenesis is regulated by both activator and inhibitor molecules. Many tumours release naturally occurring activators of angiogenesis, such as vascular endothelial growth factor (VEGF). Inhibitors of angiogenesis are also produced and there is normally a balance between inhibition and activation.³ There are many mechanisms involved in this process, which offer several targets for therapeutic intervention.

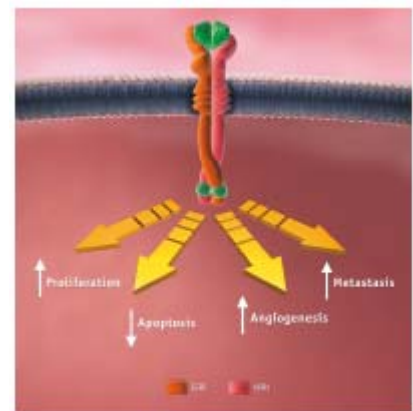


As angiogenesis plays a pivotal role in the growth of all solid tumours, angiogenesis inhibitors are being investigated in clinical studies in a broad range of cancers, including: breast, prostate, brain, pancreatic, lung and ovary, as well as some leukaemias and lymphomas.

Signal-transduction inhibitors

'Small molecule' therapies block specific enzymes and growth-factor receptors that are involved in cancer cell growth. These treatments are also called signal-transduction inhibitors.

Cell proliferation, differentiation and programmed cell death (apoptosis) are tightly regulated in healthy tissues by a variety of external signals working via receptors that activate intracellular signal-transduction pathways. Cancer cells acquire genetic mutations that deregulate these signal-transduction pathways, resulting in malignant cells that proliferate uncontrollably and that do not respond to the signals that normally activate apoptosis.



This disruption stems from the over-activity of multiple signalling pathways – for example, the epidermal growth-factor receptor (EGFR) and human epithelial receptor 2 (HER2) signalling. Over-expression of EGFR and HER2 is associated with poor prognosis and advanced-stage cancers.⁴ Inhibition of one receptor type alone may not be sufficient for optimal inhibition of tumour cell proliferation and survival. Dual EGFR and HER2 inhibition may provide a complete block of EGFR/HER family signalling.⁵

Cell-cycle kinase inhibitors

The cell cycle describes the series of events between one cell division and the next. It is the process by which a single cell develops into a mature organism and the process by which hair, skin, blood cells and some internal organs are renewed. Disruption of this process is a fundamental feature of cancer. The mitotic spindle is vital for successful cell division. Cell-cycle kinases, such as polo-like kinase 1 (Plk1), are proteins that influence the processes of cell division, such as formation of the mitotic spindle. Over-expression of Plk1 is associated with aggressiveness and a poor prognosis in many cancers.⁶ Inhibition of Plk1 induces mitotic arrest and apoptosis in *in vivo* tumour models, resulting in growth inhibition and tumour regression. Plk1 may therefore be a suitable target for cancer therapy.⁷



Monoclonal antibodies

Monoclonal antibodies (MABs) are part of the so-called biological group of therapies for the treatment of cancer; these therapies use the body's immune system to fight cancer or to reduce the side effects caused by some cancer treatments. Biological therapies are designed to repair, stimulate or enhance the immune system's responses.

The immune system is one of the body's main defences against infection and disease. It is a complex system of cells and organs that work together to defend the body against attacks by "foreign" invaders, including cancer, in a variety of ways. For example, the immune system may recognise the difference between healthy cells and cancer cells in the body and works to eliminate cancerous cells.

Some antibodies and other immune system substances can be produced in the laboratory for use in cancer treatment. These substances are often called biological response modifiers (BRMs). They alter the interaction between the body's immune defences and cancer cells to boost, direct or restore the body's ability to fight the disease. BRMs include interferons, interleukins, colony-stimulating factors, monoclonal antibodies, vaccines, gene therapy and non-specific immunomodulating agents.

MABs that have been developed for the treatment of cancer are designed to recognise specific structures on cancer cells and can be used in a number of ways:

- To react with specific types of cancer, which may enhance a patient's immune response
- To act against cell growth factors and interfere with the growth of cancer cells
- To be combined with other anticancer drugs, radioisotopes (radioactive substances), other BRMs or other toxins to help destroy cancer cells.

Examples of MABs are rituximab for the treatment of non-Hodgkin's lymphoma and trastuzumab for the treatment of breast cancer. Other MABs are being studied for a broad range of cancers, including colorectal, lung, prostate and brain.

Gene Therapy

Gene therapy is an experimental treatment that involves introducing genetic material into a person's cells to fight or prevent disease. Humans have between 30,000 and 40,000 genes – the biological units of heredity that determine traits such as hair and eye colour, as well as more subtle characteristics such as the ability of blood to carry oxygen. Genes are located on chromosomes inside cells and carry the instructions that allow cells to produce specific proteins, such as enzymes. Researchers are studying several ways to treat cancer using gene therapy, including:

- Replacing altered or missing genes with healthy genes
- Stimulating the body's natural ability to attack cancer cells
- Inserting genes into cancer cells to make them more responsive to chemotherapy or other treatments
- Preventing cancer cells from developing new blood vessels

4. What are the potential benefits compared to chemotherapy?

Chemotherapy involves using cytotoxic agents to treat cancer. These treatments are also toxic to healthy tissues and consequently are associated with a high level of side effects and complications. As these agents are often used at the limits of toxicity and efficacy in order to ensure optimal tumour response, maximising efficacy and safety are the main considerations in chemotherapy practice. Side effects and complications from treatment include:

- Nausea and vomiting
- Suppression of the immune system, leading to infections and blood disorders such as low white blood cell count and anaemia
- Hair loss
- Renal and hepatic toxicity
- Hypersensitivity reactions

Although many chemotherapy agents dramatically affect the course of the disease, success is far from universal. Certain tumour types are relatively resistant to such anti-cancer drugs. In other instances, a marked response to treatment occurs but, over time, the disease process recurs and treatments become ineffective. This is referred to as 'drug resistance'.

Conversely, targeted therapies, by their very nature, deliver their therapeutic effect directly to the cancer cell. This can often be achieved at doses below the maximum tolerated dose and so tumour response can be seen with the potential for fewer and less toxic side effects, thereby offering improved quality of life for patients and their families. In addition, many targeted treatments in development overcome the problems of resistance seen with the more 'broad spectrum' conventional chemotherapy. Of most significance is that targeted therapies will give physicians an opportunity to improve the tailoring of treatment - with the potential of individualising treatment based on the unique set of molecular targets produced by the patient's tumour.

Modern treatment approaches frequently combine conventional chemotherapy with targeted therapy, in particular in late stage disease. Targeted therapies in most cases do not increase the dose-limiting toxicities of the chemotherapy.

5. What targeted therapies is Boehringer Ingelheim developing?

Boehringer Ingelheim has a long-term commitment to deliver tomorrow's cancer therapies by discovering and developing novel treatment options that combine ground-breaking science with high therapeutic value for patients, physicians and healthcare providers. Building on breakthrough science to develop targeted therapies - biologicals and small molecules - Boehringer Ingelheim is focussing its research in areas of unmet medical need including both solid and haematological cancers. The search for new cancer treatments is currently focused on three areas:

- Angiogenesis inhibitors
- Signal transduction inhibitors
- Cell-cycle kinase inhibitors

BIBF 1120 (Vargatef™)*

BIBF 1120 (Vargatef™) is a novel triple angiokinase inhibitor that inhibits three growth factor receptors simultaneously: vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR)₈ - all crucially involved in the formation of blood vessels (angiogenesis).

BIBF 1120 is in phase III development in lung cancer. The LUME-Lung phase III clinical trial programme is investigating BIBF 1120 in combination with standard second-line chemotherapy treatments for patients with advanced NSCLC. Approximately 2,600 patients will be enrolled, making this one of the largest phase III study programmes in this NSCLC patient population to date.

Results from a phase II study suggest that BIBF 1120 monotherapy is well tolerated and may offer promising efficacy in patients with relapsed, advanced NSCLC.⁹

As angiogenesis plays a pivotal role in the growth of all solid tumours, BIBF 1120 is being investigated in a number of indications including advanced NSCLC, RCC, HCC, prostate, ovarian cancer and colorectal cancer. Indeed, new phase II data presented for the first time at ASCO show BIBF 1120 may have a role in delaying disease progression in ovarian cancer patients who had previously responded to chemotherapy. The trial represents the first data in ovarian cancer to show benefit of an angiogenesis inhibitor in direct comparison to placebo. The trial that included patients with advanced disease and dubious prognosis, indicated that progression of the disease occurred markedly later in patients treated with BIBF 1120 compared to placebo.

BIBW 2992 (Tovok™)*

BIBW 2992 (Tovok™) is a novel representative of the new generation of tyrosine kinase inhibitors. It is a potent and irreversible inhibitor of both EGFR and HER2 kinases.

BIBW 2992 is being investigated in various indications, including lung cancer (NSCLC), breast cancer, colorectal cancer, Glioblastoma, and head and neck cancer.

BIBW 2992 has entered phase IIb/III clinical development in NSCLC and has been granted fast-track designation by the US Food and Drug Administration (FDA) which means that data can be submitted to the agency on a rolling basis – an acknowledgement of the compound's clinical potential.

The LUX-Lung phase III trial programme is investigating BIBW 2992 in a number of patient populations. LUX-Lung 1 is a phase IIb/III randomised, double-blind study evaluating BIBW 2992 as monotherapy in NSCLC patients who have previously failed first generation EGFR Tyrosine Kinase Inhibitors (TKIs). Preliminary safety data from LUX-Lung 1 were presented at ASCO.

New data presented at ASCO 2009 from the ongoing phase II clinical study (LUX-Lung 2) showed patients with activating epidermal growth factor receptor (EGFR) mutations experienced a high overall response rate – more than one in two patients (64%; 43/67 patients) had a partial response – and a high rate of disease control (96%; 64/67 patients).

BI 6727*

BI 6727 represents the latest step in Boehringer Ingelheim's cell cycle kinase inhibitor programme to develop the most effective, potential first-in-class specific Plk1 inhibitor. BI 6727 is highly selective and potent, and works by inhibiting the activity of Plk1, a key regulator in the process of cell division (mitosis). Due to much higher levels of Plk1 in tumour cells compared to healthy cells, BI 6727 preferentially targets the dividing cancer cells.

Results to date for BI 6727 have indicated impressive anti-tumour activity, not normally observed in phase I studies of heavily pre-treated, cancer patients with advanced disease.¹⁰ Based on these encouraging results this compound will advance further in clinical development. The phase II programme will assess the efficacy and safety of BI 6727 in several tumour types.

Due to its unique mode of action, typical side effects induced by established anti-mitotic agents such as neuropathy have not occurred.

* BIBF 1120 (Vargatef™), BIBW 2992 (Tovok™) and BI 6727 are investigational compounds. Their safety and efficacy have not yet been fully established

References

1. Folkman J. *N Engl J Med* 1971;285:1182-1186.
2. Folkman J. *J Natl Cancer Inst* 1990;82:4-6.
3. Hanahan D. and Weinberg RA. *Cell* 2000;100:57-70.
4. Normanno N. *et al. Current Drug Targets*, 2005, 6:243-247.
5. Solca F. *Targeted Oncology* 2007;2(1S):15.
6. Eckerdt F. *et al.. Oncogene* 2005;24:267-276.
7. Liu X. and Erikson RL. *Proc Natl Acad Sci USA* 2003;100:5789-5794.
8. Hilberg F. *et al. European Journal of Cancer Supplements*. 2004; 2:50.
9. von Pawel J *et al. J Thorac Oncol*. 2008; 3(Suppl 1): Abstract 1630
10. Schöffski, P *et al. A phase I single dose escalation study of the novel polo-like kinase I inhibitor BI 6727 in patients with advanced solid tumours*. Presented Thursday 23 October 2008 at the 20th EORTC-NCI-AACR. Plenary session 5. Molecular targets-state of the science 10:15-12:00. Abstract Number: 36.