

BOEHRINGER INGELHEIM AND THE SEARCH FOR NEW TARGETED CANCER TREATMENTS

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1. About Boehringer Ingelheim

Founded in 1885, Boehringer Ingelheim is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim am Rhein, Germany, it is a family-owned, globally operating research-driven group of companies committed to the goal of serving mankind through research into diseases and the development of new treatment options of high therapeutic value for human and veterinary medicine.



The Boehringer Ingelheim group, with 138 affiliates in 47 countries across the world and almost 41,300 employees, reported net sales of almost €11.6 billion in 2008, spending over €2 billion on Research and Development, substantially in the area of Prescription Medicines.

Leaders in the areas of respiratory medicine, with its blockbuster Spiriva[®], Boehringer Ingelheim is also making significant contributions to research in cardiovascular medicine, neuroscience and urology, as well as in virology, women's health and immunology.

2. Boehringer Ingelheim's commitment to cancer

Cancer is a major public health problem and despite considerable advances remains an area of significant unmet medical need. As a research-driven pharmaceutical group of companies, 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.

More than 400 employees around the world are dedicated to the discovery and development of new cancer treatments: 200 in Vienna, Austria at the dedicated Boehringer Ingelheim cancer research centre and more than 200 across the globe associated with oncology research and development.

Their efforts, combined with close collaboration with the Research Institute of Molecular Pathology (IMP) in Austria and the expertise of many leading experts in all areas of cancer research and medicine, are focused on developing a broad range of breakthrough products to combat cancer.

Boehringer Ingelheim is committed to the clinical development of pioneering treatments for cancer through an extensive and diverse global study programme involving investigators and patients from around the world. This is supported by a significant financial investment from Boehringer Ingelheim, with the aim of developing treatments that will offer important advances and make a real difference to the lives of patients and their families.

3. Research and development in cancer treatments

Boehringer Ingelheim is using its significant resources to actively develop targeted therapies – biologicals and small molecules – in areas of unmet medical need including both solid and haematological cancers. Using technological advances and breakthrough science, the search for new cancer treatments is currently focused on three areas:

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

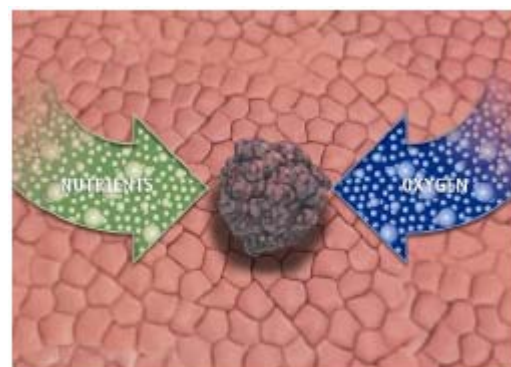
Cutting-edge research conducted at Boehringer Ingelheim's research centre in Vienna and the Institute of Molecular Pathology has resulted in several promising compounds moving into clinical development.



4. Research focus at Boehringer Ingelheim

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, 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.



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. There are many mechanisms involved in this process, which offer several targets for therapeutic intervention.

Boehringer Ingelheim is developing new treatments that target and inhibit the key biological pathways involved in stimulating angiogenesis, thereby preventing growth and spread of the tumour. 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)¹ – all crucially involved in the formation of blood vessels. As these growth factors and receptors play an important role in angiogenesis, inhibition of them may play a critical role in the prevention of tumour growth and spread.

Results from a phase II study suggest that BIBF 1120 (Vargatef™) monotherapy is well tolerated and may offer promising efficacy in patients with relapsed, advanced non-small cell lung cancer (NSCLC).¹

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. Both trials are currently recruiting patients.

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, ovarian cancer, colorectal cancer and prostate 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

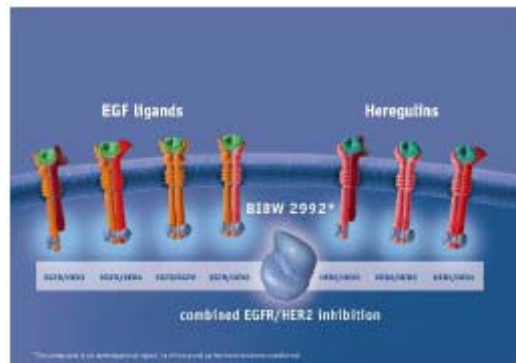
patients with advanced disease and dubious prognosis, indicated that progression of the disease occurred markedly later in patients treated with BIBF 1120 compared to placebo.²

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 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 may be associated with poor prognosis and advanced-stage cancers.³ 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.⁴

BIBW 2992 (Tovok™)*, a compound of Boehringer Ingelheim research, 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 and is being investigated for various indications including lung cancer (NSCLC), breast cancer, colorectal cancer and head and neck cancer.



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) had a partial response – and a high rate of disease control (96%; 64/67).

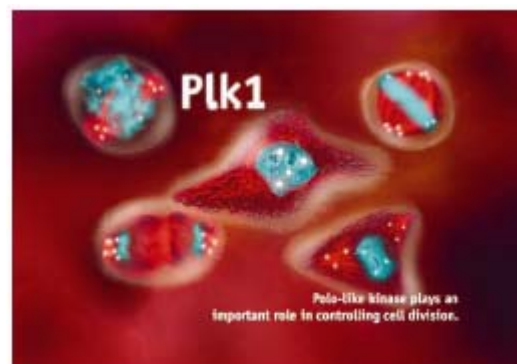
The LUX-Lung phase III trial programme is investigating BIBW 2992 in a number of patient populations. LUX-Lung 1 is a phase IIb/III randomised, double-blind study evaluating BIBW 2992 as monotherapy in NSCLC patients who have previously failed first generation EGFR Tyrosine Kinase Inhibitors (TKIs).⁵ Preliminary safety data from LUX-Lung 1 were presented at ASCO.

BIBW 2992 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.

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.^{6,7} 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.^{7,8}



From its own laboratories, Boehringer Ingelheim has discovered and developed several novel molecules in the field of Plk1 inhibition, being the first company to advance Plk1 inhibitors into clinical development.

BI 6727* represents the latest step in Boehringer Ingelheim's programme to develop the most effective, potential first-in class specific Plk1 inhibitor.

New phase I data for BI 6727 has shown encouraging anti-tumour activity, not necessarily expected in a phase 1 study of heavily pre-treated, cancer patients with advanced disease.⁸ Based on these encouraging results, BI 6727 will advance further in clinical development. The phase II programme will assess the efficacy and safety of BI 6727 in several tumour types.

BI 6727 inhibits a key regulator in the process of cell division (mitosis), called Plk1. 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 with BI 6727 indicate the compound to be well tolerated and no serious side effects have been detected.⁹

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

References

1. von Pawel J. *et al.* *J Thorac Oncol.* 2008; 3(Suppl 1): Abstract 163O.
2. Ledermann, J. A. "A randomised Phase II placebo-controlled trial using maintenance therapy to evaluate the vascular targeting agent BIBF 1120 following treatment of relapsed ovarian cancer (OC)." Oral presentation, Clinical Science Symposium. Monday, 1 June 2009, Session Time 9:45AM - 11:15AM. # 5501
3. Normanno N. *et al.* *Current Drug Targets.* 2005;6: 243-247.
4. Solca F. *Targeted Oncology* 2007;2(1S):15.
5. Shih J-Y *et al.* "A Phase II study of BIBW 2992, a novel irreversible dual EGFR and HER2 tyrosine kinase inhibitor (TKI), in patients with adenocarcinoma of the lung and activating EGFR mutations after failure of 1 line of chemotherapy (LUX-Lung 2)." Poster Discussion Presentation. 1 June 2009, Session Time: 8:00AM - 12:00PM. #8013
6. Eckerdt F. *et al.* *Oncogene.* 2005;24:267-276.
7. Strebhardt K, and Ullrich A. *Nature.* April 2006, 6:322-330.
8. Liu X. and Erikson RL. *Proc Natl Acad Sci. USA* 2003;100:5789-5794.
9. 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.