

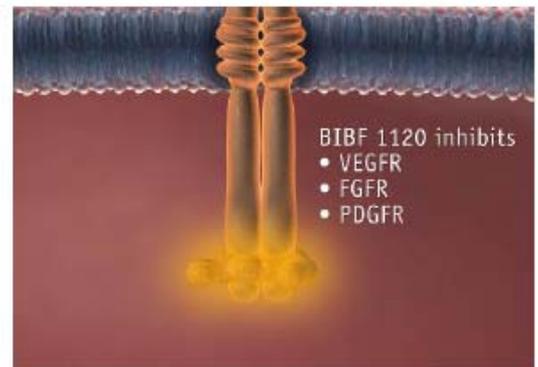
BIBF 1120 (VARGATEF™)

1. Overview
2. Mechanism of action
3. Development status
4. Data overview
5. Clinical potential

1. Overview

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 three growth factors are crucially involved in the formation of blood vessels (angiogenesis) and inhibition of them may play a critical role in the prevention of tumour growth and spread.

BIBF 1120 (Vargatef™) is currently being investigated in a number of indications including advanced non-small cell lung cancer (NSCLC), prostate cancer, ovarian cancer and colorectal cancer.



2. Mechanism of action

Angiogenesis 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 solid cancer, in which the new blood vessels feed diseased tissues with oxygen and nutrients, encouraging tumour growth and spread (metastases).

The process of tumour angiogenesis starts with cancerous tumour cells releasing molecules that send 'signals' to surrounding normal healthy tissue. Angiogenesis inhibitors, such as BIBF 1120 (Vargatef™), interfere with steps in the angiogenesis signalling cascade therefore preventing growth and spread of the tumour. BIBF 1120 (Vargatef™) targets three receptor classes involved in angiogenesis:

- VEGFR – Vascular Endothelial Growth Factor Receptors. For instance VEGFR 2 regulates the proliferation and migration of cells that create blood vessels
- PDGFR – Platelet Derived Growth Factor Receptors control the migration and adherence of cells that provide support and stability to vessel walls
- FGFR – Fibroblast Growth Factor Receptors also control the migration and adherence of cells that provide support and stability to vessel walls



*BIBF 1120 (Vargatef™) is an investigational compound. Its safety and efficacy have not yet been fully established.

BIBF 1120 (Vargatef™)'s inhibition of VEGFR and FGFR is thought to have an impact on the formation of new tumour blood vessels and its inhibition of FGFR and PDGFR may have an effect on the maintenance of the vascular integrity.

3. Development status

The first phase III clinical trial programme has commenced for BIBF 1120 (Vargatef™) with the introduction of the LUME-Lung 1 and LUME-Lung 2 trials. They will assess BIBF 1120 (Vargatef™) in combination with standard chemotherapy agents docetaxel and pemetrexed in patients with advanced NSCLC. The decision to progress BIBF 1120 (Vargatef™) into phase III / late stage development was based on encouraging phase II results.

4. Data overview

Efficacy and Safety

In studies to date, BIBF 1120 (Vargatef™) has shown the following signs of efficacy and activity:

- In all pre-clinical models tested to date BIBF 1120 (Vargatef™) has shown significant tumour growth inhibition either as monotherapy or in combination with different standard chemotherapies such as pemetrexed or docetaxel.¹
- In vitro studies have found that BIBF 1120 (Vargatef™) is a potent inhibitor of tumour cell proliferation and in vivo research found BIBF 1120 (Vargatef™) reduced tumour blood flow and vessel density.¹
- Results from a phase II study of 73 patients with locally advanced or metastatic NSCLC suggest that BIBF 1120 (Vargatef™) mono-therapy is well tolerated and may offer promising efficacy in this patient population.² Of particular note were results from a subset of 57 patients with 'good disease state' (ECOG+ performance status of 0 or 1): these patients experienced longer overall survival (median overall survival was 9.5 months), longer progression-free survival (PFS; median PFS was 2.9 months) and a higher stable disease rate of 59% compared with the overall study population.
- In phase I studies, BIBF 1120 (Vargatef™) was observed to be well tolerated at a dose of 200mg twice daily when given in combination with pemetrexed³ or paclitaxel/carboplatin⁴ in NSCLC patients and when given in combination with docetaxel in hormone refractory prostate cancer patients. In addition, initial signs of clinical efficacy were observed.³⁻⁵
- New phase II data presented for the first time at ASCO 2009 show BIBF 1120 may have a role in delaying disease progression in ovarian cancer patients who has 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.⁶
- BIBF 1120 (Vargatef™) has demonstrated superior activity to vatalanib and bevacizumab in a colon carcinoma model (HT-29) and similar activity to sunitinib in a head and neck carcinoma model (FaDu).⁷

Tolerability

Studies so far have indicated that BIBF 1120 (Vargatef™) administered orally twice daily, is generally well tolerated by patients. Adverse events including nausea, vomiting and diarrhoea were mostly mild to moderate.² Importantly, unlike some angiogenesis inhibitors, hand/foot syndrome and haematological toxicity were not evident^{2,8} and raised liver enzymes were reversible.^{2,8}

+ ECOG Definition: The Eastern Cooperative Oncology Group performance status are scales and criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living activities of the patient, and determine appropriate treatment and prognosis.

5. Clinical potential

Because BIBF 1120 (Vargatef™) potently inhibits VEGFR, PDGFR and FGFR, it has the potential to be effective where agents inhibiting only VEGFR are no longer effective.

As a triple angiokinase inhibitor simultaneously acting on VEGFR, PDGFR and FGFR, BIBF 1120 (Vargatef™) has the potential to offer important clinical benefits across a broad range of indications. In addition, this molecule showed a favourable safety profile based on more than 500 cancer patients treated thus far. It is hoped that the extensive ongoing phase II development programme investigating BIBF 1120 (Vargatef™) in various indications and the recently commenced phase III clinical programme on NSCLC, will confirm the positive early results already reported.

References

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