

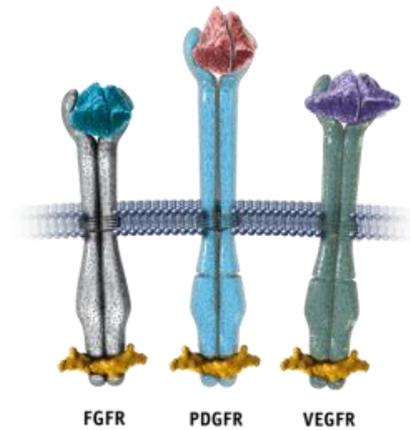
VARGATEF[®] (NINTEDANIB*)

BACKGROUND

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1. WHAT IS VARGATEF[®] (NINTEDANIB*)

Nintedanib* is a triple angiokinase inhibitor which targets the three key receptors involved in angiogenesis and tumour growth. In oncology, nintedanib* is approved in the European Union (EU) for use in combination with docetaxel in adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

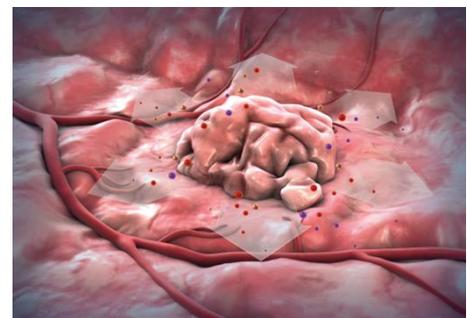


Nintedanib* is an oral agent that simultaneously inhibits vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR) and fibroblast growth factor receptors (FGFR).¹

Growing scientific evidence shows that these three receptors play an important role in the formation and maintenance of new blood vessels (angiogenesis); their blockade may lead to the inhibition of angiogenesis, which promotes tumour growth.^{2,3,4}

2. HOW DOES VARGATEF[®] (NINTEDANIB*) WORK?

Angiogenesis is an essential process for normal growth and development occurring in the body.² It is necessary for important functions such as embryonic development, wound healing and restoring blood flow to damaged tissues.³ However, it is also vital for tumours to grow and spread to other organs.³ Growth of a tumour beyond a certain size requires the development of new capillary blood vessels, which supply the tumour with oxygen and nutrients, encouraging growth.⁵



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Angiogenesis is controlled by growth factors. To continue growth, cancerous tumour cells release growth factors which bind to and activate growth factor receptor tyrosine kinases. These receptors cause a cascade of signalling. Angiokinase inhibitors, such as nintedanib* interfere with steps in the angiogenesis signalling pathway with the aim of impacting tumour growth and spread.^{2,3,4}

Nintedanib* uses an anti-angiogenic strategy that is different from other approved treatments that target angiogenesis.⁶ Nintedanib* is a small molecule that targets three receptors known to be involved in angiogenesis and tumour growth:⁶

- VEGF binds to and activates the VEGFR, stimulating endothelial cells to grow, divide, resist apoptosis and migrate.⁷
- PDGF binds to and activates the PDGFR, controlling the migration and adherence of cells and providing support and stability to vessel walls.⁸
- FGF binds to and activates the FGFR, leading to signalling which also promotes the migration and adherence of cells and thus plays a role in the development and stabilisation of new blood vessels.⁹

Inhibiting VEGFR and FGFR is thought to have an impact on the formation of new blood vessels within tumours. Also, inhibition of FGFR and PDGFR may hinder vessel maturation and maintenance, the consequence of which may be an impact on tumour growth.^{10,11}

3. DATA OVERVIEW

LUME-Lung 1 Trial

LUME-Lung 1 was a randomised, double-blind, Phase III study comparing nintedanib* plus docetaxel in patients with locally advanced/metastatic NSCLC after first-line therapy, with placebo plus docetaxel.¹ The study included 1,314 patients, in Europe, Asia and South Africa, randomised to receive nintedanib* 200mg twice daily plus docetaxel 75mg/m² once a day, for 3 weeks (n=655) or placebo plus docetaxel (n=659).¹

The trial met its primary endpoint by nintedanib* plus docetaxel significantly prolonging progression free survival (PFS: length of time before the tumour starts to progress) from 2.7 to 3.4 months compared to docetaxel alone for all NSCLC patients, regardless of histology (p=0.0019; HR:0.79).¹ Overall survival was the key secondary endpoint.¹

Results from this trial were published in the *Lancet Oncology* in 2014.¹

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Efficacy and Safety Profile

The LUME-Lung 1 Phase III clinical trial results showed that nintedanib* when added to docetaxel demonstrated over one year (12.6 months) median overall survival for patients with advanced adenocarcinoma, after first-line chemotherapy compared to 10.3 months for patients receiving placebo plus docetaxel.¹

Key results from LUME-Lung 1 trial:

- The trial met the primary endpoint by nintedanib* plus docetaxel significantly prolonging progression free survival (PFS: length of time before the tumour starts to progress) from 2.7 to 3.4 months compared to docetaxel alone for all NSCLC patients, regardless of histology (p=0.0019; HR:0.79).¹
- Nintedanib* plus docetaxel extended median overall survival (secondary endpoint) from 10.3 to 12.6 months, compared to docetaxel alone (p=0.0359; HR:0.83, CI 0.70-0.99) for patients with advanced adenocarcinoma after first-line chemotherapy.¹
- Nintedanib*, when added to docetaxel, enabled 1 in 4 patients with advanced adenocarcinoma to live for 2 years or more, after first-line chemotherapy, compared to docetaxel alone (patient survival at 24 months – nintedanib* + docetaxel 25.7% vs. placebo + docetaxel 19.7%).¹

In addition, the data demonstrated that nintedanib* provided a greater survival benefit to lung cancer patients with advanced adenocarcinoma the earlier their first-line chemotherapy stopped working.¹

- Nintedanib*, when added to docetaxel, extended median overall survival from 7.9 months to 10.9 months compared to docetaxel alone (p=0.0073; HR:0.75, CI 0.60-0.92) for patients with advanced adenocarcinoma who experienced disease progression within 9 months of starting first-line chemotherapy (T<9 months).¹
- Aggressive adenocarcinoma of the lung, where patients progress within 9 months of starting first-line chemotherapy, is typically very difficult to manage and affected over 60% of all adenocarcinoma patients in this study.¹

LUME-Lung 2 Trial

The LUME-Lung 2 trial investigated the efficacy and safety of nintedanib* plus standard pemetrexed therapy, versus placebo plus pemetrexed in patients with advanced or recurrent non-squamous NSCLC who had previously received first-line chemotherapy.¹²

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The trial did not pass the pre-defined interim analysis from external independent experts and was prematurely halted due to an investigator-assessed PFS analysis, but at the same time there were no safety concerns. However, the final results showed a significant improvement of the primary endpoint, centrally assessed PFS.¹³

Based on the data from LUME-Lung 2, T<9 months was identified as a potential predictive clinical biomarker for benefiting from second-line nintedanib* plus chemotherapy which was later confirmed in LUME-Lung 1.^{1,14}

Tolerability

In the LUME-Lung 1 trial, nintedanib* showed a manageable side-effect profile without further compromising patients' overall health-related quality of life. Adding nintedanib* to docetaxel did not significantly increase discontinuation rates, compared to docetaxel alone.¹

In addition, the most common side-effects for patients taking nintedanib* plus docetaxel included gastrointestinal side-effects and reversible liver enzyme elevations which were manageable with either supportive treatment and/or dose reduction.¹

4. CLINICAL POTENTIAL

As an angiokinase inhibitor simultaneously acting on three relevant receptors for angiogenesis; VEGFR, PDGFR and FGFR, nintedanib* may have the potential to offer important clinical benefits across a broad range of cancers.

Nintedanib* is currently being investigated in patients with various solid tumours including Phase III studies in advanced NSCLC¹, advanced colorectal cancer¹⁵ and ovarian cancer¹⁶ and also in Phase II studies in mesothelioma¹⁷, kidney cancer (renal cell carcinoma)¹⁸ and liver cancer (hepatic cell carcinoma).¹⁹

It is hoped that the extensive ongoing Phase II development programme in various indications and the Phase III clinical programmes in NSCLC, colorectal and ovarian cancer, will provide more clinical data to further establish the efficacy and safety of nintedanib* demonstrated in earlier studies.

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5. VARGATEF[®] (NINTEDANIB*) APPROVAL STATUS

In November 2014 the European Commission granted marketing authorisation for nintedanib* for use in combination with docetaxel in adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology, after first-line chemotherapy.

Nintedanib* will be marketed in oncology within the EU under the brand name Vargatef[®] and is under regulatory review by health authorities in other countries outside the EU. The European Commission (EC) and the U.S. Food and Drug Administration (FDA) have approved nintedanib* capsules under the brand name OFEV[®] for oral use for the treatment of IPF.

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