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# Nintedanib in Oncology Backgrounder


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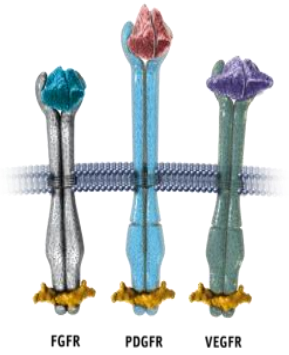
## 1. WHAT IS NINTEDANIB*?

Nintedanib (Vargatef®) 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) and 20 other countries** 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.

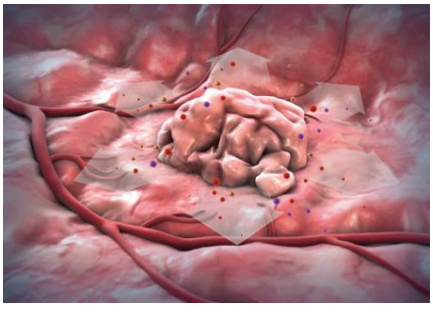



Nintedanib* is an oral agent that simultaneously inhibits vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and ß) and fibroblast growth factor receptors (FGFR 1-3).[1]

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 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]



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 docetaxel 75 mg/m² by intravenous infusion on day 1 plus either nintedanib 200 mg orally twice daily or matching placebo on days 2–21, every 3 weeks until unacceptable adverse events or disease progression.[1]
The primary endpoint was progression free survival, while overall survival was the key secondary endpoint.[1]

Results from this trial were published in the Lancet Oncology in 2014.[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]

The trial did not pass the pre-planned futility analysis of investigator-assessed PFS conducted by an independent data monitoring committee and was prematurely halted, 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. ADDITIONAL CLINICAL DATA

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 mesothelioma and ovarian cancer[15] and also among others in Phase II trials in, kidney cancer (renal cell carcinoma)[16] and liver cancer (hepatic cell carcinoma).[17]

**Malignant Pleural Mesothelioma[18]**

Updated results from the LUME-Meso phase II pivotal trial investigating the efficacy and safety of nintedanib + pemetrexed/cisplatin versus placebo + pemetrexed/cisplatin for the treatment of patients with advanced malignant pleural mesothelioma (MPM) was presented at 2017 American Society of Clinical Oncology (ASCO) in Chicago. The results show:

- Nintedanib*, when added to standard chemotherapy demonstrated a clinically meaningful 46% reduction in the risk of disease progression in patients with unresectable malignant pleural mesothelioma, compared to standard chemotherapy alone
    - A significantly improved median PFS of 3.7 months (9.4 vs 5.7 months) in the overall study population (patients with either an epithelioid or biphasic cell type) compared to placebo plus standard chemotherapy alone
- A trend for improved overall survival with the addition of nintedanib to standard chemotherapy
- In patients with an epithelioid cell type, nintedanib plus chemotherapy demonstrated a greater median progression-free survival with a 51% reduction in the risk of disease, compared to standard chemotherapy alone
    - In patients with an epithelioid cell type, nintedanib plus chemotherapy demonstrated a greater median PFS benefit of 4 months (9.7 vs. 5.7 months) compared to placebo plus standard chemotherapy alone

## 5. 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.

Nintedanib is also approved in the US, EU, Japan and other territories for the treatment of idiopathic pulmonary fibrosis (IPF) under the brand name OFEV® (150mg twice daily). Along with this, the EC and US Food and Drug Administration (FDA) have granted Orphan Drug Designation to nintedanib (150mg twice daily) for the treatment of systemic sclerosis (SSc, also known as scleroderma), including the associated interstitial lung disease (SSc-ILD).

* *Nintedanib is approved in the EU under the brand name VARGATEF® for use in combination with docetaxel in adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy. Nintedanib is under regulatory review by health authorities in other countries outside the EU. Nintedanib is not approved in other oncology indications.*

*** Other countries where Vargatef® is approved for NSCLC 2nd line are: Australia, New Zealand, Kuwait, Lebanon, Israel, Kazakhstan, Russia, Serbia, Argentina, Chile, Ecuador, Mexico, Paraguay, Peru, Uruguay, India, Macao, Philippines, Singapore and Thailand*

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