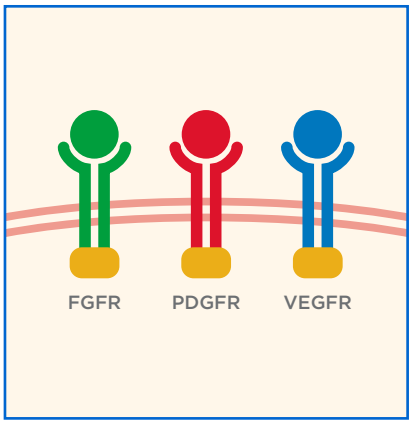
NINTEDANIB* IN ONCOLOGY BACKGROUNDER

1. WHAT IS NINTEDANIB?

Nintedanib is a triple angiokinase inhibitor which targets the three key receptors involved in angiogenesis and tumor growth.[1,2] In oncology, nintedanib is approved in the European Union (EU)[1] and several other countries worldwide for use in combination with docetaxel in adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumor histology after first-line chemotherapy.

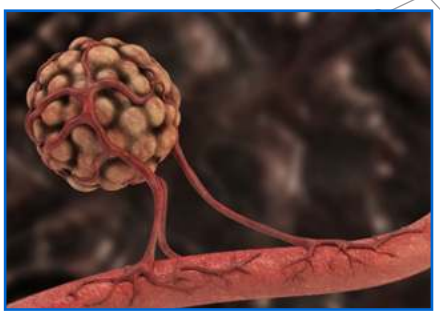


Nintedanib is an oral agent that simultaneously inhibits vascular endothelial growth factor receptors (VEGFR) 1–3, platelet-derived growth factor receptors (PDGFR) α and ß and fibroblast growth factor receptors (FGFR) 1–3.[1,2]

Preclinical evidence shows that these three receptors play an important role in the formation and maintenance of new blood vessels (angiogenesis). Blocking these receptors can limit tumor growth through the inhibition of angiogenesis.[3–6]

**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 tumor histology after first-line chemotherapy. Nintedanib is not approved in other oncology indications.*
This information is from an international website which is intended for healthcare professionals located outside the United States of America (USA) and the United Kingdom (UK).
Nintedanib is subject to country-specific regulations, and the approved product label may vary from country to country. Information on this website is derived from the approved European Summary of Product Characteristics. Please refer to your local product label for full details. For the full list of country-specific information, please visit https://www.vargatef.com/countries

2. HOW DOES NINTEDANIB WORK?



Angiogenesis is an essential process for normal growth and development occurring in the body.[3] It is necessary for important functions such as embryonic development, wound healing and restoring blood flow to damaged tissues.[4] However, it is also vital for tumors to grow and spread to other organs.[4] Growth of a tumor beyond a certain size requires the development of new capillary blood vessels, which supply the tumor with oxygen and nutrients, encouraging growth.[4,5,7]

Angiogenesis is controlled by growth factors. To continue growth, cancerous tumor cells release growth factors which bind to and activate growth factor receptor tyrosine kinases. These receptors cause a cascade of signaling.[3–5] Angiokinase inhibitors (such as nintedanib) interfere with steps in the angiogenesis signaling pathway with the aim of impacting tumor growth and spread.[1]

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 tumor growth:[6]

- VEGF binds to and activates the VEGFR, stimulating endothelial cells to grow, divide, resist apoptosis and migrate[8]
- PDGF binds to and activates the PDGFR, controlling the migration and adherence of cells and providing support and stability to vessel walls[9]
- FGF binds to and activates the FGFR, leading to signaling, which also promotes the migration and adherence of cells and, thus, plays a role in the development and stabilization of new blood vessels[10]

Inhibiting VEGFR and FGFR is thought to have an impact on the formation of new blood vessels within tumors.[11] Also, inhibition of FGFR and PDGFR may hinder vessel maturation and maintenance, the consequence of which may be an impact on tumor growth.[11,12]

Date: September 2020

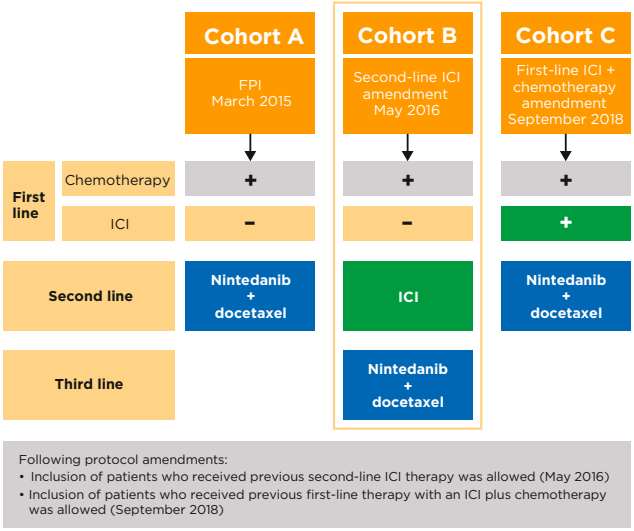
3. DATA OVERVIEW

VARGADO study

VARGADO is an ongoing, observational, prospective, non-interventional, multicenter study of nintedanib plus docetaxel after first-line chemotherapy in the routine clinical treatment of patients with locally advanced, metastatic or locally recurrent adenocarcinoma NSCLC.[13]

Three patient cohorts in VARGADO are being evaluated (Figure 1). The most recent interim analysis results from Cohort B (first-line chemotherapy followed by a second-line immune checkpoint inhibitor [ICI], N=65) were shared at ESMO 2020.[14]

Figure 1. Patient cohorts in VARGADO[13,14]



FPI: First patient in; ICI: Immune checkpoint inhibitor.

Patients received docetaxel (75 mg/m^2) by intravenous infusion on Day 1, plus oral nintedanib (200 mg twice daily) on Days 2–21 of each 21-day cycle.[13] Patients were followed up for safety and efficacy during routine clinic visits for up to 24 months after the start of treatment.[13]

The primary endpoint is overall survival (OS) rate 1 year after the start of treatment, while progression free survival (PFS), OS, objective response rate, disease control rate and safety are all secondary endpoints.[13]

Key results from VARGADO Cohort B interim analysis:[14]

- At the time of this interim analysis (data cut-off: April 1, 2020), median duration of follow-up was 7.0 months for patients treated with nintedanib plus docetaxel
- Median PFS was 6.5 months (95% CI: 4.8–7.3; n=55) among patients treated with third-line nintedanib plus docetaxel after failure of second-line ICI therapy
- Median OS from the start of first-line therapy was 34.5 months (95% CI: 25.5–37.5; n=61)
- Median OS from the start of third-line therapy was 12.2 months (95% CI: 11.4–14.1; n=62)
- In 52 evaluable patients, the objective response rate was 26/52 (50%), while the disease control rate was 43/52 (83%)
- No new safety signals were identified among the 65 patients treated with nintedanib plus docetaxel

This updated analysis of the VARGADO study continues to support the encouraging clinical benefit and manageable safety profile of nintedanib plus docetaxel in patients who progressed on previous chemotherapy and ICI therapy.[14] The clinical benefit was consistent across multiple outcomes: PFS, OS, response rate and disease control rate.

Rational sequencing of an anti-angiogenic agent after ICI therapy may be a promising treatment approach in this patient population that warrants further investigation.[14]

For more information on the VARGADO study, please visit:
https://www.inoncology.com/marketedproducts/nintedanib/nsclc/post-ici-therapy

LUME-Lung 1 Trial

LUME-Lung 1 was a randomized, double-blind, Phase III study comparing nintedanib plus docetaxel in patients with locally advanced/metastatic NSCLC after first-line therapy, with placebo plus docetaxel.[2] The study included 1,314 patients in Europe, Asia and South Africa, randomized to receive docetaxel 75 mg/m^2 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.[2] The primary endpoint was PFS, with OS as the key secondary endpoint.[2]

Results from this trial were published in The Lancet Oncology in 2014.[2]

Key results from LUME-Lung 1 trial:[2]

- The trial met the primary endpoint of nintedanib plus docetaxel significantly prolonging PFS from 2.7 to 3.4 months compared with docetaxel alone for all patients with NSCLC, regardless of histology (p=0.0019; HR=0.79)
- Nintedanib plus docetaxel extended median OS (secondary endpoint) from 10.3 to 12.6 months compared with docetaxel alone (p=0.0359; HR=0.83, CI: 0.70–0.99) for patients with advanced adenocarcinoma after first-line chemotherapy
- 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 with docetaxel alone (patient survival at 24 months was 25.7% for nintedanib + docetaxel vs 19.7% for placebo + docetaxel)

Additionally, 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:[2]

- Nintedanib plus docetaxel extended median OS from 7.9 months to 10.9 months compared with 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)
  - 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
  - A 4.7-month improvement in median OS was retrospectively observed in the European adenocarcinoma population treated with nintedanib plus docetaxel compared with placebo plus docetaxel (13.4 vs 8.7 months) (HR=0.79, 95% CI: 0.65–0.97)**[15]

For more information on the LUME-Lung 1 trial, please visit:
https://www.inoncology.com/marketedproducts/nintedanib/nsclc/LUME-Lung-1

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 with docetaxel alone.[2]

Additionally, 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.[2]

***These results are from a retrospective additional exploratory analysis of the LUME-Lung 1 study.[15]*
This information is from an international website which is intended for healthcare professionals not located in the United States of America (USA) and the United Kingdom (UK).

Date: September 2020

4. NINTEDANIB APPROVAL STATUS

Nintedanib is approved in the oncology indication[1] and marketed within the EU and several countries worldwide under the brand name VARGATEF® and is under regulatory review by health authorities in some other countries. Different brand names may be used in countries outside the EU.

The ESMO guidelines for the treatment of NSCLC recommend nintedanib in combination with chemotherapy as a second-line treatment following prior chemotherapy +/- ICIs.[16]

Nintedanib is also approved in over 80 countries for the treatment of idiopathic pulmonary fibrosis under the brand name OFEV® (150 mg twice daily).[17] Nintedanib has also been approved in the US (September 2019), Japan (December 2019) and the EU (April 2020) to treat patients with systemic sclerosis-associated interstitial lung disease.[17] Nintedanib has been granted Breakthrough Therapy Designation by the FDA and received subsequent approval for the treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype in the US (March 2020), Japan (May 2020) and the EU (July 2020).[17] Nintedanib in respiratory indications is under regulatory review in further countries worldwide.

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For further information, please visit:
https://www.ema.europa.eu/documents/product-information/vargatef-epar-product-information_en.pdf

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