NINTEDANIB*

BACKGROUND

1. What is nintedanib?
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1. WHAT IS NINTEDANIB?

Nintedanib is an angiokinase inhibitor targeting three key growth factor receptor classes crucially involved in angiogenesis regulation and tumour growth; vascular endothelial growth factor receptors (VEGFR) 1–3, platelet-derived growth factor receptors (PDGFR) α and β and fibroblast growth factor receptors (FGFR) 1–3.\(^1,2\) Blockade of these three classes of receptor leads to the inhibition of angiogenesis, which plays a critical role in tumour growth and spread.\(^3–5\)

Nintedanib, in combination with docetaxel, is approved in the European Union (EU) for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.\(^1\) Nintedanib is also approved in several other countries worldwide and is under regulatory review by health authorities in other countries outside the EU.

Nintedanib is also currently in Phase III development in mesothelioma.\(^6,7\)

2. HOW DOES NINTEDANIB WORK?

Angiogenesis is an essential process for normal growth and development of cells during embryonic development, wound healing and restoring blood flow to damaged tissues. It also plays a key role in tumour development, as the growth of a tumour beyond a certain size requires the development of new blood vessels to supply oxygen and nutrients, facilitating expansion and metastasis.\(^8\)

Angiogenesis is a highly regulated process controlled by growth factors that bind to and activate growth factor receptor tyrosine kinases to drive downstream signalling.\(^9\) During cancer progression, growth factors can be secreted from cancerous cells to stimulate angiogenesis.\(^9\) Angiokinase inhibitors block steps of this angiogenesis signalling cascade, affecting tumour growth and spread.\(^9,10\)

Inhibitors that are able to bind to multiple receptors are effective in angiogenesis inhibition, and may potentially avoid tumour escape mechanisms that can occur with single VEGF/VEGFR blockade.\(^11\)

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\(^*\)Nintedanib is approved in the EU under the brand name VARGATEF\(^5\) 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 not approved in other oncology indications.

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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.

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Nintedanib targets three growth factor receptor families that are crucially involved in angiogenesis:\textsuperscript{1,11,12}

- VEGF binds to and activates VEGFR, stimulating endothelial cells to grow, divide, resist apoptosis and migrate\textsuperscript{13}
- PDGF binds to and activates PDGFR, controlling the migration and adherence of cells and providing support and stability to vessel walls\textsuperscript{14}
- FGF binds to and activates FGFR, leading to signalling that also promotes the migration and adherence of cells and thus plays a role in the development and stabilisation of new blood vessels\textsuperscript{15}

Inhibition of VEGFR and FGFR affects the formation of new tumour blood vessels, while inhibition of FGFR and PDGFR hinders vessel maturation and maintenance of the vascular integrity, impacting on tumour growth.\textsuperscript{14,15,16} Additionally, some tumours harbour an over-amplification of the FGFR or PDGFR genes and inhibition of these pathways may provide an additional, direct antitumour effect.\textsuperscript{15}

Figure 1. Triple angiokinase inhibition and target cells of nintedanib.\textsuperscript{12}

PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor

3. DATA OVERVIEW: THE LUME-LUNG CLINICAL TRIAL PROGRAMME

Efficacy and safety

Results from the LUME-Lung 1 Phase III clinical trial showed that nintedanib was the first lung cancer treatment, following first-line chemotherapy, to convey an extension of overall survival (OS) beyond 1 year in patients with adenocarcinoma.\textsuperscript{2} A further increased relative survival benefit was observed in

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patients with an aggressive course of disease: a median OS improvement of 3.0 months was seen in a prespecified group of patients who progressed within 9 months after starting first-line therapy (10.9 vs 7.9 months).\(^1\,^2\) A median OS improvement of 3.5 months was observed following retrospective analysis of the subgroup refractory to first-line therapy (progressive disease as best response; 9.8 vs 6.3 months).\(^{17}\)

<table>
<thead>
<tr>
<th>LUME-Lung 1(^1,^{2},^{17})</th>
<th>(nintedanib + docetaxel vs placebo + docetaxel)</th>
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<tbody>
<tr>
<td><strong>PFS in all histologies</strong></td>
<td>(primary endpoint)</td>
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<td>• 3.4 vs 2.7 months (HR 0.79 [95% CI 0.68–0.92], p=0.0019)</td>
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<tr>
<td><strong>OS in adenocarcinoma patients</strong></td>
<td>(secondary endpoint)</td>
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<td>• Median OS 12.6 vs 10.3 months (HR 0.83 [95% CI 0.70–0.99], p=0.0359)</td>
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<td>• The 1-year OS was 52.7% vs 44.7%; 2-year OS was 25.7% vs 19.1%</td>
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<tr>
<td><strong>OS in adenocarcinoma patients who progressed within 9 months after starting first-line therapy</strong></td>
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<tr>
<td>• Median OS 10.9 vs 7.9 months (HR 0.75 [95% CI: 0.60–0.92], p=0.0073)</td>
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<tr>
<td><strong>OS in adenocarcinoma patients refractory to first-line therapy</strong>(^**)</td>
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<td>• Median OS 9.8 months vs 6.3 months (HR 0.62 [95% CI: 0.41–0.94], p=0.0246)</td>
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<tr>
<td><strong>OS in European adenocarcinoma patients</strong>(^**)</td>
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<tr>
<td>• Median OS 13.4 months vs 8.7 months (HR 0.79 [95% CI: 0.65–0.97], p=0.0254)</td>
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<td><strong>AEs</strong></td>
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<td>• AEs were more frequent in the nintedanib + docetaxel than in placebo+ docetaxel groups. Grade ≥3 AEs were diarrhoea (6.6% vs 2.6%), reversible increases in alanine aminotransferase (7.8% vs 0.9%), and reversible increases in aspartate aminotransferase (3.4% vs 0.5%)</td>
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<td>• Most AEs were manageable with supportive treatment or dose reduction</td>
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</tbody>
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AE, adverse event; PFS, progression free survival; OS, overall survival. **Retrospective analysis

The LUME-Lung 2 trial evaluated nintedanib in combination with pemetrexed in patients with advanced NSCLC after initial chemotherapy had failed.\(^{18}\,^{19}\) The study was stopped prematurely, based on the results of the preplanned futility analysis, which was performed using the investigator-assessed PFS and was carried out by the Data Monitoring Committee.\(^{20}\) Despite having been stopped early, LUME-Lung 2 met its primary endpoint: addition of nintedanib to pemetrexed significantly increased PFS compared with placebo (median PFS: 4.4 vs 3.6 months, respectively; HR: 0.83 [95% CI: 0.70–0.99]; p=0.0435).\(^{18}\) Retrospective evaluation indicated that the outcome of the futility analysis may have been different if it had been performed at another timepoint or used centrally reviewed PFS data.\(^{20}\)

**Tolerability**

In LUME-Lung 1, nintedanib administered orally twice daily was generally well tolerated. Grade 3 or worse adverse events (AE) that were more common in the docetaxel plus nintedanib group than in the docetaxel plus placebo group were diarrhoea (6.6% vs 2.6%), reversible increases in alanine aminotransferase (7.8% vs 0.9%), and reversible increases in aspartate aminotransferase (3.4% vs 0.5%). Most AEs were manageable with supportive treatment or dose reduction. Discontinuation rates

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were comparable between the nintedanib plus docetaxel and placebo plus docetaxel treatment groups (22.7% [148 of 652] vs 21.7% [142 of 655], respectively).²

The safety profile observed in earlier studies was confirmed in LUME-Lung 1. The side effects considered to be antiangiogenic class side effects such as thromboembolic events and bleeding were comparable between the treatment arms. Only a slightly increased frequency of Grade 1/2, but not Grade ≥3, hypertension was observed. Mucositis and hand–foot syndrome was not experienced by any of the study participants.²

More information on the dosing of nintedanib can be found here and also in the Summary of Product Characteristics.¹
REFERENCES


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Abbreviated EU SmPC:

For further information, please click on the following link: http://www.inoncology.com/connect/smpcs