Nintedanib + docetaxel after immunotherapy in adenocarcinoma non-small cell lung cancer: first results from the non-interventional LUME-BioNIS study

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INTRODUCTION

- Nintedanib is an oral, triple angiokinase inhibitor of vascular endothelial growth factor receptors 1–3, platelet-derived growth factor receptors α/β and fibroblast growth factor receptors 1–3, as well as the oncogenic kinases FLT-3 and RET\(^1,2\)

- In the randomised Phase III LUME-Lung 1 trial, nintedanib + docetaxel significantly increased progression-free survival (PFS) compared with placebo + docetaxel in patients with non-small cell lung cancer (NSCLC) that had progressed on one previous line of chemotherapy.\(^3\) Significant overall survival (OS) benefit was demonstrated in patients with tumours of adenocarcinoma histology\(^3\)

- These data have led to the approval of nintedanib in 63 countries worldwide for use with docetaxel to treat locally advanced, metastatic or locally recurrent adenocarcinoma NSCLC after first-line chemotherapy\(^1\)

- Since the approval of nintedanib, options for treatment of advanced NSCLC have expanded to include several immunotherapies, which activate antitumour immunity by blocking inhibitory immune checkpoint proteins.\(^4,5\) Nivolumab, pembrolizumab and atezolizumab have indications for use after chemotherapy, whereas pembrolizumab and atezolizumab are also approved for use in combination with first-line chemotherapy regimens\(^6–8\)
INTRODUCTION (CONT’D)

- Currently, limited data are available regarding the effectiveness and safety of nintedanib + docetaxel after immunotherapy treatment. In the non-interventional VARGADO study, 32 patients treated with third-line nintedanib + docetaxel after first-line chemotherapy and second-line immunotherapy achieved a median PFS of 7.1 months and disease control rate (DCR) of 79.2%. Updated results from this cohort will be presented at this meeting (Poster 66P)

- LUME-BioNIS is a non-interventional study of nintedanib + docetaxel after first-line chemotherapy for adenocarcinoma NSCLC
  - Although the study was not originally planned to include an immunotherapy-pretreated subgroup, such patients were eligible and were enrolled as a result of changes in the treatment landscape since study inception
  - Here, we present initial results from the subgroup of patients who had previously received both chemotherapy and immunotherapy treatment
METHODS

Study design

- LUME-BioNIS (NCT02671422) is a prospective, European, multicentre, non-interventional study of patients with advanced adenocarcinoma NSCLC who initiated nintedanib + docetaxel in routine practice according to the approved Vargatef® (nintedanib) EU label (Figure 1)\textsuperscript{12}

- The primary objective is to explore whether genomic or protein-based molecular biomarkers, alone or combined with clinical covariates, could predict OS. These analyses are ongoing and will be reported elsewhere

- Clinical data, including dates of progression and death, are prospectively collected during follow-up via an electronic case report form

- The primary endpoint is OS. Further endpoints include PFS, response rates and safety

- Clinical outcomes were analysed in the subgroup of patients whose treatment history included immunotherapy prior to enrolment
**Figure 1. LUME-BioNIS non-interventional study design**

Advanced adenocarcinoma NSCLC after first-line chemotherapy
- Women and men aged ≥18 years
- Locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology
- Initiating nintedanib in accordance with the approved label
- Available FFPE tumour tissue routinely obtained at diagnosis and/or at re-biopsy before initiation of first-line treatment
- Written informed consent

N=260

Nintedanib 200 mg bid⁴ + docetaxel 75 mg/m²³

PD

Follow-up for OS

**Baseline data collection**
- Demographics, medical history and ECOG PS
- Tumour biomarker status (if available)
- LDH levels (if available)
- Prior anticancer therapy

**Follow-up**
- Date of PD (based on clinical assessment or RECIST)
- Dates of and reasons for discontinuation of nintedanib and/or docetaxel
- Subsequent anticancer therapy
- Date of death
- All serious and non-serious ADRs
- All fatal AEs

*To enable biomarker analyses; †On Days 2–21 of each 21-day cycle; ‡iv infusion on Day 1 of each 21-day cycle.

ADR, adverse drug reaction; AE, adverse event; bid, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed and paraffin-embedded; iv, intravenous; LDH, lactate dehydrogenase; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.
RESULTS

Patient population

- Of 260 patients enrolled between March 2016 and October 2019, 67 (25.8%) had previously received immunotherapy as well as chemotherapy and were included in this subgroup analysis.

- Baseline characteristics indicated a group with a relatively poor prognosis (Table 1).

- The majority of patients (n=57; 85.1%) received nintedanib + docetaxel as third- or later-line treatment, with only 10 patients (14.9%) receiving this combination in the second line.

- Median duration of treatment with nintedanib was 3.9 months (range: 0.2–25.5).

- A total of 25 patients (37.3%) received subsequent anticancer therapy, which included further chemotherapy in 21 patients (31.3%) and immunotherapy in two patients (3.0%).
Table 1. Baseline characteristics in patients with prior immunotherapy (n=67)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>40 (59.7)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>63 (31–80)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (35.8)</td>
</tr>
<tr>
<td>1</td>
<td>36 (53.7)</td>
</tr>
<tr>
<td>2</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>3</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>46 (68.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>14 (20.9)</td>
</tr>
<tr>
<td>Stage IV disease at diagnosis, n (%)</td>
<td>51 (76.1)</td>
</tr>
<tr>
<td>No. of metastatic sites at baseline, n (%)</td>
<td></td>
</tr>
<tr>
<td>Two or fewer</td>
<td>22 (32.8)</td>
</tr>
<tr>
<td>More than two</td>
<td>41 (61.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (6.0)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status.
### Table 1. Baseline characteristics in patients with prior immunotherapy (n=67) (cont’d)

<table>
<thead>
<tr>
<th>Location of metastatic sites at baseline, n (%)</th>
<th>Brain</th>
<th>11 (16.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver</td>
<td>18 (26.9)</td>
</tr>
<tr>
<td></td>
<td>Adrenal glands</td>
<td>17 (25.4)</td>
</tr>
<tr>
<td>Line of prior immunotherapy, n (%)</td>
<td>First</td>
<td>20 (29.9)</td>
</tr>
<tr>
<td></td>
<td>Second or later</td>
<td>47 (70.1)</td>
</tr>
<tr>
<td>Type of prior immunotherapy, n (%)</td>
<td>Nivolumab</td>
<td>39 (58.2)</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td>14 (20.9)</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>11 (16.4)</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td></td>
<td>Tremelimumab</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Line of nintedanib treatment, n (%)</td>
<td>Second</td>
<td>10 (14.9)</td>
</tr>
<tr>
<td></td>
<td>Third</td>
<td>46 (68.7)</td>
</tr>
<tr>
<td></td>
<td>Fourth or later</td>
<td>11 (16.4)</td>
</tr>
</tbody>
</table>
RESULTS (CONT’D)

Effectiveness

• Median follow-up for patients with prior immunotherapy was 19.9 months (95% confidence interval [CI]: 15.7–21.9)

• At the time of the OS analysis, 54 patients (80.6%) had died

• Median OS was 8.8 months (95% CI: 7.0–11.5) (Figure 2)

• At the time of the PFS analysis, 59 patients (88.1%) had progressed or died

• Median PFS was 4.6 months (95% CI: 3.5–5.7) (Figure 3)

• Among 55 patients with available tumour response data, best response was partial response in 10 patients (18.2%) and stable disease in 33 patients (60.0%), providing a DCR of 78.2% (Table 2)
Figure 2. OS in patients with prior immunotherapy (n=67)

Median OS: 8.8 months
(95% CI: 7.0–11.5)

Ci, confidence interval; OS, overall survival.
Figure 3. PFS in patients with prior immunotherapy (n=67)

Median PFS: 4.6 months (95% CI: 3.5–5.7)

CI, confidence interval; PFS, progression-free survival.
Table 2. Best tumour response in patients with prior immunotherapy and available response data (n=55)

<table>
<thead>
<tr>
<th>Response category</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>33 (60.0)</td>
</tr>
<tr>
<td>Disease control</td>
<td>43 (78.2)</td>
</tr>
</tbody>
</table>
RESULTS (CONT’D)

Effectiveness (cont’d)

• There was no apparent relationship between the duration of prior therapy and response to nintedanib + docetaxel (Figure 4)
  - Remarkably, the duration of nintedanib + docetaxel treatment frequently exceeded that of prior lines
  - Furthermore, many patients had a duration of disease control of more than 10 months with nintedanib + docetaxel
Patients could have initiated nintedanib + docetaxel up to 7 days before inclusion in the study; **If prior chemotherapy and immunotherapy overlapped, they were considered to have been given in the same line of therapy. OS, overall survival.

*Figure 4. Swimmer plot showing treatment duration and response in patients with prior immunotherapy (n=67)*
RESULTS (CONT’D)

Safety

- Among 65 patients with available safety data, adverse events (AEs)/adverse drug reactions (ADRs) were reported for 59 patients (90.8%) during the on-treatment period.
- Of those, 39 patients (60.0%) had events that were considered to be related to treatment.
- The most common AEs/ADRs were diarrhoea, nausea, vomiting and malignant neoplasm progression (Table 3).
- The worst intensity of AEs/ADRs was mild in four patients (6.2%), moderate in 17 patients (26.2%) and severe in 38 patients (58.5%).
- AEs led to nintedanib dose reduction in eight patients (12.3%) and nintedanib discontinuation in 30 patients (46.2%).
Table 3. AEs/ADRs reported in ≥10% of patients during the on-treatment period in patients with prior immunotherapy (n=65)

<table>
<thead>
<tr>
<th>AE/ADR*</th>
<th>Patients, n (%) (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>21 (32.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (15.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (10.8)</td>
</tr>
<tr>
<td>Malignant neoplasm progression</td>
<td>19 (29.2)</td>
</tr>
</tbody>
</table>

*Coded according to Medical Dictionary for Regulatory Activities, version 22.0. ADR, adverse drug reaction; AE, adverse event.
CONCLUSIONS

• Used according to the approved nintedanib label in routine practice, nintedanib + docetaxel showed clinical effectiveness in patients with adenocarcinoma NSCLC previously treated with chemotherapy and first- or later-line immunotherapy

  - The median PFS of 4.6 months, median OS of 8.8 months and DCR of 78.2% are encouraging given the use of nintedanib + docetaxel in third or later lines in 85.1% of patients (with only 14.9% receiving this therapy in second line)

  - The clinical effectiveness of nintedanib + docetaxel compares favourably with reports from prior European observational studies in third-line treatment of advanced NSCLC\textsuperscript{13,14}

  - These data provide independent confirmation of the activity signals with nintedanib + docetaxel observed in a very similar patient population in the non-interventional VARGADO study, in which a similar DCR was attained.\textsuperscript{9,10} The most recent results from VARGADO will be presented at this meeting (Poster 66P)\textsuperscript{11}

• Safety findings were consistent with the known safety profile of nintedanib + docetaxel in patients with advanced NSCLC

• These data add to the real-world evidence that can inform clinical decision-making and help to optimise treatment sequencing in the changing therapeutic landscape for NSCLC

• Ongoing biomarker analyses are evaluating potential translational markers correlated with patient outcomes in this study
REFERENCES


ACKNOWLEDGEMENTS

Disclosures: The authors were fully responsible for all content and editorial decisions, were involved in all stages of poster development and have approved the final version. KS has received fees for honoraria, consulting and advisory roles from F. Hoffmann-La Roche, AstraZeneca, BMS and MSD. During the preparation of this poster, medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Mark Dyson, DPhil (Berlin, Germany) on behalf of Syneos Health (London, UK).

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