Change in non-small-cell lung cancer tumor size in patients treated with nintedanib plus docetaxel: analyses from the Phase III LUME-Lung 1 study

Martin Reck1
Anders Mellemgaard2
Silvia Novello3
Pieter E Postmus4
Birgit Gaschler-Markefski5
Rolf Kaiser5,6
Hannes Buchner7

1Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), Member of the German Center for Lung Research (DZL), Grosshansdorf, Germany; 2Department of Internal Medicine and Oncology, Bornholms Hospital, Ronne, Denmark; 3Department of Oncology, University of Turin, S. Luigi Hospital, Torino, Italy; 4Leiden University Medical Center, Leiden, the Netherlands; 5Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; 6Institute of Pharmacology, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany; 7Staburo GmbH, Munich, Germany

Background: Nintedanib in combination with docetaxel is approved in the European Union and other countries for the treatment of patients with advanced non-small-cell lung cancer (NSCLC) of adenocarcinoma histology after first-line chemotherapy, based on the overall survival findings of Phase III LUME-Lung 1 study. Change in target lesion size over time as a treatment effect was assessed in patients from this study.

Methods: Tumor size was evaluated using predefined tumor measurements. Mixed-effects models were used to quantify individual relationships between time from randomization and tumor burden, measured as the sum of longest diameter (SLD) of target lesions and assessed by an independent review (Response Evaluation Criteria In Solid Tumors [RECIST] v1.0). Exploratory analyses were conducted on the overall adenocarcinoma population, adenocarcinoma patients with time from start of first-line therapy <9 months (TSFLT <9), adenocarcinoma patients who had progressive disease as best response to first-line therapy (PD-FLT), and in squamous cell carcinoma patients.

Results: Estimated mean baseline SLD was 82.5 mm in the adenocarcinoma (n=658), 88.3 mm in the TSFLT <9 (n=405), 98.1 mm in the PD-FLT (n=117), and 94.3 mm in the squamous cell carcinoma (n=555) populations. Treatment with nintedanib/docetaxel showed a significant reduction in tumor size over time (P<0.0001) in patients with adenocarcinoma compared with placebo/docetaxel, and in patients with squamous cell carcinoma (P=0.0049). Treatment difference at 6 months was 9.7 mm in the overall adenocarcinoma population, 16.8 mm in the TSFLT <9 population, 19.7 mm in the PD-FLT population, and 6.8 mm in the squamous cell carcinoma population. SLD at 2 months post-randomization was identified as a surrogate endpoint for overall survival, in addition to progression-free survival, for all except the PD-FLT population.

Conclusion: Treatment with nintedanib/docetaxel significantly decreased tumor burden and decelerated tumor size over time compared with placebo/docetaxel in the overall adenocarcinoma population, including in patients with the poorest prognosis due to aggressive tumor dynamics.

Keywords: adenocarcinoma, non-small-cell lung cancer, sum of longest diameters, surrogate OS endpoints, squamous cell carcinoma, tumor burden

Introduction

The ultimate aim of any anticancer treatment is to reduce progressive disease (PD) and prolong overall survival (OS) of patients.1,2 Measurement of tumor burden has been shown to be associated with clinical outcomes in advanced non-small-cell lung cancer (NSCLC),3,4 when measured by the sum of longest diameter (SLD) of target lesions, baseline tumor burden is a predictor of survival duration.3,4 Tumor growth rate is an
independent prognostic factor for patients with lung cancer. Measuring tumor volume changes (eg, tumor size rate, time to tumor size, early tumor shrinkage, SLD at specific time points, depth of tumor response/nadir) during treatment of different tumor types, and in multiple treatment settings, provides a quantitative and dynamic evaluation of tumor response that can potentially identify early treatment sensitivity and has been correlated with survival outcomes.6–12

The randomized, double-blind, placebo-controlled, Phase III LUME-Lung 1 study (ClinicalTrials.gov NCT00805194; 1199.13), comparing the triple angiokinase inhibitor nintedanib in combination with docetaxel with placebo/docetaxel, demonstrated a significant improvement in OS in patients with NSCLC of adenocarcinoma histology after failure of first-line chemotherapy (median OS: 12.6 vs 10.3 months; hazard ratio [HR]: 0.83 [95% CI: 0.70–0.99]; P=0.0359).13 A correlation between OS benefit from nintedanib treatment and the continuous variable “time from start of first-line treatment” (TSFLT) has been observed.13,14 In adenocarcinoma patients with TSFLT <9 months (TSFLT <9), OS was significantly longer in the nintedanib arm than in the placebo arm, with a 3.0-month improvement (median OS 10.9 vs 7.9 months; HR: 0.75 [95% CI: 0.60–0.92]; P=0.0073).13

The outcomes of the LUME-Lung 1 study contributed to the approval of nintedanib in the European Union and other countries for the treatment of patients with locally advanced, metastatic, or locally recurrent NSCLC of adenocarcinoma histology after first-line chemotherapy.15

In the LUME-Lung 1 study, predefined sensitivity analyses of OS used the prognostic factor of baseline SLD of target lesions as an adjustment for baseline tumor burden. When the model was adjusted for the baseline SLD, OS remained significantly improved with nintedanib/docetaxel in the overall adenocarcinoma population and in adenocarcinoma patients with TSFLT <9, and was significant even in all patients. In patients with squamous cell carcinoma, there was no difference in OS (HR: 1.01 [95% CI: 0.85–1.21]; P=0.8907) in the primary analysis; however, adjustment for SLD resulted in a notable decrease in the HR to 0.92 (95% CI: 0.77–1.10; P=0.365). Overall, a greater tumor burden was associated with a greater treatment effect in the nintedanib arm.13,16

These observations suggest that tumor characteristics, including tumor burden and the dynamics of PD, may have predictive potential for nintedanib therapy.17 The current investigation extends the analyses of tumor burden. We explored the impact of tumor size over time, including the identification of surrogate endpoints of survival, as well as the time to occurrence of new lesions as a treatment effect in patients from the Phase III LUME-Lung 1 study, with a specific focus on patients with a poorer prognosis due to more aggressive tumors.

Methods

Study design and assessments

Details of the LUME-Lung 1 study design and assessments have been reported previously13 and are briefly summarized below. Patients in the randomized, double-blind, placebo-controlled, Phase III LUME-Lung 1 study received standard intravenous docetaxel (75 mg/m²) on Day 1 and nintedanib (200 mg twice daily; nintedanib arm) or matching placebo (placebo arm) on Days 2–21, until PD or non-tolerability.13 Target lesions were assessed by central independent review using modified Response Evaluation Criteria In Solid Tumors (RECIST) v1.0 at baseline and every 6 weeks after the first administration of docetaxel.

All patients provided written informed consent, and the study protocol was approved by independent ethics committees or institutional review boards at each center (Table S1). Here, we specifically report exploratory analyses for the overall adenocarcinoma population, the population of patients with adenocarcinoma and TSFLT <9, and adenocarcinoma patients with PD as their best response to first-line therapy (PD-FLT), as well as the population with squamous cell carcinoma.

Efficacy outcomes for this study have been previously reported.13,18 Treatment with nintedanib/docetaxel significantly improved efficacy outcomes in the analyzed adenocarcinoma populations (Table S2).

Assessment of tumor size

Tumor size was evaluated using all available tumor measurements from patients who had at least two evaluable assessments. Tumor burden was measured as the SLD of target lesions, assessed by an independent central review (RECIST v1.0) preferentially, although data from investigator assessment (if available) were used for patients without two evaluable central independent review measurements.

New lesions

The time to occurrence of new lesions, as recorded by RECIST v1.0, was analyzed using a Cox model, Kaplan–Meier curves, and a log-rank test, similar to the primary analysis. Two exploratory sensitivity analyses were carried out: first, patients were recorded as being censored using the OS results (time to new lesion) and, second, death was counted as an event and patients could have either an event or be censored using the OS results (new lesion-free survival).
Surrogate endpoints for OS

Variables proposed in literature related to tumor size over time were evaluated for their predictive value for OS. These variables, together with baseline characteristics, were included in the stepwise algorithm to determine surrogate endpoints for OS, while additionally adjusting for important prognostic baseline variables. Baseline characteristics were investigated for being predictive for OS. The baseline characteristics included the trial’s stratification factors (Eastern Cooperative Oncology Group performance status [0 vs 1], prior receipt of bevacizumab [yes vs no], presence of brain metastases at baseline [yes vs no]), as well as other characteristics that were predefined in the protocol (sex [female vs male], age [<65 vs ≥65 years], geographic region, race category [Asian vs non-Asian], smoking status [current smoker vs ex-smoker/never smoked], use of bisphosphonates at baseline [yes vs no], best response to first-line therapy [complete response/partial response/stable disease vs PD], number of metastatic organs [≤2 vs >2], adrenal metastases [yes vs no], liver metastases [yes vs no], and lactate dehydrogenase at baseline [yes vs no], as well as other characteristics that were predefined in the protocol (sex [female vs male], age [<65 vs ≥65 years], geographic region, race category [Asian vs non-Asian], smoking status [current smoker vs ex-smoker/never smoked], use of bisphosphonates at baseline [yes vs no], best response to first-line therapy [complete response/partial response/stable disease vs PD], number of metastatic organs [≤2 vs >2], adrenal metastases [yes vs no], liver metastases [yes vs no], and lactate dehydrogenase at baseline [yes vs no]), as well as other characteristics that were predefined in the protocol (sex [female vs male], age [<65 vs ≥65 years], geographic region, race category [Asian vs non-Asian], smoking status [current smoker vs ex-smoker/never smoked], use of bisphosphonates at baseline [yes vs no], best response to first-line therapy [complete response/partial response/stable disease vs PD], number of metastatic organs [≤2 vs >2], adrenal metastases [yes vs no], liver metastases [yes vs no], and lactate dehydrogenase at baseline [yes vs no]), as well as other characteristics that were predefined in the protocol (sex [female vs male], age [<65 vs ≥65 years], geographic region, race category [Asian vs non-Asian], smoking status [current smoker vs ex-smoker/never smoked], use of bisphosphonates at baseline [yes vs no], best response to first-line therapy [complete response/partial response/stable disease vs PD], number of metastatic organs [≤2 vs >2], adrenal metastases [yes vs no], liver metastases [yes vs no], and lactate dehydrogenase at baseline [yes vs no]), as well as other characteristics that were predefined in the protocol (sex [female vs male], age [<65 vs ≥65 years], geographic region, race category [Asian vs non-Asian], smoking status [current smoker vs ex-smoker/never smoked], use of bisphosphonates at baseline [yes vs no], best response to first-line therapy [complete response/partial response/stable disease vs PD], number of metastatic organs [≤2 vs >2], adrenal metastases [yes vs no], liver metastases [yes vs no], and lactate dehydrogenase at baseline [yes vs no]), as well as other characteristics that were predefined in the protocol (sex [female vs male], age [<65 vs ≥65 years], geographic region, race category [Asian vs non-Asian], smoking status [current smoker vs ex-smoker/never smoked], use of bisphosphonates at baseline [yes vs no], best response to first-line therapy [complete response/partial response/stable disease vs PD], number of metastatic organs [≤2 vs >2], adrenal metastases [yes vs no], liver metastases [yes vs no], and lactate dehydrogenase at baseline [yes vs no]), as well as other characteristics that were predefined in the protocol (sex [female vs male], age [<65 vs ≥65 years], geographic region, race category [Asian vs non-Asian], smoking status [current smoker vs ex-smoker/never smoked], use of bisphosphonates at baseline [yes vs no], best response to first-line therapy [complete response/partial response/stable disease vs PD], number of metastatic organs [≤2 vs >2], adrenal metastases [yes vs no], liver metastases [yes vs no], and lactate dehydrogenase at baseline [yes vs no]), as well as other characteristics that were predefined in the protocol (sex [female vs male], age [<65 vs ≥65 years], geographic region, race category [Asian vs non-Asian], smoking status [current smoker vs ex-smoker/never smoked], use of bisphosphonates at baseline [yes vs no], best response to first-line therapy [complete response/partial response/stable disease vs PD], number of metastatic organs [≤2 vs >2], adrenal metastases [yes vs no], liver metastases [yes vs no], and lactate dehydrogenase at baseline [yes vs no]).

Based on previous clinical methodology and in accordance with RECIST recommendations, these variables related to tumor size included the “absolute reduction in SLD from baseline to 2 months after randomization”;[19,20] “percentage reduction in SLD from baseline to 2 months after randomization”; “SLD at 2 months after randomization”; “maximum reduction in SLD compared to baseline”; “maximum reduction in percentage of SLD compared to baseline”; “SLD at nadir (lowest tumor burden after randomization)”;[21] “estimated SLD at baseline”; “time to tumor growth (time to nadir)” (Figure S1);[22,23] “early tumor shrinkage” analyzed both as any tumor increase (but without new metastases) and as minor shrinkage (both analyses took “new metastases” as the reference population);[7,8,10] “time to return to baseline SLD”; “observed SLD at baseline”;[4] “progression-free survival (PFS) duration”, including patients who were censored in the analysis of PFS; and “PFS flag”, referring to the patients who were censored in the analysis of PFS. These censored patients were compared with patients who had a PFS event (censoring vs event).

Statistical analyses and use of surrogate endpoints

Mixed-effects models were used to quantify the nonlinear individual relationships between time from randomization (t) and tumor burden. Several models were evaluated and the model that performed best in terms of Akaike Information Criterion (a measure of the relative quality of statistical models) was used: \[ \text{SLD}(t) = \beta_1 t + \beta_2 \ln(t+1) + b_1 t + b_2 \ln(t+1), \] where \( i = 1, \ldots, n, \) \( n = \) number of patients, and \( b_1 \) and \( b_2 \) are random effects. The selected model was flexible, allowing for a wide range of differently shaped growth curves (U-shaped, J-shaped, N-shaped, and linear-shaped). Cox regression and Kaplan–Meier plots were used to evaluate and visualize the predictive value of surrogate endpoints. A stepwise selection method was used, with inclusion and exclusion significance of 0.1.

Results

Patient population

In the LUME-Lung 1 study, there were 658 patients with adenocarcinoma histology. Of these, 405 had TSFLT <9 and 117 had PD-FLT. In addition, there were 555 patients with squamous cell carcinoma. Most patients had metastatic cancer at screening; this included 94.2% of the overall adenocarcinoma population, 96.8% of the TSFLT <9 adenocarcinoma population, 95.7% of the PD-FLT adenocarcinoma population, and 86.3% of the squamous cell carcinoma population (Table 1). Approximately half the patients had one or two metastatic sites at screening (Table S3). In the overall adenocarcinoma population, the median duration of treatment with nintedanib/docetaxel was 4.2 months (range 0–41.5) and with placebo/docetaxel was 3.0 months (range 0–31.7), while in the squamous cell carcinoma population, the median duration of treatment with nintedanib/docetaxel was 2.8 months (range 0–34.9) and with placebo/docetaxel was 2.5 months (range 0–35.6).

Tumor evaluation and baseline tumor SLD

A summary of radiologic assessments and baseline SLD is shown in Table 2. Most patients had at least one valid post-baseline image taken by computed tomography or a magnetic resonance imaging scan, with the same method used consistently for an individual patient (93.3% of the overall adenocarcinoma population, 92.3% of the TSFLT <9 adenocarcinoma population, 89.7% of the PD-FLT adenocarcinoma population, and 90.5% of the squamous cell carcinoma population). The estimated mean baseline SLD measurements were larger in the population with the worse prognosis (PD-FLT).

Tumor size over time

Estimated tumor size curves for the adenocarcinoma populations evaluated in this study are shown in Figure 1. Tumor size patterns were consistent between treatment arms in all adenocarcinoma populations. For adenocarcinoma patients
Table 1 Metastatic sites at screening

<table>
<thead>
<tr>
<th>Metastatic sites at screening, n (%)</th>
<th>Patients with adenocarcinoma histology NSCLC</th>
<th>Patients with squamous cell histology NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nintedanib (n=322)</td>
<td>Placebo (n=336)</td>
</tr>
<tr>
<td>Patients with metastases at screening</td>
<td>300 (93.2)</td>
<td>320 (95.2)</td>
</tr>
<tr>
<td>Metastatic sites at screening, n (%)</td>
<td>22 (6.8)</td>
<td>16 (4.8)</td>
</tr>
<tr>
<td>0</td>
<td>187 (58.1)</td>
<td>196 (58.3)</td>
</tr>
<tr>
<td>1–2</td>
<td>113 (35.1)</td>
<td>124 (36.9)</td>
</tr>
<tr>
<td>Location of metastatic sites at screening, n (%)</td>
<td>Lung ipsilateral</td>
<td>163 (50.6)</td>
</tr>
<tr>
<td>Lung contralateral</td>
<td>140 (43.5)</td>
<td>144 (42.9)</td>
</tr>
<tr>
<td>Bone</td>
<td>92 (28.6)</td>
<td>100 (29.8)</td>
</tr>
<tr>
<td>Liver</td>
<td>63 (19.6)</td>
<td>53 (15.8)</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>42 (13.0)</td>
<td>56 (16.7)</td>
</tr>
<tr>
<td>Brain</td>
<td>26 (8.1)</td>
<td>23 (6.8)</td>
</tr>
<tr>
<td>Other</td>
<td>138 (42.9)</td>
<td>156 (46.4)</td>
</tr>
</tbody>
</table>

Abbreviations: NSCLC, non-small-cell lung cancer; PD-FLT, progressive disease as the best response to first-line therapy; TSFLT, time from start of first-line therapy.

OncoTargets and Therapy 2018:11

Table 2 Radiological assessments and baseline SLD of target lesions

<table>
<thead>
<tr>
<th>Patients with adenocarcinoma histology NSCLC</th>
<th>Patients with squamous cell histology NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nintedanib (n=322)</td>
</tr>
<tr>
<td>Patients with at least one valid post-baseline image, n (%)</td>
<td>306 (95.0)</td>
</tr>
<tr>
<td>Number of valid post-baseline images</td>
<td>1,273</td>
</tr>
<tr>
<td>Number of valid post-baseline images per patient, median (range)</td>
<td>3 (1–28)</td>
</tr>
<tr>
<td>Estimated mean (range) baseline SLD* measurements (mm)</td>
<td>82.5 (10.9–391.2)</td>
</tr>
</tbody>
</table>

Notes: Either CT or MRI scan, with the same method used consistently for an individual patient. Estimated fixed effects of longitudinal mixed model; the intercept of SLD was at Month 0.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NSCLC, non-small-cell lung cancer; PD-FLT, progressive disease as the best response to first-line therapy; SLD, sum of longest diameter; TSFLT <9, time from start of first-line therapy <9 months.
Figure 1 Tumor size over time, measured by SLD of target lesions, in patients with adenocarcinoma.

Notes: Trajectories are based on the estimated fixed effects of the mixed model. (A) All patients with adenocarcinoma. (B) Patients with adenocarcinoma who progressed within 9 months after start of first-line therapy (TSFLT <9). (C) Patients with adenocarcinoma with PD-FLT.

Abbreviations: PD-FLT, progressive disease as the best response to first-line therapy; SLD, sum of longest diameter; t, time from randomization; TSFLT <9, time from start of first-line therapy <9 months.
the likelihood ratio test of the treatment effect ($P<0.0001$ for the overall adenocarcinoma population). The treatment difference at 6 months was even more pronounced in patients with a poor prognosis ($P<0.0001$ for the TSFLT <9 adenocarcinoma population; $P=0.0004$ for the PD-FLT adenocarcinoma population), as shown in Figure 1B and C.

In all groups, nintedanib/docetaxel produced a significant reduction in tumor size over time compared with placebo/docetaxel. Disease stabilization was greater in patients receiving nintedanib than in patients receiving placebo (Table S2). Following the same trend, in squamous cell carcinoma patients, treatment with nintedanib/docetaxel produced a significant reduction in tumor size over time compared with placebo ($P=0.0049$; Figure 2). Further estimates for the parameterization of the longitudinal model for tumor size are reported in Table S4.

Throughout the whole study, there was a sustained difference in the average SLD of target lesions between the two arms, with lower tumor burden in the nintedanib arm (Figure 3).

### New lesions

The analysis of the time to occurrence of new lesions favored the nintedanib arm and in the second sensitivity analysis was significantly longer with nintedanib in the TSFLT <9 and PD-FLT populations (Table 3). The frequency for each site was mostly balanced across the two treatment arms. There was no specific pattern for the location of new lesions associated with either treatment arm (Table S5).

### Surrogate endpoints for OS

Several variables related to tumor size were selected by the algorithm as surrogate endpoints for OS (Table 4) in patients with a baseline and at least one post-baseline measurement (614 patients with adenocarcinoma, 374 patients with TSFLT <9 adenocarcinoma, 105 patients with PD-FLT adenocarcinoma, and 502 patients with squamous cell carcinoma). The algorithm demonstrated that PFS duration and PFS censorship were both predictive for OS in all populations evaluated, with the exception of the PD-FLT population,
Table 3 Time to occurrence of new lesions

<table>
<thead>
<tr>
<th>Patients with adenocarcinoma histology NSCLC</th>
<th>Patients with squamous cell histology NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Nintedanib (n=322)</td>
</tr>
<tr>
<td>Sensitivity analysis 1*</td>
<td></td>
</tr>
<tr>
<td>Patients with event, n (%)</td>
<td>142 (44.1)</td>
</tr>
<tr>
<td>Time to occurrence of new lesions (months)</td>
<td>Median (months)</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI); P-value</td>
</tr>
<tr>
<td>Sensitivity analysis 2*</td>
<td></td>
</tr>
<tr>
<td>Patients with event, n (%)</td>
<td>285 (88.5)</td>
</tr>
<tr>
<td>New lesions</td>
<td>142 (44.1)</td>
</tr>
<tr>
<td>Death</td>
<td>143 (44.4)</td>
</tr>
<tr>
<td>Time to occurrence of new lesions (months)</td>
<td>Median (months)</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI); P-value</td>
</tr>
</tbody>
</table>

Notes: *In sensitivity analysis 1, patients were recorded as being censored using the OS results (time to new lesion). *In sensitivity analysis 2, death was counted as an event and patients could have either an event or be censored using the OS results (new lesion-free survival).

Abbreviations: HR, hazard ratio; NR, not reached; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-FLT, progressive disease as the best response to first-line therapy; TSFLT <9, time from start of first-line therapy <9 months.

Discussion

Our analysis showed that the nintedanib/docetaxel combination slowed down the tumor dynamics compared with placebo/docetaxel, with the largest effect seen in patients with the poorest prognosis. Corresponding well with the OS findings of LUME-Lung 1, the analyses of data on the a finding probably associated with the low numbers of censored patients in this population (n=14 [12%]). Regarding SLD, a smaller SLD at 2 months was predictive for longer OS in all the populations evaluated, except for the PD-FLT population. Baseline variables that were selected as being predictive for OS can be found in Table S6.

Table 4 Surrogate endpoints for OS (tumor size variables)

<table>
<thead>
<tr>
<th>Population</th>
<th>Variable</th>
<th>HR (95% CI)*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with adenocarcinoma histology NSCLC</td>
<td>SLD of target lesions at 2 months after randomization (cm)</td>
<td>1.005 (1.003–1.006)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>ETS (any tumor increase, without new metastases vs new metastases)</td>
<td>0.574 (0.422–0.781)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>ETS (minor tumor shrinkage vs new metastases)</td>
<td>0.711 (0.542–0.934)</td>
<td>0.0143</td>
</tr>
<tr>
<td></td>
<td>PFS duration (months)</td>
<td>0.994 (0.992–0.995)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>PFS flag (PFS censoring vs PFS event)</td>
<td>0.570 (0.445–0.730)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>TSFLT &lt;9 months</td>
<td>SLD of target lesions at 2 months after randomization (cm)</td>
<td>1.004 (1.002–1.006)</td>
</tr>
<tr>
<td></td>
<td>PFS duration (months)</td>
<td>0.994 (0.992–0.995)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>PFS flag (PFS censoring vs PFS event)</td>
<td>0.566 (0.416–0.770)</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>PD-FLT</td>
<td>SLD of target lesions at baseline (cm)</td>
<td>1.007 (1.003–1.010)</td>
</tr>
<tr>
<td></td>
<td>PFS duration (months)</td>
<td>0.992 (0.989–0.995)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Time to return to baseline SLD of target lesions (months)</td>
<td>1.001 (1.000–1.002)</td>
<td>0.0021</td>
</tr>
<tr>
<td>Patients with squamous cell histology NSCLC</td>
<td>SLD of target lesions at 2 months after randomization (cm)</td>
<td>1.006 (1.004–1.007)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>TTT (months)</td>
<td>1.080 (1.015–1.148)</td>
<td>0.0143</td>
</tr>
<tr>
<td></td>
<td>PFS duration (months)</td>
<td>0.993 (0.992–0.995)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>PFS flag (PFS censoring vs PFS event)</td>
<td>0.474 (0.351–0.639)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Notes: *Please note that the HRs are not treatment effects. An HR of 1.005 as in line 1 means that an uptake in SLD at 2 months of 10 cm increases the risk of death by 5%. *Score test.

Abbreviations: ETS, early tumor shrinkage; HR, hazard ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-FLT, progressive disease as the best response to first-line therapy; PFS, progression-free survival; SLD, sum of longest diameter; TSFLT, time from start of first-line therapy to randomization; TTG, time to tumor growth.
impact of the change in target lesion size over time as a
treatment effect showed that nintedanib/docetaxel signifi-
cantly decreased tumor burden and decelerated tumor size
compared with placebo/docetaxel in all patients with adeno-
carcinoma and squamous histology. The improvements in
tumor burden were greatest in the adenocarcinoma PD-FLT
population, comprising those patients with larger baseline
tumor burden (poorest prognosis), similar to OS findings.13
In LUME-Lung 1, in adenocarcinoma patients with PD-FLT,
the median OS in the nintedanib arm (9.8 months) improved
by 3.5 months compared with the placebo arm (6.3 months),
with a 38% reduced risk of new lesions or death. The decrease
in tumor size was also greatest in this patient population, with
a treatment difference of 19.7 mm favoring the nintedanib
arm 6 months after randomization.

Among the adenocarcinoma patient populations ana-
yzed, baseline tumor burden, as measured by the SLD
target lesions or by the number of metastatic sites, was
largest in patients with the poorest prognosis (PD-FLT,
followed by TSFLT < 9). However, the treatment effect of
nintedanib was larger in these patients. The insensitivity
toward chemotherapy observed in the PD-FLT popula-
tion could represent a distinct biology of tumors that are
potentially more dependent on angiogenesis and in which
inhibition of angiongenesis might be more effective. Reach-
ning and maintaining a large tumor burden may depend
heavily on the development of new blood vessels to ensure
high levels of oxygen and nutrients, rendering them more
sensitive to the effects of antiangiogenic treatment than
patients with lower tumor burden. Although nintedanib is
not approved in squamous patients, we included this patient
population in our analysis for if a meaningful
treatment effect could be observed in squamous patients.
Previous meta-analysis has shown that standardized uptake
value, a semi-quantitative simplified measurement of tissue
deoxylucose metabolic rate, has prognostic significance for
survival in NSCLC.24 Whether differences in standardized
uptake values may account for the treatment effects observed
here has not been evaluated, but may be a potential area of
further investigation.

Decreased tumor burden, slowing increases in tumor
size, and longer time without new lesions are outcomes that
provide further evidence of the treatment benefit with ninte-
danib and suggest that further evaluation of the implications
of these findings for patients with adenocarcinoma is war-
tanted. The current analyses provide a valuable analysis and
description of the antitumor effect of nintedanib that might
not be evident from the response rates alone, and as such,
future trials should consider evaluating tumor dynamics as
a study endpoint. These analyses confirm that more aggres-
sive tumors obtain the largest benefit from the nintedanib/
docetaxel treatment combination. Another consideration is
that early assessment of tumor growth kinetics may contribute
to our understanding of tumor hyperprogression in patients
undergoing immunotherapy, and as such warrants further
clinical evaluation. Although what decrease in tumor size
represents a clinically meaningful improvement for a patient
has not been established in the literature, measuring change
in tumor size from a clinical perspective allows for an earlier
assessment of therapeutic activity and has been correlated
with survival outcomes.5–11

The analyses presented here are exploratory and have
several limitations. Formal validation of these variables, and
their potential for use as surrogate endpoints, was beyond
the scope of this analysis. The study did not systematically
collect imaging data post-progression on the timing and
appearance of new lesions beyond PD. It should be noted
that analyses only included data from selected representative
lesions based on RECIST that were predefined during the
trial and may not be representative of all lesions. Individual
patient heterogeneity should also be considered as some
SLD data may reflect the size of the primary tumor, while
other data may reflect the sum of several metastatic lesions
measured. A further limitation is that our analysis explored
the PD-FLT and TSFLT < 9 subgroups of adenocarcinoma
patients, but the same subgroups were not studied in the
patients with squamous cell carcinoma.

Conclusion

Corresponding well with the OS findings of the LUME-
Lung 1 study, treatment with nintedanib/docetaxel resulted
in trends toward decreased tumor burden, decelerated tumor
size over time, and increased time to new occurrences of
lesions compared with placebo/docetaxel in the overall ade-
ocarcinoma population, with significant benefits observed
for patients with the poorest prognosis due to aggressive
tumor dynamics.

Acknowledgments

Statistical analysis was conducted by Hannes Buchner
of Staburo GmbH on behalf of Boehringer Ingelheim
Pharma GmbH & Co. KG, Munich, Germany. The stud-
ies on which these analyses were based were sponsored
by Boehringer Ingelheim. Analyses were conducted by
Boehringer Ingelheim. Medical writing assistance, sup-
ported financially by Boehringer Ingelheim, was provided
by Syneos Health Communications during the preparation of this manuscript.

Disclosure

Martin Reck reports personal fees from Boehringer Ingelheim, Hoffmann-La Roche, Eli Lilly, Merck Sharp & Dohme Limited (MSD), Bristol-Myers Squibb (BMS), AstraZeneca, Celgene, Merck and Pfizer, outside the submitted work; Anders Mellemgaard reports personal fees from advisory boards from Boehringer Ingelheim, MSD, and Eli Lilly and as a speaker from Boehringer Ingelheim, outside the submitted work; Silvia Novello reports personal fees (Speaker Bureau) from MSD, BMS, Eli Lilly, AstraZeneca, and Roche, outside the submitted work. Pieter Postmus reports personal fees from advisory boards from Boehringer Ingelheim (during the conduct of the study), AstraZeneca, AbbVie, BMS, Eli Lilly, Janssen, G1 Therapeutics, MSD, Novartis, and Roche, outside the submitted work; Birgit Gaschler-Markefski is an employee of Boehringer Ingelheim; Rolf Kaiser is an employee of Boehringer Ingelheim and reports a patent issued (EP 2994125); and Hannes Buchner reports personal fees from Boehringer Ingelheim during the conduct of the study. The authors report no other conflicts of interest in this work.

References


