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Analysis of patient-reported outcomes from the LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled, Phase III study of second-line nintedanib in patients with advanced non-small cell lung cancer.

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Abstract

Introduction

The LUME-Lung 1 trial (NCT00805194; Study 1199.13) demonstrated a significant overall survival (OS) advantage for nintedanib plus docetaxel compared with placebo plus docetaxel as second-line therapy for patients with advanced non-small cell lung cancer (NSCLC) and adenocarcinoma histology. Patient-reported outcomes (PROs) for symptoms and health-related quality of life (QoL) are reported here.

Methods

PROs were assessed at screening, on Day 1 of each 21-day treatment cycle, at the end of active treatment, and at the first follow-up visit. PRO instruments were the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and Lung Cancer-13 supplement, and the EuroQol disease-generic questionnaire (EQ-5D and EQ-VAS). Analyses of PRO items for lung cancer-specific symptoms of cough, dyspnoea and pain were prespecified.

Results

Rates of questionnaire completion were high. There was no significant difference in time to deterioration of global health status/QoL, or symptoms of cough, dyspnoea or pain, between the treatment groups for both the overall study population and the adenocarcinoma population. Time to deterioration of some gastrointestinal events was shorter with nintedanib versus placebo. Longitudinal analysis for the adenocarcinoma population showed comparable changes between the groups in symptom scores over time, with numerical differences in favour of nintedanib for cough and pain scales, and significant reductions in some pain items with nintedanib versus placebo. There was no statistically significant difference in EQ-5D or EQ-VAS between the groups.

Conclusion

The significant OS benefit observed with the addition of nintedanib to docetaxel therapy was achieved with no detrimental effect on patient self-reported QoL.

Keywords

- Anti-angiogenesis;
- Docetaxel;
- Nintedanib;
- Non-small cell lung cancer;
- Quality of life

1. Introduction

The number of approved second-line treatment options for non-small cell lung cancer (NSCLC) remains limited [1], and some options are restricted to patients with tumours of a specific histology or molecular profile [2] and [3]. Newer agents—such as crizotinib, and where available, afatinib, ceritinib and gefitinib—are only indicated for those patients with oncogene-dependent tumours [4], [5], [6] and [7]. Currently approved oncogene-independent options include the cytotoxics docetaxel and pemetrexed, but the survival benefit associated with these two agents is modest [8] and [9], and pemetrexed is limited to patients with non-squamous histology [10]. Erlotinib is also indicated as second-line therapy irrespective of epidermal growth factor receptor (*EGFR*) mutational status [11].

Thus there remains a need for additional effective, well-tolerated second-line treatment options with wide application for relapsed/refractory NSCLC. Anti-angiogenic agents have been intensely investigated as potential new treatment options. Angiogenesis is critical for the growth, progression and metastasis of many solid tumour types, and so it represents a fundamental target for cancer therapy [12] and [13]. Yet several clinical trials in NSCLC with different anti-angiogenic tyrosine

kinase inhibitors have failed to show an overall survival (OS) benefit [14] . To date, first-line bevacizumab remains the only approved anti-angiogenic treatment in the therapeutic armamentarium for advanced NSCLC.

Nintedanib (formerly called BIBF 1120) is a novel, potent, oral, small-molecule angiokinase inhibitor that targets three receptor classes involved in angiogenesis: vascular endothelial growth factor receptors (VEGFR) 1–3, platelet-derived growth factor receptors (PDGFR) α/β and fibroblast growth factor receptors (FGFR) [15] . In a recent large-scale, Phase III, randomised trial (LUME-Lung 1; NCT00805194; Study 1199.13), second-line treatment with nintedanib plus docetaxel significantly improved progression-free survival (PFS) versus placebo plus docetaxel (primary end-point) in the overall population of patients with advanced NSCLC (median PFS 3.4 versus 2.7 months [hazard ratio [HR] 0.79, 95% confidence interval [CI] : 0.68–0.92, $p = 0.0019$) and in prespecified populations of patients with adenocarcinoma histology (HR 0.77, 95% CI: 0.62–0.96, $p = 0.0193$) and with adenocarcinoma histology and poor prognosis (defined as progression within 9 months of starting prior first-line therapy) (median PFS 3.6 versus 1.5 months [HR 0.63, 95% CI: 0.48–0.83, $p = 0.0008$]) [16] . In the hierarchical analysis, nintedanib plus docetaxel also significantly improved OS versus placebo plus docetaxel (secondary end-point) in the population with adenocarcinoma histology and poor prognosis (median OS 10.9 versus 7.9 months [HR 0.75, 95% CI: 0.60–0.92; $p = 0.0073$]) and the adenocarcinoma population (median OS 12.6 versus 10.3 months [HR 0.83, 95% CI: 0.70–0.99; $p = 0.0359$]), but not in the overall population [16] .

The extension of OS with nintedanib in the LUME-Lung 1 trial is notable because no study in the preceding decade had shown an OS benefit with second-line treatment of advanced NSCLC. However, minimising adverse events and maintaining patient quality of life (QoL) are also important goals in the second-line setting, where the scope for extension of survival is in any case limited [17] , [18] and [19] . The LUME-Lung 1 study used patient-reported outcomes (PROs) as secondary end-points to assess patients' subjective perception of their symptom burden and health-related QoL to supplement the objective measures of efficacy and safety. The PROs from the LUME-Lung-1 trial are reported here.

2. Patients and methods

2.1. Study design

LUME-Lung 1 was a randomised, placebo-controlled Phase III trial conducted at 211 centres across 27 countries [16] . Eligible patients were adults with confirmed stage III/IV (according to the American Joint Committee on Cancers) recurrent NSCLC (all histologies) who had received one previous chemotherapy regimen and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were randomised (1:1) to receive docetaxel (75 mg/m² on Day 1) plus nintedanib (200 mg twice daily on Days 2–21) or docetaxel plus placebo in a 21-day treatment cycle. Randomisation was stratified by ECOG performance status (0 versus 1), previous bevacizumab treatment (yes versus no), histology (squamous versus non-squamous) and the presence of brain metastases (yes versus no). Full details of the study design and methodology have been reported previously [16] .

2.2. Patient-reported outcome measures

PROs were assessed at the screening visit, on Day 1 of each 21-day treatment cycle, at the end of active treatment (EOT) and at the first follow-up visit. The questionnaires were completed by patients before seeing the investigator, and before they were provided with any new information about their disease status, to avoid influencing responses.

PRO instruments consisted of the 30-item European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) [20] ; its 13-item, lung cancer-specific supplement (QLQ-LC13) [21] ; and the EuroQol disease-generic questionnaire, comprising the EQ-5D overall utility and EQ-visual analogue scale (VAS) [22] . EQ-5D utility scores were calculated for each subject at each visit from the five-item scores using United Kingdom (UK) or Belgium data preference weightings [23] .

The QLQ-C30 incorporates both multi-items scales and single-item measures, which include one global health status/QoL scale, five functional scales, three symptoms scales and six single items to assess dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties [20] . The QLQ-LC13 incorporates one multi-item scale to assess dyspnoea, and a series of single items to assess pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia and haemoptysis [21] . The analysis plan included evaluation of the effects of study treatment on prespecified lung cancer-specific symptoms of interest, which were cough (Question Q1 on the QLQ-LC13); dyspnoea (composite of Q3–5 on the QLQ-LC13); and pain (composite of Q9 and Q19 on the QLQ-C30).

2.3. Scoring of the scales/items

The EORTC questionnaire scales/items followed the EORTC scoring algorithm [24] . To aid interpretation, a linear transformation was applied to standardise the raw score for each scale/item to a range from 0 to 100. For the global health status/QoL scale and functional scales, a value of 100 was equivalent to the best possible score and 0 to the worst possible

score. For the symptom scales and symptom items, 100 was equivalent to the highest burden of symptoms and 0 to the lowest burden. Completed questionnaires with missing data were handled in line with EORTC guidelines, including the exception for the dyspnoea composite for which all three responses were required for an individual's score to be used [24] .

2.4. Statistical analyses

Analyses were performed for adenocarcinoma patients with a time since start of first-line therapy to randomisation into this study <9 months, for the population of patients with adenocarcinoma histology, and the overall population (all histologies) in a hierarchical order, as prespecified for the analysis of OS [16] .

Time to deterioration (TTD) in PROs was measured from randomisation to first appearance of a minimal clinically important difference in the score, defined as ≥ 10 -point change lower (for global health status/QoL and functional scales) or higher (for symptom scales and items) [25] . TTD was analysed using a log-rank test stratified by the four stratification factors. A stratified Cox proportional hazards model was used to estimate the HRs and CIs of TTD. Patients without documented PRO item deterioration were censored at the time of the patient's last PRO assessment.

Changes in PROs over the duration of the median follow-up period were assessed using longitudinal models. These were mixed-effects growth curve models with the average profile over time for each PRO end-point described using a piecewise linear model. A mean score per patient for each PRO was calculated from the area under the estimated growth curve (AUC) up to the median follow-up time. Treatment group mean scores were then derived from the patient scores. The treatment effect was estimated as the average difference between the treatment group scores, together with the 95% CIs and associated *p*-values based on a *t*-statistic with degrees of freedom calculated using the Kenward–Roger method [26] .

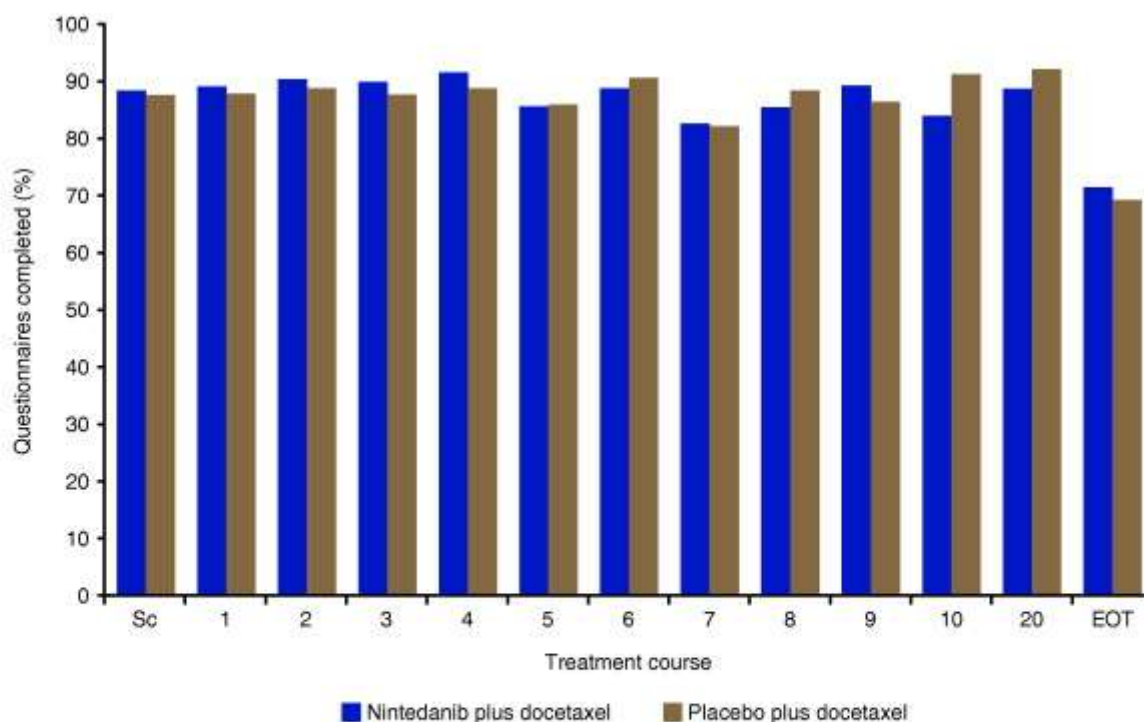
Potential correlation between missing PRO data and outcome variables was assessed using Kendall's tau statistic. The potential effect of missing PRO data to introduce bias was assessed in sensitivity analyses using joint models, which consisted of the longitudinal model and a time-to-event variable representing the withdrawal process. Time to last PRO assessment was used as the time-to-event variable, and it was assumed to have a Weibull distribution.

3. Results

3.1. Patients

A total of 1773 patients were screened, of whom 1314 were eligible and randomised to study treatment (655 to nintedanib plus docetaxel [322 with adenocarcinoma] and 659 to placebo plus docetaxel [336 with adenocarcinoma]) [16] . Patient demographics and baseline clinical characteristics were well balanced across the treatment arms for both the overall population and the prespecified population of patients with adenocarcinoma [16] .

More than 80% of patients included in the overall population completed the EORTC QLQ-C30/LC13 and EQ-5D over the first 10 courses of study treatment with comparable proportions of responders between the two treatment arms (Fig. 1). Approximately 70% of patients completed the QLQ-C30 at the EOT visit. Similar numbers of responses were also achieved for patients with adenocarcinoma.



Number of expected responses		Sc	1	2	3	4	5	6	7	8	9	10	20	EOT
Nintedanib plus docetaxel	655	654	595	465	414	337	307	240	223	170	150	26	637	
Placebo plus docetaxel	659	658	596	416	372	280	248	178	161	117	103	25	643	

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire, 30 items; EOT=end of treatment; Sc=screening.

Fig. 1.

Patient compliance with EORTC QLQ-C30 in overall population.

3.2. Baseline patient-reported outcomes

In the overall population, mean global health status/QoL at baseline was relatively high, indicating reasonable levels of QoL, with comparable scores for the nintedanib versus placebo groups (mean score 61.2 [standard deviation (SD) 19.9] versus 62.3 [SD 19.9]). Baseline scores for the prespecified lung cancer-specific symptoms of interest—cough (39.6 [SD 27.0] versus 35.9 [SD 26.4]), dyspnoea (29.8 [SD 20.5] versus 28.3 [SD 20.4]) and pain (27.0 [SD 26.9] versus 27.6 [SD 26.5])—were relatively low in both groups, indicating a low to moderate perception of burden for these symptoms. Similar results were observed for the adenocarcinoma population.

3.3. Patient-reported outcomes for the overall population

There was no difference in TTD for cough, dyspnoea or pain between the two treatment arms in the overall population (Table 1). Patients' global health status/QoL was also maintained with nintedanib relative to placebo (Table 1). TTD for gastrointestinal (GI) symptoms of diarrhoea (HR 1.94, 95% CI: 1.67–2.26), decreased appetite (HR 1.17, 95% CI: 1.01–1.35) and nausea and vomiting (HR 1.27, 95% CI: 1.09–1.47) were all significantly shorter in the nintedanib arm compared with placebo, reflecting a greater incidence of these GI adverse events with nintedanib compared with placebo, as previously reported [16].

Table 1.

Time to deterioration of patient-reported global health status/QoL and symptom scales/items.

	Hazard ratio [□] (95% CI)		
	Overall population	Adenocarcinoma population	Patients with adenocarcinoma and time since start of first-line therapy <9 months

	Hazard ratio [□] (95% CI)		
	Overall population	Adenocarcinoma population	Patients with adenocarcinoma and time since start of first-line therapy <9 months
Global health status/QoL	0.95 (0.83–1.10)	0.86 (0.71–1.05)	0.90 (0.69–1.18)
<i>Prespecified lung cancer-specific symptoms of interest</i>			
Cough	0.90 (0.77–1.05)	0.97 (0.78–1.20)	0.90 (0.67–1.19)
Dyspnoea	1.05 (0.91–1.20)	1.04 (0.86–1.26)	0.98 (0.77–1.26)
Pain	0.95 (0.82–1.09)	0.93 (0.76–1.14)	0.80 (0.61–1.04)

CI = confidence interval; QoL = quality of life.

□

Number <1 indicates benefit with nintedanib; number >1 indicates benefit with placebo.

3.4. Patient-reported outcomes for patients with adenocarcinoma

Consistent with findings in the overall population, TTD of cough, dyspnoea or pain for patients with adenocarcinoma showed no difference between the two treatment arms (Table 1 and Fig. 2A–C). A similar pattern was observed for adenocarcinoma patients with a duration since start of first-line therapy <9 months (Table 1). There was a small numerical difference in TTD of global health status/QoL in favour of nintedanib over placebo, but it did not reach statistical significance (Table 1).

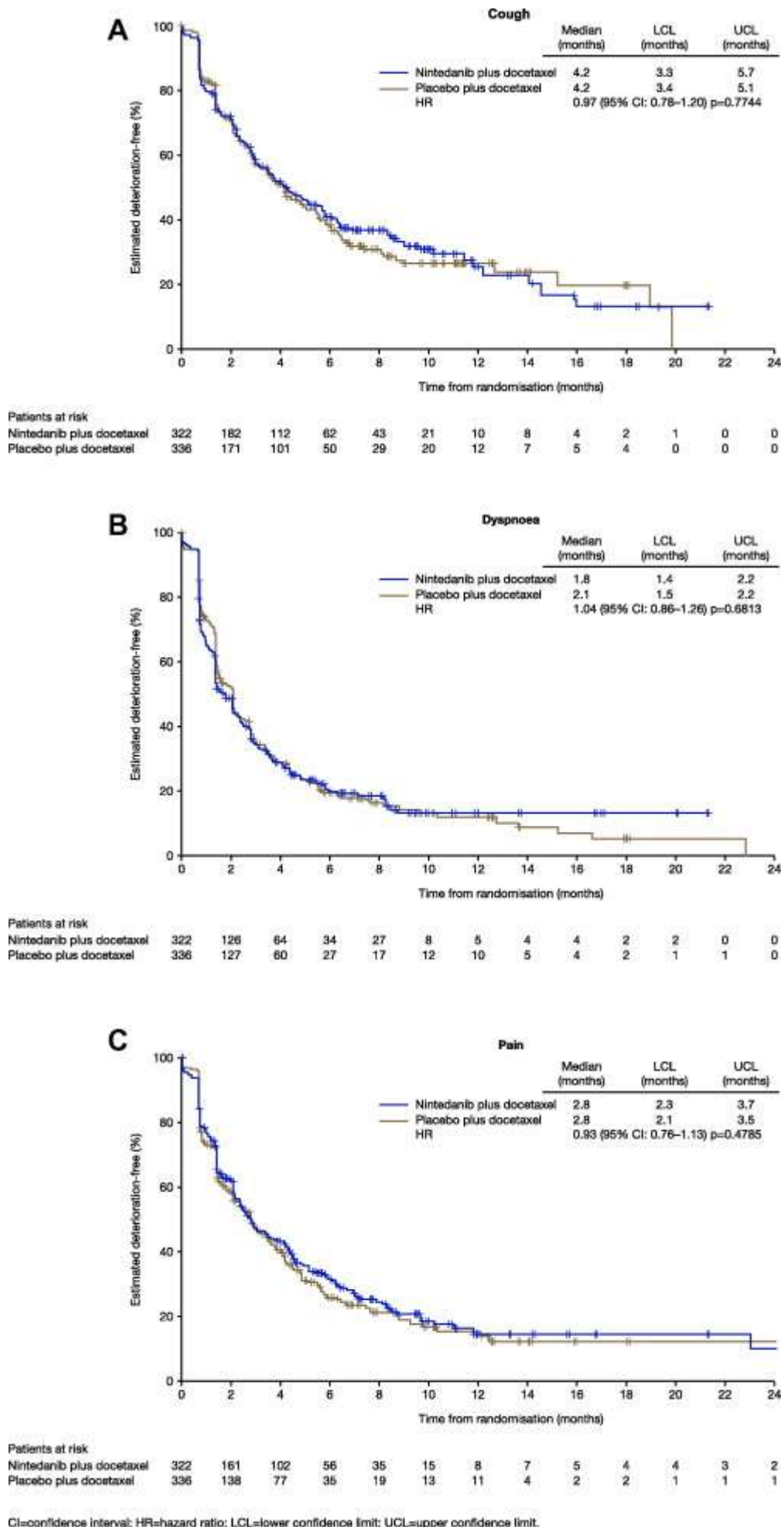


Fig. 2.

Kaplan–Meier curves for time to deterioration of (A) cough, (B) dyspnoea and (C) pain in the adenocarcinoma population.

There were few significant differences between the treatment groups for the TTD of individual QLQ-C30 or QLQ-LC13 questions (Table 2). TTD of ‘pain in arm or shoulder’ and ‘quality of life rating’ were significantly longer with nintedanib versus placebo (Table 2). TTD for items corresponding to the GI symptoms of diarrhoea, decreased appetite and nausea and vomiting were all significantly shorter with nintedanib versus placebo (Table 2).

Table 2.

Time to deterioration of individual EORTC QLQ-C30 and QLQ-LC13 items for the adenocarcinoma population.

Item	Hazard ratio [□] (95% CI)	p-Value
<i>EORTC QLQ-C30</i>		
Q1. Trouble with strenuous activities	0.83 (0.67–1.03)	NS
Q2. Trouble taking a long walk	0.95 (0.77–1.17)	NS
Q3. Trouble taking a short walk	0.92 (0.74–1.14)	NS
Q4. Need to stay in bed	0.88 (0.71–1.08)	NS
Q5. Trouble eating/dressing	0.88 (0.70–1.15)	NS
Q6. Trouble with daily activities	0.96 (0.78–1.18)	NS
Q7. Trouble with leisure activities	1.07 (0.87–1.32)	NS
Q8. Short of breath	1.04 (0.84–1.29)	NS
Q9. Have pain	0.97 (0.78–1.20)	NS
Q10. Need to rest	1.08 (0.87–1.33)	NS
Q11. Insomnia	0.97 (0.78–1.20)	NS
Q12. Felt weak	1.02 (0.83–1.25)	NS
Q13. Appetite loss	1.13 (0.92–1.38)	NS
Q14. Nauseated	1.27 (1.03–1.57)	0.0262
Q15. Vomited	1.42 (1.11–1.81)	0.0047
Q16. Constipation	0.89 (0.70–1.13)	NS
Q17. Diarrhoea	1.86 (1.51–2.29)	<0.0001
Q18. Tired	0.97 (0.79–1.19)	NS
Q19. Pain affecting daily activities	0.94 (0.76–1.17)	NS
Q20. Trouble concentrating	1.08 (0.86–1.35)	NS

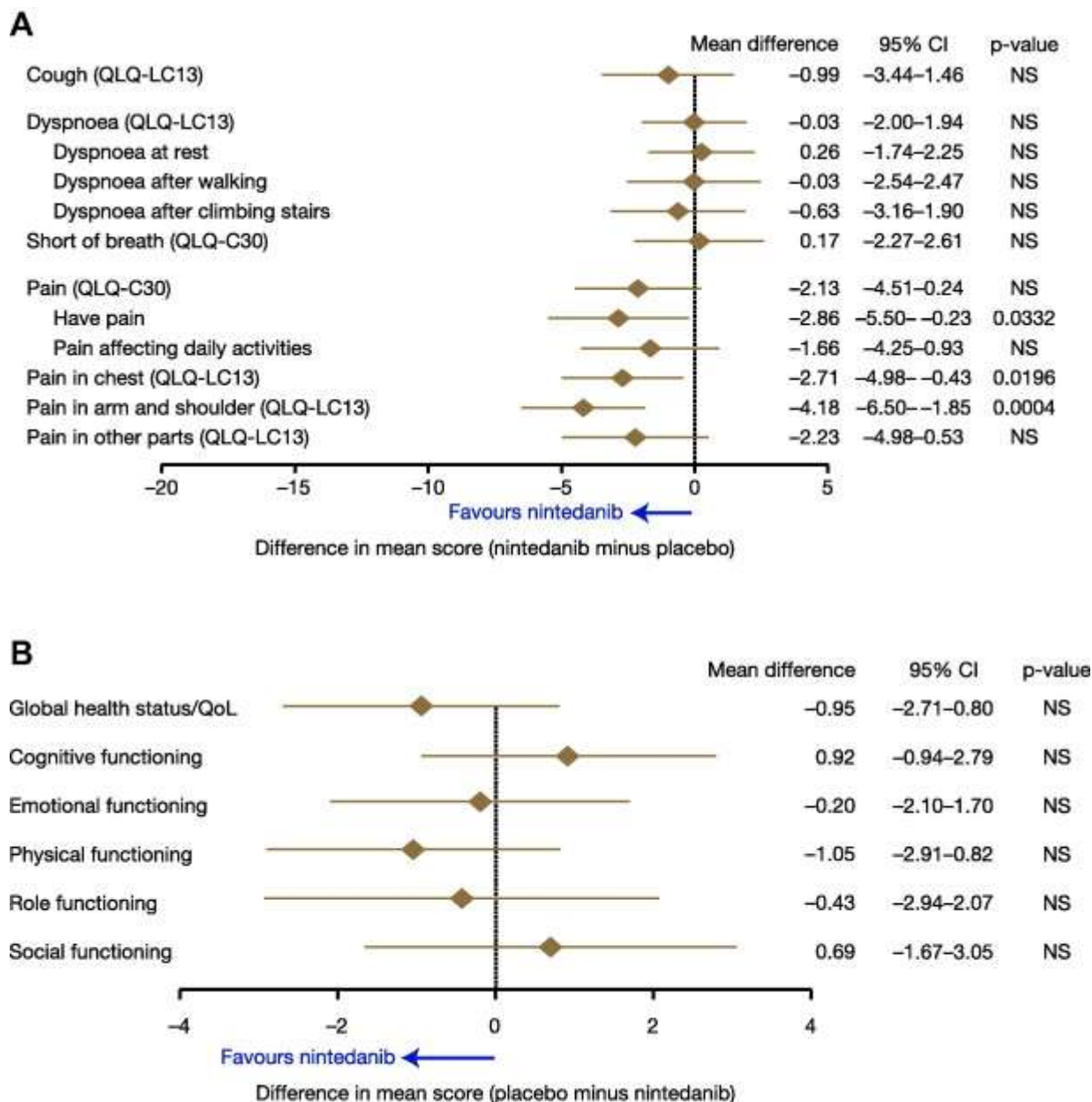
Item	Hazard ratio [□] (95% CI)	p-Value
Q21. Felt tense	1.11 (0.89–1.38)	NS
Q22. Worried	1.03 (0.82–1.28)	NS
Q23. Irritable	1.04 (0.84–1.29)	NS
Q24. Depressed	1.00 (0.80–1.25)	NS
Q25. Trouble remembering	1.08 (0.86–1.35)	NS
Q26. Family life affected	1.05 (0.85–1.30)	NS
Q27. Social life affected	1.02 (0.82–1.26)	NS
Q28. Financial difficulties	1.07 (0.84–1.35)	NS
Q29. Overall health rating	0.92 (0.76–1.12)	NS
Q30. Quality of life rating	0.82 (0.68–1.00)	0.0470
EORTC QLQ-LC13[†]		
Q1. Coughing	0.97 (0.78–1.20)	NS
Q2. Haemoptysis	0.88 (0.66–1.16)	NS
Q3. Dyspnoea (rested)	0.92 (0.73–1.15)	NS
Q4. Dyspnoea (walked)	0.97 (0.79–1.20)	NS
Q5. Dyspnoea (climbed stairs)	1.02 (0.82–1.26)	NS
Q6. Sore mouth	1.04 (0.82–1.31)	NS
Q7. Dysphagia	0.92 (0.72–1.17)	NS
Q8. Peripheral neuropathy	1.06 (0.85–1.31)	NS
Q9. Alopecia	0.85 (0.71–1.03)	NS
Q10. Pain in chest	1.05 (0.84–1.30)	NS
Q11. Pain in arm or shoulder	0.79 (0.63–1.00)	0.0470
Q12. Pain in other part	0.84 (0.67–1.06)	NS

CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; QLQ-C30 = Core Quality of Life Questionnaire, 30 items; LC13 = Lung cancer module, 13 items; NS = not significant.

□ Number <1 indicates benefit with nintedanib; number >1 indicates benefit with placebo.

† Question 13, an optional question regarding concomitant medication, was not analysed.

Longitudinal analysis of symptom scores and subscores for the three key lung cancer symptoms (cough, dyspnoea and pain) showed an overall trend towards improvement with nintedanib in patients with adenocarcinoma compared with placebo (Fig. 3A). Although statistical significance was not achieved, nintedanib-treated patients achieved numerically lower scores than placebo-treated patients for both cough (mean difference: -0.99 [$-3.44, 1.46$]; $p = 0.43$) and pain (mean difference: -2.13 [$-4.51, 0.24$]; $p = 0.08$), with significant differences observed relative to placebo for three of the individual pain items (have pain [QLQ-C30 Q9], pain in chest [QLQ-LC13 Q10] and pain in arm and shoulder [QLQ-LC13 Q11]; Fig. 3A). Very little difference between the two treatments was observed for dyspnoea scores (mean difference: -0.03 [$-2.00, 1.94$]; $p = 0.98$). Longitudinal analysis of global health status/QoL and functional scales showed no significant difference, although there were numerical differences in emotional, physical and role functioning favouring the nintedanib group (Fig. 3B).



CI=confidence interval; NS=not significant; QLQ-C30=Quality of Life Questionnaire, 30 items; LC13=Lung Cancer 13-item supplement; QoL=quality of life.

Fig. 3.

Longitudinal model estimates of differences in (A) symptom scores for cough, dyspnoea and pain and (B) function scores for the adenocarcinoma population.

For the adenocarcinoma population, there was no statistically significant difference in EQ-5D (Fig. 4A) or EQ-VAS (Fig. 4B) between the two treatment arms; similar results were seen for adenocarcinoma patients who had received first-line therapy <9 months previously. Means calculated from AUC scores over time also showed no statistical difference. Estimated effects of disease progression on EQ-5D utilities and changes in EQ-VAS scores revealed that progression was associated with statistically highly significant deterioration in utility ($p < 0.0001$).

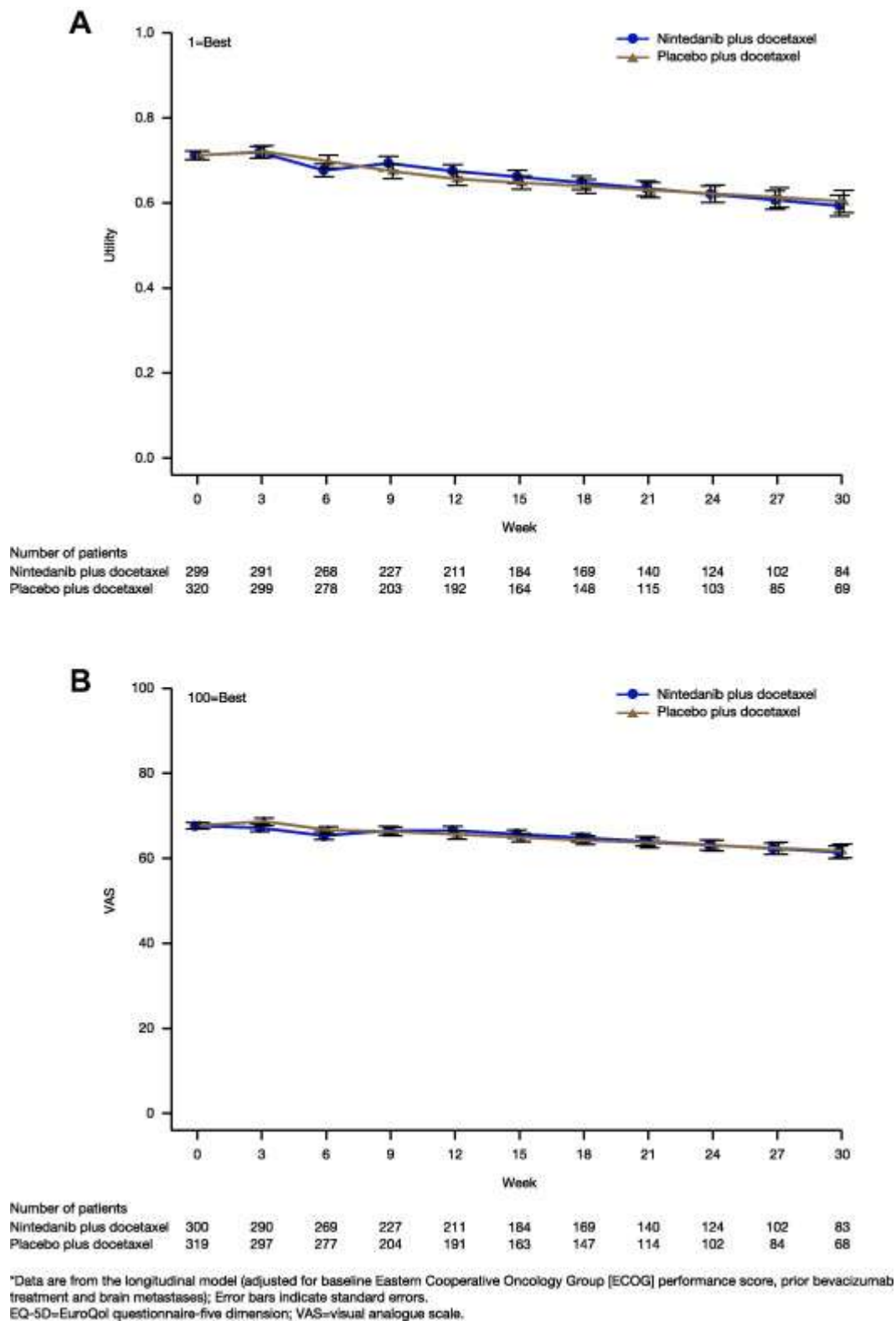


Fig. 4.

Estimated* (A) EQ-5D UK utility scores and (B) EQ-VAS scores over time in the adenocarcinoma population.

3.5. Missing data

Missingness of PRO assessments was weakly correlated to randomised treatment (because of earlier withdrawal in the placebo group), and to baseline cough and dyspnoea scores. Moderate correlations (Kendall's tau between 0.15 and 0.25) were found between missingness and pain, and between missingness and EQ-5D UK utility scores at baseline. Moderate correlations were also found between missingness and cough, dyspnoea and pain as well as EQ-5D UK utility scores at EOT. In all cases, correlations were in the direction of greater missingness with increasing severity of symptoms/worse utility.

4. Discussion

As reported previously [16], the LUME-Lung 1 trial demonstrated a significant improvement in PFS with nintedanib plus docetaxel compared with placebo plus docetaxel as second-line therapy in patients with relapsed/refractory NSCLC independent of histology. Furthermore, a significant and clinically meaningful improvement of 2.3 months in median OS was observed with nintedanib plus docetaxel compared with placebo plus docetaxel in patients with adenocarcinoma [16]. Median OS for adenocarcinoma patients was greater than 1 year with nintedanib plus docetaxel, and a significant improvement of 3.0 months in median OS was also observed for adenocarcinoma patients with a poor prognosis (time since start of first-line therapy <9 months). As already published, adverse events that were more common with nintedanib plus docetaxel versus placebo plus docetaxel included gastrointestinal adverse events (i.e. diarrhoea, nausea, decreased appetite and vomiting) and elevations in liver enzymes [16].

While extending patient survival remains a goal of second-line treatment for NSCLC, the impact of adverse events on patient QoL must be considered in the absence of a potential for remission. This analysis demonstrates that the survival benefits achieved with nintedanib combined with docetaxel in the LUME-Lung 1 trial were not at the expense of patient QoL. No significant differences in the PRO composites for cough, dyspnoea or pain were observed between the treatment groups, which is expected since the predominant effect of nintedanib in the LUME-Lung 1 trial was to stabilise disease rather than promote tumour shrinkage [16]. However, the addition of nintedanib to docetaxel chemotherapy provided significant benefit in some aspects of pain relative to placebo. In the nintedanib plus docetaxel-treated group, there were trends towards improvements in TTD for global health status/QoL in the adenocarcinoma population, and for pain in adenocarcinoma patients with a time since start of first-line therapy <9 months compared with the placebo plus docetaxel-treated group. PRO scores for nausea and vomiting, appetite loss and diarrhoea reflected the adverse event profile of nintedanib in the LUME-Lung 1 trial, showing a greater deterioration in patients who received nintedanib plus docetaxel than in those who received placebo plus docetaxel. However, the comparable global health status/QoL between the groups demonstrates that these GI events with nintedanib did not impair patients' overall health-related QoL.

The absence of deterioration in QoL in the LUME-Lung 1 trial is consistent with the results of other studies of second-line treatment of NSCLC. A recent systematic review of the impact of second-line agents on health-related QoL in NSCLC revealed that the majority of studies reported no significant difference in overall QoL between treatment groups [17]. Statistically significant improvements in overall QoL, domain/symptom QoL, and QoL over time were more frequent in single-arm studies and in studies that included a treatment arm with a less toxic regimen (e.g. monotherapy or regimens with lower intensity). Impairment in QoL due to adverse events related to docetaxel, which was included in both treatment arms of the LUME-Lung 1 study, is likely to have overwhelmed any differences in QoL associated with nintedanib versus placebo in this analysis. Nevertheless, it is reassuring to note that there was no significant deleterious effect on overall QoL with the addition of nintedanib to docetaxel.

Interpretation of the results reported here should consider the strengths and limitations of the analysis. The study protocol prespecified analyses of PROs, and the EORTC QLQ-C30 and QLQ-LC13 instruments used in this study are well validated for the accurate assessment of health-related QoL in patients with lung cancer. Furthermore, high rates of questionnaire completion were achieved throughout the study. Missing data did show a moderate correlation with lung-cancer specific symptoms and QoL utilities indicating a potential for bias. However, sensitivity analyses conducted for PROs of global health status/QoL, cough, dyspnoea, pain and EQ-5D UK utility showed that the longitudinal model was relatively insensitive to alternative assumptions for data missingness (data not shown), indicating that missing responses did not affect data interpretation.

In conclusion, the significant improvement in PFS in the overall population and the significant survival benefit in patients with adenocarcinoma observed with the addition of nintedanib to docetaxel therapy had no detrimental effect on patient-reported QoL relative to the addition of placebo. Thus, the combination of nintedanib and docetaxel represents an attractive second-line treatment option for patients with relapsed/refractory NSCLC, and in particular for patients with adenocarcinoma histology.

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Conflict of interest statement

S.N. has received honoraria from AstraZeneca, Roche, Eli Lilly and Boehringer Ingelheim as a member of advisory boards or as an invited speaker. A.M. has served as a member of advisory boards for Boehringer Ingelheim. J.-Y.D. has received honoraria from AstraZeneca, Roche, Novartis and Boehringer Ingelheim as a member of advisory boards or as an invited speaker. S.O. reports payments to his institute for consulting services. M.K., I.B. and M.L. report no conflicts of interest. J.v.P. reports payments to his institute for consulting services from Daiichi Sankyo, Vertex, Pfizer, Clovis, Novartis and AbbVie. M.R. has received honoraria from AstraZeneca, Roche, Eli Lilly, Novartis, Pfizer, Bristol-Myers Squibb and Boehringer Ingelheim. M.G. has previously served as a board member for a pharmaceutical company and has received support for travel to an

Investigator's Meeting from Boehringer Ingelheim. R.K., J.B., B.G.-M. and I.G. are employees of Boehringer Ingelheim. M.P. has received fees from Boehringer Ingelheim for statistical analyses of the data.

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