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Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial

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Summary

Background The phase 3 LUME-Lung 1 study assessed the efficacy and safety of docetaxel plus nintedanib as second-line therapy for non-small-cell lung cancer (NSCLC).

Methods Patients from 211 centres in 27 countries with stage IIIB/IV recurrent NSCLC progressing after first-line chemotherapy, stratified by ECOG performance status, previous bevacizumab treatment, histology, and presence of brain metastases, were allocated (by computer-generated sequence through an interactive third-party system, in 1:1 ratio), to receive docetaxel 75 mg/m² 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. Investigators and patients were masked to assignment. The primary endpoint was progression-free survival (PFS) by independent central review, analysed by intention to treat after 714 events in all patients. The key secondary endpoint was overall survival, analysed by intention to treat after 1121 events had occurred, in a prespecified stepwise order: first in patients with adenocarcinoma who progressed within 9 months after start of first-line therapy, then in all patients with adenocarcinoma, then in all patients. This trial is registered with ClinicalTrials.gov, number NCT00805194.

Findings Between Dec 23, 2008, and Feb 9, 2011, 655 patients were randomly assigned to receive docetaxel plus nintedanib and 659 to receive docetaxel plus placebo. The primary analysis was done after a median follow-up of 7·1 months (IQR 3·8–11·0). PFS was significantly improved in the docetaxel plus nintedanib group compared with the docetaxel plus placebo group (median 3·4 months [95% CI 2·9–3·9] *vs* 2·7 months [2·6–2·8]; hazard ratio [HR] 0·79 [95% CI 0·68–0·92], p=0·0019). After a median follow-up of 31·7 months (IQR 27·8–36·1), overall survival was significantly improved for patients with adenocarcinoma histology who progressed within 9 months after start of first-line treatment in the docetaxel plus nintedanib group (206 patients) compared with those in the docetaxel plus placebo group (199 patients; median 10·9 months [95% CI 8·5–12·6] *vs* 7·9 months [6·7–9·1]; HR 0·75 [95% CI 0·60–0·92], p=0·0073). Similar results were noted for all patients with adenocarcinoma histology (322 patients in the docetaxel plus nintedanib group and 336 in the docetaxel plus placebo group; median overall survival 12·6 months [95% CI 10·6–15·1] *vs* 10·3 months [95% CI 8·6–12·2]; HR 0·83 [95% CI 0·70–0·99], p=0·0359), but not in the total study population (median 10·1 months [95% CI 8·8–11·2] *vs* 9·1 months [8·4–10·4]; HR 0·94, 95% CI 0·83–1·05, p=0·2720). Grade 3 or worse adverse events that were more common in the docetaxel plus nintedanib group than in the docetaxel plus placebo group were diarrhoea (43 [6·6%] of 652 *vs* 17 [2·6%] of 655), reversible increases in alanine aminotransferase (51 [7·8%] *vs* six [0·9%]), and reversible increases in aspartate aminotransferase (22 [3·4%] *vs* three [0·5%]). 35 patients in the docetaxel plus nintedanib group and 25 in the docetaxel plus placebo group died of adverse events possibly unrelated to disease progression; the most common of these events were sepsis (five with docetaxel plus nintedanib *vs* one with docetaxel plus placebo), pneumonia (two *vs* seven), respiratory failure (four *vs* none), and pulmonary embolism (none *vs* three).

Interpretation Nintedanib in combination with docetaxel is an effective second-line option for patients with advanced NSCLC previously treated with one line of platinum-based therapy, especially for patients with adenocarcinoma.

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Introduction

Lung cancer is the leading cause of cancer deaths worldwide.[1] Most patients are diagnosed with advanced or metastatic disease[2] and although about 70% of patients initially achieve clinical remission or disease stabilisation with first-line platinum-containing therapy, nearly all have disease progression and need second-line therapy.[2,3] Currently approved second-line treatments in non-small-cell lung cancer (NSCLC) consist of monotherapy with docetaxel, erlotinib, or pemetrexed.[2,3]

As part of efforts to further improve treatment for patients with advanced NSCLC, more than 15 large

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randomised phase 3 studies have been done in the past 10 years, but only the BR21[4] and TAX317[5] trials have shown an improvement in overall survival. Several studies of new agents have failed to show significant improvement in overall survival in the second-line setting (appendix pp 7–9). Therefore, there is still a high unmet need for new effective second-line treatments for patients with NSCLC.

Nintedanib (formerly BIBF 1120; Boehringer Ingelheim, Ingelheim, Germany) is a potent, oral angiokinase inhibitor that targets the pro-angiogenic pathways mediated by VEGFR1–3, fibroblast growth factor receptors (FGFR) 1–3, and platelet-derived growth factor receptors (PDGFR) α and β.[6] Additionally, receptor kinases of RET, FLT3, and the Src family are also inhibited (data available from authors on request).[6] Preclinical studies with nintedanib have shown sustained (>30 h) blockade of VEGFR2 in vitro, and delay or arrest of tumour growth in xenograft models of human solid tumours.[6] In phase 1/2 clinical trials, nintedanib showed a manageable safety profile and antitumour activity in patients with solid tumours, including NSCLC.[7,8] Limited drug–drug interactions based on its pharmacokinetic profile and absence of interaction with CYP450 enzymes allows combination of nintedanib with cytotoxic chemotherapies, such as docetaxel or pemetrexed.[9,10] The combination of nintedanib with pemetrexed has been investigated in LUME-Lung 2, a phase 3 trial in the second-line treatment of patients with non-squamous NSCLC.[11,12]

We present the results of the LUME-Lung 1 study, a phase 3 trial that assessed the efficacy and safety of the combination of nintedanib and docetaxel in patients with advanced NSCLC progressing after first-line chemotherapy.

Methods

Patients

We did this study at 211 centres in 27 countries (23 European countries, China, South Korea, India, and South Africa). Adult (≥18 years) patients with histologically or cytologically confirmed stage IIIB/IV recurrent NSCLC (all histologies) who had received one previous chemotherapy regimen were enrolled. Only patients with relapse or failure of one previous first-line chemotherapy regimen were allowed to enter the study. In the case of recurrent disease one additional previous regimen was allowed for adjuvant, neoadjuvant, or neoadjuvant plus adjuvant therapy. Eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and at least one target lesion measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.[13] Patients with active brain metastases (defined as stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, or requiring treatment with anticonvulsants), were excluded, as were those who had received previous docetaxel or VEGFR inhibitors with the exception of bevacizumab. Patients with radiographic evidence of cavitary or necrotic tumours, centrally located tumours with radiographic evidence (CT or MRI) of local invasion of major blood vessels, or a recent history (<3 months) of clinically significant haemoptysis or a major thrombotic or clinically relevant major bleeding event in the past 6 months were also excluded from the study. Detailed eligibility criteria are in appendix pp 11–12.

All patients provided written informed consent. The study complied with the protocol and Declaration of Helsinki, and was done in accordance with good clinical practice or regulatory guidelines and relevant local legislation. The protocol was approved by independent ethics committees or institutional review boards at each centre. An independent data monitoring committee was responsible for periodic assessment (about every 4 months and as necessary) of safety and efficacy data in the study.

Randomisation and masking

Patients were randomised in a 1:1 ratio to docetaxel plus nintedanib or docetaxel plus placebo. Patients were stratified by ECOG performance status (0 *vs* 1), previous bevacizumab treatment (yes *vs* no), histology (squamous *vs* non-squamous), and presence of brain metastases (yes *vs* no). Treatment was assigned by an interactive third-party telephone via an interactive voice response system, or web-based randomisation via interactive web-based response system. Randomisation was done in blocks per country for administrative reasons. "Country" was not predefined as a stratification factor for the primary analysis. The randomisation lists were provided by a completely separate group within the sponsor, the Clinical Trial Support Group, using a validated randomisation number generating system. Patients and investigators were masked to assignment, and none of the individuals directly involved in the conduct and analysis of the study had access to treatment allocation before the final database lock. Appendix p 3 provides details of circumstances that required data unmasking before final database lock.

Procedures

Patients were assigned to docetaxel 75 mg/m² by intravenous infusion on day 1 plus nintedanib 200 mg twice daily orally or matching placebo on days 2–21, every 3 weeks. Treatment was continued until unacceptable adverse events or disease progression. Patients were comedicated with oral corticosteroids for 3 days, starting the day before docetaxel infusion. In case of related adverse events up to two nintedanib dose reductions were permitted, first to 150 mg twice daily and then to 100 mg twice daily. Docetaxel dose reductions were allowed according to label recommendations (appendix p 12). Patients who had to discontinue combination therapy because of docetaxel-related adverse events were allowed to continue nintedanib or placebo monotherapy if they had completed at least four cycles of combination therapy. Patients with unacceptable nintedanib-related adverse events were permitted to continue standard-dose

docetaxel monotherapy. Target lesions were assessed by central independent review using modified RECIST,[13] at baseline (within 4 weeks of randomisation) and every 6 weeks after the first administration of docetaxel. Adverse events, classified according to Common Terminology Criteria for Adverse Events version 3.0, were recorded during the study period and follow-up. A serious adverse event was defined as any adverse event that resulted in death, was immediately life-threatening, resulted in persistent or significant disability or incapacity, needed admission to hospital or prolonged admission to hospital, or was a congenital anomaly or birth defect. Other events were deemed serious if, on the basis of appropriate medical judgment, the event might jeopardise the patient and need medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Patients were monitored for adverse events throughout the study according to the visit schedule defined in the protocol. Patients were assessed for adverse events on a weekly basis during the first cycle, thereafter on the day of docetaxel administration, the week after docetaxel administration, and on demand. In case of an adverse event, patients were monitored more closely until they recovered. Blood samples were taken for laboratory analyses on a weekly basis throughout the first cycle; thereafter, at day of administration of docetaxel and the week after docetaxel administration. For patients assigned to nintedanib monotherapy, safety laboratory tests were only done in case of abnormal laboratory values.

Outcomes

The primary endpoint was progression-free survival (PFS; defined as time from randomisation to progression or death) by central independent review. Overall survival was predefined as a key secondary outcome; other secondary outcomes were investigator-assessed PFS, tumour response by central review and investigator assessment, safety, and tolerability (appendix p 5). Patient-reported quality of life, clinical improvement, and pharmacokinetics of nintedanib were also secondary endpoints; these results are being analysed and will be reported separately.

Statistical analysis

Assuming a median overall survival of 9 months in the control group,[5] about 29 months of recruitment (45–60 patients per month), and 10% loss to follow-up, 1300 patients were to be randomised. The primary endpoint of independently assessed PFS was analysed on an intention-to-treat basis. A stratified log-rank test was used for the primary efficacy analysis at a two-sided 5% level of significance, in all randomised patients. 713 PFS events were needed for the primary analysis, as defined in the protocol, to detect an hazard ratio (HR) of 0·78 with 90% power. A preplanned futility analysis was to be done by the independent data monitoring committee after 50% of the events for the primary PFS analysis had been identified (about 356 events; appendix p 3 provides further details of this futility analysis).

For the final analysis of the prespecified key secondary endpoint of overall survival, 1151 deaths would provide 80% power to detect a HR of 0·85 with the use of a stratified log-rank test and a two-look Lan-DeMets group sequential design with an O'Brien-Fleming-type boundary[14] at a two-sided cumulative 5% level of significance. This analysis could also be done after 48 months and before the 1151 deaths had been accrued, as predefined in the protocol. At the time of the primary PFS analysis and final overall survival analysis, 423 and 1121 deaths, respectively, had occurred. To adjust for the interim analysis, the Lan-DeMets procedure described was applied and the final α level for testing of the final overall survival analysis was 0·04984. A hierarchical procedure was applied to control the type I error rate when analysing the secondary endpoint of overall survival. Formal statistical testing for overall survival was only allowed if the difference in the primary endpoint PFS was significant and confirmed with a PFS analysis at the time of final overall survival analysis. Overall survival was analysed on an intention-to-treat basis in a prespecified stepwise fixed-sequence order: first in patients with adenocarcinoma histology who progressed during or shortly after the end of their first-line treatment (defined as time elapsed since start of first-line therapy of less than 9 months until randomisation into the trial),[15] followed by all patients with adenocarcinoma histology and then in all patients independent of histology. The stepwise analyses of the prespecified key secondary endpoint of overall survival in the LUME-Lung 1 study were introduced prospectively before database lock for overall survival, but after the primary analysis for PFS had been done. The analyses were extended beyond the original specifications of the analysis plan to validate findings from a hypothesis-generating analysis of the LUME-Lung 2 study.[12] At that timepoint the LUME-Lung 1 data were still masked to investigators, patients, and the team involved in the study conduct; all patients in the LUME-Lung 1 study had already been randomised, and most were undergoing follow-up for overall survival (appendix p 3 provides more details of the stepwise analysis). In this analysis, time from the start of first-line therapy was identified as the only prognostic and predictive clinical marker for the treatment effect of nintedanib in combination with pemetrexed in second-line treatment of patients with non-squamous-cell cancer.[11,12,15] Using a cutoff of less than 9 months of time elapsed since start of first-line therapy defined a population of patients with poor prognosis—ie, patients who had progressed during or shortly after first-line therapy.

For both PFS and overall survival, time-to-event distribution was estimated using the Kaplan-Meier

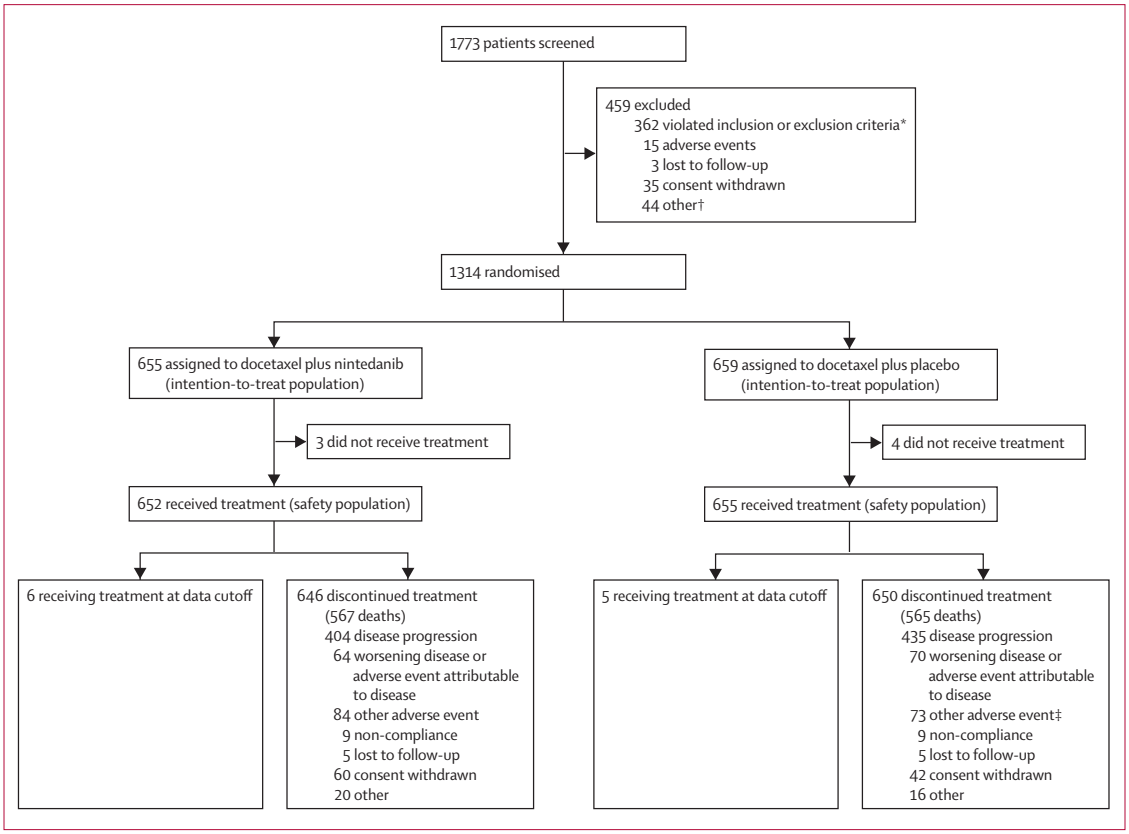

Figure 1: **Trial profile**
*151 (41·7%) patients had active brain metastases; 82 (22·7%) had radiographic evidence of a cavitary or necrotic tumour, or a centrally located tumour, or both; 64 (17·7%) did not have at least one measurable lesion; 26 (7·2%) had increased alanine aminotransferase, increased aspartate aminotransferase, or increased bilirubin. †22 (50·0%) patients had imaging problems (no image, image not approved or delayed); 13 (29·5%) had administrative problems (screening period extended, too ill, died, or refused to participate); eight (18·2%) did not meet eligibility criteria; one (2·3%) was deemed non-eligible with one patient study number but was randomised with another number. ‡One patient had an adverse event (depression) with onset in the screening period that led to treatment discontinuation. This adverse event was not included in the safety analysis of treatment-emergent adverse events leading to discontinuation.

method. The HRs and corresponding 95% CIs were estimated using a stratified Cox proportional hazards model. HRs of less than 1 favour nintedanib. The p value for the stratified log-rank test was obtained from the score test. HRs and treatment interaction p values were produced to investigate the consistency of the treatment effect for predefined baseline characteristics. Appendix p 5 provides further details of the statistical analyses of the primary and secondary efficacy endpoints, including the preplanned sensitivity analyses and exploratory subgroup analyses. All other secondary efficacy endpoints were analysed by intention to treat.

Safety data were analysed descriptively in all treated patients. Adverse events were also categorised into special search categories by pooling Medical Dictionary for Regulatory Activities preferred terms using standardised queries and individually tailored searches. Median follow-up time was calculated using the Kaplan-Meier estimator method proposed by Schemper and Smith with loss of follow-up treated as an event and death treated as a censored observation.[16] All statistical analyses were done using SAS (version 9.2).

This trial is registered with ClinicalTrials.gov, number NCT00805194.

Role of the funding source

The study was jointly designed by academic investigators and representatives of the sponsor, Boehringer Ingelheim. Parexel, a clinical research organisation, was contracted to monitor the study and collect the data. The statistical analyses were done by the sponsor's statistical team (of which BG-M is a member). MR along with RK and BG-M, employees of the sponsor, contributed to the conception and design of the study. MR along with RK, C-NG, JB, and BG-M, employees of the sponsor, had access to the raw data and were involved in data analysis and data interpretation. MR and RK jointly prepared the initial draft of the report and contributed equally. All authors actively contributed to subsequent drafts and provided final approval to submit the report for

publication. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Patients were enrolled between Dec 23, 2008 and Feb 9, 2011. Of the 1773 patients screened, 1314 were randomised (655 to docetaxel plus ninetedanib, 659 to docetaxel plus placebo) and comprised the intention-to-treat population (figure 1). The main reason for exclusion after screening was the presence of newly detected brain metastases. Of the 1314 randomised patients, 1307 went on to receive at least one dose of study drug, and comprised the safety population (figure 1). As of the data cutoff (Feb 15, 2013), six patients in the docetaxel plus nintedanib group and five in the docetaxel plus placebo group were still receiving treatment, either combination therapy (one patient per group) or nintedanib or placebo monotherapy (remaining patients). Demographics and baseline characteristics, including previous response to first-line therapy, were well balanced between the two treatment groups (table 1). There were 658 patients with adenocarcinoma histology and 555 patients with squamous-cell carcinoma. For these major histologies, demographics and baseline characteristics, including the predefined stratification factors, were balanced across treatment groups (data not shown).

The median duration of treatment with nintedanib was 3·4 months (IQR 1·4–6·2) and with placebo was 2·8 months (1·4–5·4). The median number of docetaxel courses administered was four (IQR two to six) in both groups. The mean dose intensity of nintedanib was 92·09% (SD 15·41) and that of placebo was 94·91% (11·50). The mean dose intensity of docetaxel was 98·33% (SD 4·22) in the nintedanib group and 98·74% (3·71) in the placebo group. Median follow-up was 7·1 months (IQR 3·8–11·0) at the time at the primary PFS analysis and 31·7 months (27·8–36·1) at the time of the final overall survival analysis.

PFS, as determined by central independent review, was significantly longer in the docetaxel plus nintedanib group than in the docetaxel plus placebo group (median PFS 3·4 months [95% CI 2·9–3·9] *vs* 2·7 months [2·6–2·8]; HR 0·79 [95% CI 0·68–0·92], p=0·0019; figure 2A). Similar results were noted both in patients with adenocarcinoma and patients with squamous-cell carcinoma (figure 2B, 2C). The results of predefined sensitivity analyses were much the same as the results of the primary PFS analysis (appendix p 13). The effect of nintedanib on PFS was also consistent in the prespecified subgroup analyses (appendix p 21). The HR for PFS was 0·85 (95% CI 0·75–0·96, p=0·0070) at the time of the final overall survival analysis, which included all PFS events (1057 events) collected by that point. At the final analysis, median PFS in the total population of patients was 3·5 months (95% CI 3·0–4·0) in the docetaxel plus nintedanib group versus 2·7 months (2·6–2·8) in the docetaxel plus placebo group.

	Docetaxel plus nintedanib (n=655)	Docetaxel plus placebo (n=659)
Age (years)	60 (53–67)	60 (54–66)
Age ≥65 years	200 (30·5%)	214 (32·5%)
Sex		
Men	476 (72·7%)	479 (72·7%)
Women	179 (27·3%)	180 (27·3%)
Race		
White	533 (81·4%)	530 (80·4%)
Asian	116 (17·7%)	123 (18·7%)
Black or African American	4 (0·6%)	5 (0·8%)
American Indian or Alaskan native	2 (0·3%)	1 (0·2%)
ECOG performance status*		
0	187 (28·5%)	189 (28·7%)
1	467 (71·3%)	470 (71·3%)
Smoking history		
Current or ex-smoker	490 (74·8%)	498 (75·6%)
Never smoker	165 (25·2%)	161 (24·4%)
Clinical stage at diagnosis (UICC/AJCC)†		
Stage <IIIB	105 (16·0%)	105 (15·9%)
Stage IIIB	148 (22·6%)	146 (22·2%)
Stage IV	399 (60·9%)	408 (61·9%)
Missing	3 (0·5%)	0
Metastases at screening	588 (89·8%)	605 (91·8%)
Brain metastases at baseline	38 (5·8%)	38 (5·8%)
Histology‡		
Squamous-cell carcinoma	276 (42·1%)	279 (42·3%)
Adenocarcinoma	322 (49·2%)	336 (51·0%)
Large-cell carcinoma	25 (3·8%)	16 (2·4%)
Combination	4 (0·6%)	5 (0·8%)
Other	28 (4·3%)	23 (3·5%)
Baseline sum of longest diameters§ (mm)	81·3 (49·0–123·4)	75·8 (48·5–121·0)
Months since first diagnosis	8·8 (5·4–13·6)	8·6 (5·4–13·6)
Previous surgery	143 (21·8%)	142 (21·5%)
Previous radiotherapy	191 (29·2%)	188 (28·5%)
Previous first-line therapy¶	646 (98·6%)	651 (98·8%)
Platinum-based therapy	628 (97·2%)	636 (97·7%)
Non-platinum-based therapy	18 (2·8%)	15 (2·3%)
First-line bevacizumab	27 (4·1%)	23 (3·5%)
Best response to first-line therapy		
Complete response	13 (2·0%)	19 (2·9%)
Partial response	214 (33·1%)	177 (27·2%)
Stable disease	249 (38·5%)	249 (38·2%)
Progressive disease	127 (19·7%)	139 (21·4%)
Not known or unavailable	43 (6·7%)	67 (10·3%)

Data are median (IQR) or n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. UICC/AJCC=Union Internationale Contre le Cancer/American Joint Committee on Cancers (6th or 7th edition). *One patient receiving docetaxel plus nintedanib had an ECOG performance status of 2. †The 6th edition was used to stage 709 of 1314 patients (54·0%) and the 7th edition was used to stage 602/1314 patients (45·8%). ‡Histological classification was missing for one patient receiving docetaxel plus placebo; however, at stratification via interactive voice response system it was indicated that this patient had squamous-cell carcinoma. §Tumour assessment by central independent review. ¶Nine patients in the docetaxel plus nintedanib group and eight patients in the docetaxel plus placebo group did not receive first-line therapy.

Table 1: **Demographics and baseline disease characteristics**

In the predefined population of patients with adenocarcinoma who had progressed within 9 months after start of first-line therapy, overall survival was significantly longer in the docetaxel plus nintedanib group than in the docetaxel plus placebo group (median overall survival 10·9 months [95% CI 8·5–12·6] *vs* 7·9 months [6·7–9·1]; HR 0·75 [95% CI 0·60–0·92], p=0·0073; figure 3A). Notably, in this population of patients, median PFS was significantly longer in the docetaxel plus nintedanib group, both at the time of the primary PFS analysis (3·6 months [95% CI 2·8–4·3] *vs* 1·5 months [1·4–2·6]; HR 0·63 [95% CI 0·48–0·83], p=0·0008]) and at the time of the final overall survival analysis (4·2 months [95% CI 3·2–4·4] *vs* 1·5 months [1·4–2·6]; HR 0·68 [95% CI 0·54–0·84], p=0·0005).

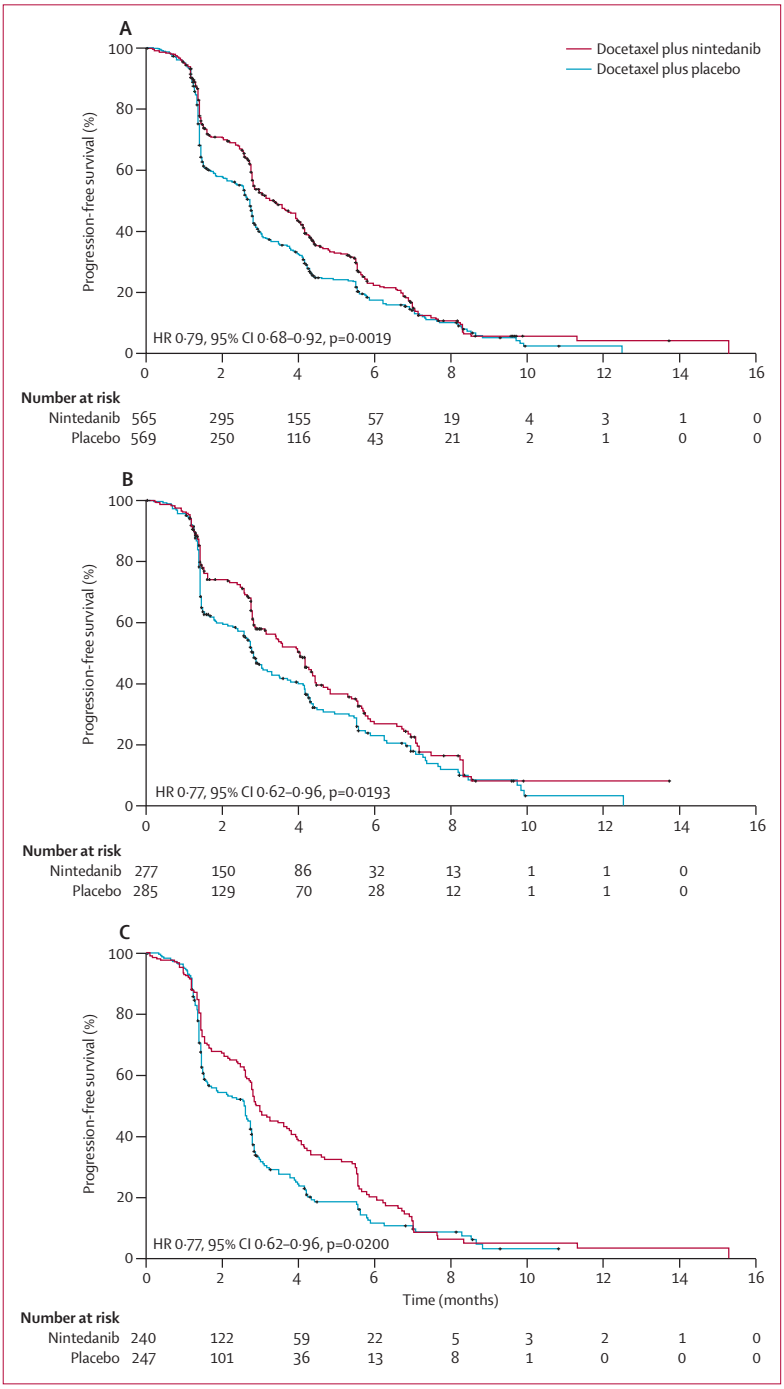

Figure 2: **Kaplan-Meier curves for progression-free survival by central independent review at the time of primary analysis**
(A) Total population. (B) Patients with adenocarcinoma histology. (C) Patients with squamous-cell carcinoma histology. Patients without documented disease progression or death were censored at the last tumour assessment. HR=hazard ratio.

In all patients with adenocarcinoma, overall survival was significantly longer in the docetaxel plus nintedanib group than in the docetaxel plus placebo group (median overall survival 12·6 months [95% CI 10·6–15·1] months *vs* 10·3 [95% CI 8·6–12·2] months; HR 0·83 [95% CI 0·70–0·99], p=0·0359); the Kaplan-Meier survival curves separate at 6 months, continuing throughout the 36-month study observation period (figure 3B). 1 year overall survival was 52·7% (95% CI 46·8–57·9) in the docetaxel plus nintedanib group compared with 44·7% (38·9–49·8) in the docetaxel plus placebo group; 2 year overall survival was 25·7% (95% CI 20·5–30·2) in the docetaxel plus nintedanib group compared with 19·1% (14·4–23·2) in the docetaxel plus placebo group. The effect of nintedanib on overall survival was consistent in most of the prespecified subgroup analyses of patients with adenocarcinoma histology (figure 4B).

In the total population of patients (all histologies), there was no difference in overall survival between the two groups: median overall survival was 10·1 months (95% CI 8·8–11·2) in the docetaxel plus nintedanib group compared with 9·1 (8·4–10·4) months in the docetaxel plus placebo group (HR 0·94 [95% CI 0·83–1·05], p=0·2720; figure 3C). After adjustment, as predefined in the protocol, for the prognostic factor of baseline sum of longest diameters of target lesions,[17] a difference in overall survival was noted (HR 0·88 [95% CI 0·78–0·99], p=0·0365; appendix p 13). The investigation of the interaction between treatment and this variable showed that greater tumour burden was associated with a greater treatment effect for docetaxel plus nintedanib.[18] No imbalance of this baseline variable between the groups was identified (table 1). The effect of nintedanib on PFS and overall survival was consistent in most of the prespecified subgroup analyses of patients with adenocarcinoma histology (figure 4) and for all patients (appendix p 21). There was no difference in overall survival between the two groups for patients with squamous-cell carcinoma (HR 1·01 [95% CI 0·85–1·21], p=0·8907; appendix p 22).

An exploratory analysis was done in the subset of adenocarcinoma patients most refractory to first-line treatment. These patients were reported by the investigators to have achieved no better than progressive disease in response to first-line therapy. In these 117 patients (53 in the docetaxel plus nintedanib group

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and 64 in the docetaxel plus placebo group), overall survival was longer in the docetaxel plus nintedanib group compared with the docetaxel plus placebo group (median overall survival 9·8 months [95% CI 6·1–15·5] *vs* 6·3 months [5·0–8·1]; HR 0·62 [95% CI 0·41–0·94], p=0·0246). The HR for PFS at the time of the final overall survival analysis was 0·67 (95% CI 0·43–1·04, p=0·0725) for this subgroup of patients; median PFS was 4·2 months (95% CI 2·8–4·5) in the docetaxel plus nintedanib group versus 1·6 months (95% CI 1·4–2·8) in the docetaxel plus placebo group.

Subsequent anticancer treatments were balanced between both groups across all populations of patients; slightly fewer patients with squamous-cell carcinoma (265 of 555 [48%]) received follow-up anticancer drugs than did patients with adenocarcinoma (367 of 658 [56%]; appendix p 14).

Investigator-assessed PFS results were much the same as those of the independent central review analysis (appendix p 6). Objective responses by central review at the time of the final analysis were noted in much the same proportion of patients in the two groups for the overall study population (29 of 655 [4·4%] with docetaxel plus nintedanib *vs* 22 of 659 [3·3%] with docetaxel plus placebo; odds ratio [OR] 1·34 [95% CI 0·76–2·39], p=0·3067) and in patients with adenocarcinoma (15 of 322 [4·7%] *vs* 12 of 336 patients [3·6%]; OR 1·32 [95% CI 0·61–2·93], p=0·4770), but were more common in patients with adenocarcinoma and time since start of first-line therapy of less than 9 months in the docetaxel plus nintedanib group than in the docetaxel plus placebo group (ten of 206 [4·9%] *vs* three of 199 [1·5%]; OR 3·54, 95% CI 1·06–16·03, p=0·0393; table 2). Investigator-assessed tumour response results were much the same as those of the central review analysis (appendix p 6). Disease control was more common in the docetaxel plus nintedanib group than in the docetaxel plus placebo group for all patients (354 of 655 [54·0%] *vs* 272 of 659 [41·3%]; OR 1·68 [95% CI 1·35–2·09], p<0·0001), in patients with adenocarcinoma (194 of 322 [60·2%] *vs* 148 of 336 [44·0%]; OR 1·93 [95% CI 1·42–2·64], p<0·0001), and in patients with adenocarcinoma and time since start of first-line therapy of less than 9 months (122 of 206 [59·2%] *vs* 66 of 199 [33·2%]; OR 2·90 [95% CI 1·94–4·38]; p=0·0009). Similarly, in patients with squamous-cell carcinoma, disease control was more common in the docetaxel plus nintedanib group than in the docetaxel plus placebo group (136 of 276 [49·3%] *vs* 99 of 279 [35·5%]; OR 1·78 [95% CI 1·26–2·51], p<0·0001), although the proportion of patients who achieved an objective response was much the same in both groups (13 of 276 [4·7%] *vs* seven of 279 patients [2·5%]; OR 1·93 [95% CI 0·78–5·20], p=0·1594; appendix p 15).

Docetaxel plus nintedanib also led to a significant decrease from baseline in tumour size of the target lesions in the total population of patients, in patients with adenocarcinoma, and in patients with adenocarcinoma and time since start of first-line treatment of less than 9 months (appendix p 23).

Adverse events that were more common (≥5% difference) in the docetaxel plus nintedanib group than

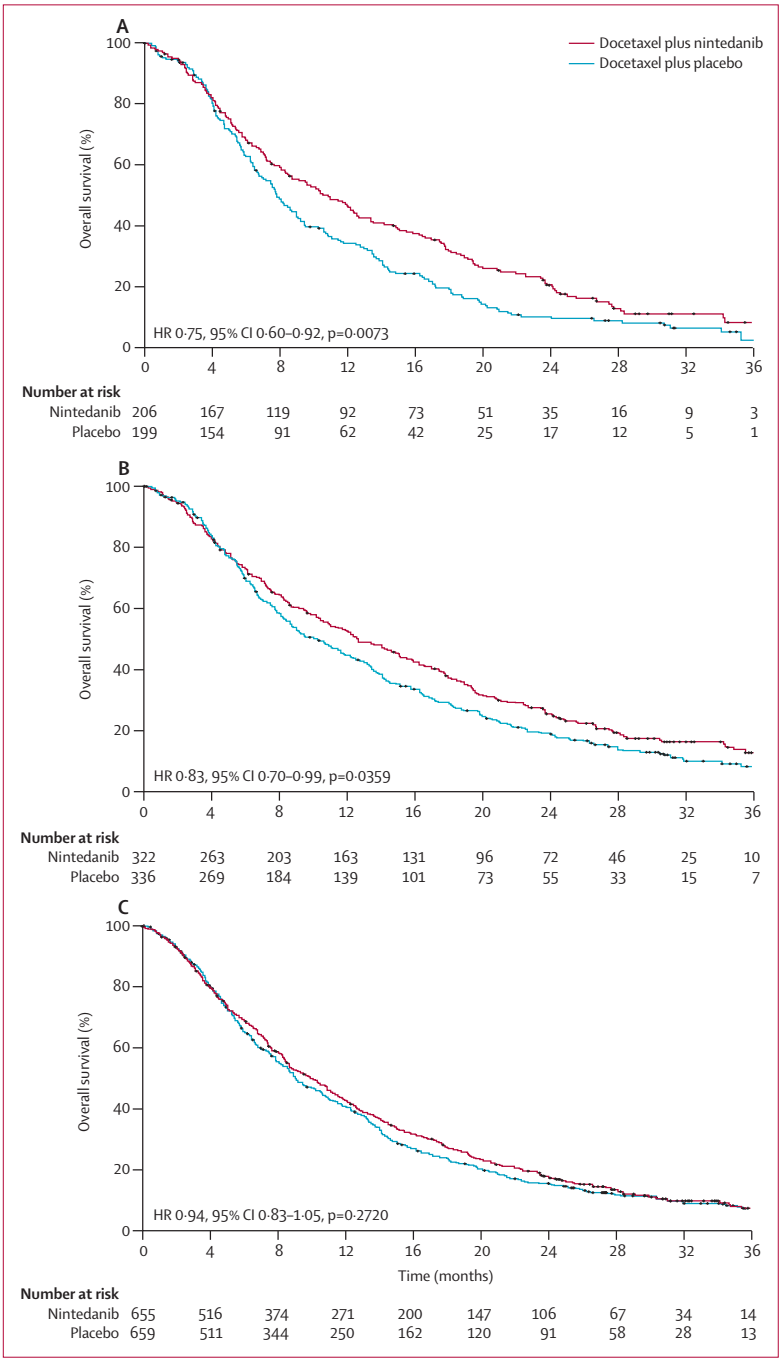

***Figure 3*: Kaplan-Meier curves for overall survival at the time of final analysis**
(A) Patients with adenocarcinoma histology and time since start of first-line therapy of less than 9 months. (B) All patients with adenocarcinoma histology. (C) Total population. Patients without documented death were censored at the date of last contact when the patient was known to be alive. HR=hazard ratio.

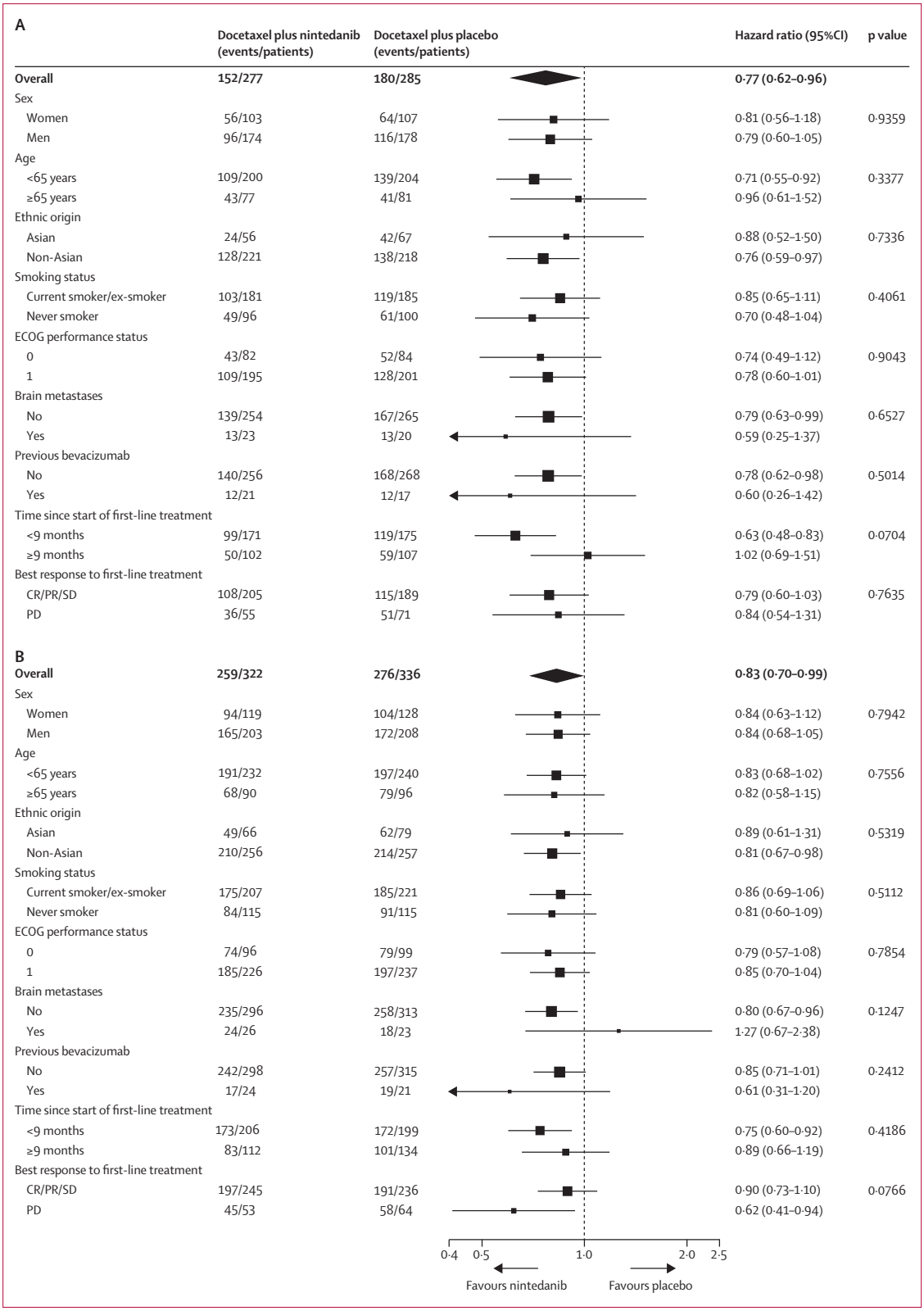

Figure 4: **Effect of treatment on survival in subgroups by baseline characteristics in patients with adenocarcinoma histology**
(A) Progression-free survival at time of primary analysis. (B) Overall survival at time of final analysis. Bubble size represents number of events. ECOG=Eastern Cooperative Oncology Group. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease.

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the docetaxel plus placebo group were: diarrhoea (all grades, 276 of 652 [42·3%] *vs* 143 of 655 patients [21·8%]; grade ≥3, 43 [6·6%] *vs* 17 [2·6%]), increases in alanine aminotransferase (all grades, 186 [28·5%] *vs* 55 [8·4%]; grade ≥3, 51 [7·8%] *vs* six [0·9%]), nausea (all grades, 158 [24·2%] *vs* 118 [18·0%]; grade ≥3, five [0·8%] *vs* six [0·9%]), increases in aspartate aminotransferase (all grades, 147 [22·5%] *vs* 43 [6·6%]; grade ≥3, 22 [3·4%] *vs* three [0·5%]), decreased appetite (all grades, 145 [22·2%] *vs* 102 [15·6%]; grade ≥3, nine [1·4%] *vs* eight [1·2%]), and vomiting (all grades, 110 [16·9%] *vs* 61 [9·3%]; grade ≥3, five [0·8%] *vs* three [0·5%]; table 3). Most of these adverse events were manageable with supportive treatment or dose reduction.

121 of 650 (18·6%) patients in the docetaxel plus nintedanib group and 41 of 650 (6·3%) patients in the docetaxel plus placebo group needed at least one dose reduction of nintedanib or placebo. Docetaxel dose reductions were needed in 102 of 652 (15·6%) patients in the docetaxel plus nintedanib group and in 78 of 655 (11·9%) patients in the docetaxel plus placebo group. Haematological adverse events were the main reason for docetaxel dose reduction and gastrointestinal adverse events and increases in liver enzymes accounted for most of the nintedanib dose reductions. Increases in liver enzymes were reversible. 75 of 652 (11·5%) patients in the docetaxel plus nintedanib group had an adverse event of grade 3 or higher leading to dose reductions of nintedanib, compared with 26 of 655 (4·0%) patients in the docetaxel plus placebo group requiring dose reductions of placebo. Analyses of adverse events of special interest for adverse events commonly associated with antiangiogenic agents, such as hypertension, bleeding, and gastrointestinal perforation, were much the same in both groups (appendix p 18).

Adverse events led to permanent discontinuation of last study drug in 148 of 652 (22·7%) patients in the docetaxel plus nintedanib group and in 142 of 655 (21·7%) patients in the docetaxel plus placebo group. Adverse events leading to death related to disease progression occurred in 72 of 652 (11·0%) patients in the docetaxel plus nintedanib group and in 52 of 655 (7·9%) patients in the docetaxel plus placebo group. Adverse events leading to death possibly unrelated to disease progression were reported in 35 of 652 (5·4%) patients in the docetaxel plus nintedanib group and in 25 of 655 (3·8%) patients in the docetaxel plus placebo group. Fatal adverse events possibly unrelated to disease progression occurring in more than two patients in either group were sepsis (five patients in the docetaxel plus nintedanib group *vs* one patient in the docetaxel plus placebo group), pneumonia (two *vs* seven), respiratory failure (four *vs* none), and pulmonary embolism (none *vs* three; appendix pp 17–18). The safety profile of docetaxel plus nintedanib in patients with adenocarcinoma was much the same as that for the total study population (appendix pp 21–22).

	Docetaxel plus nintedanib	Docetaxel plus placebo
Total study population*		
Objective response	29 (4·4%)	22 (3·3%)
Disease control	354 (54·0%)†	272 (41·3%)
Best confirmed tumour response		
Complete response	0	1 (0·2%)
Partial response	29 (4·4%)	21 (3·2%)
Stable disease	325 (49·6%)	250 (37·9%)
Progressive disease	200 (30·5%)	298 (45·2%)
Other‡	101 (15·4%)	89 (13·5%)
Patients with adenocarcinoma§		
Objective response	15 (4·7%)	12 (3·6%)
Disease control	194 (60·2%)¶	148 (44·0%)
Best confirmed tumour response		
Complete response	0	0
Partial response	15 (4·7%)	12 (3·6%)
Stable disease	179 (55·6%)	136 (40·5%)
Progressive disease	87 (27·0%)	147 (43·8%)
Other‡	41 (12·7%)	41 (12·2%)
Patients with adenocarcinoma and time since start of first-line therapy <9 months‖		
Objective response	10 (4·9%)**	3 (1·5%)
Disease control	122 (59·2%)††	66 (33·2%)
Best confirmed tumour response		
Complete response	0	0
Partial response	10 (4·9%)	3 (1·5%)
Stable disease	112 (54·4%)	63 (31·7%)
Progressive disease	58 (28·2%)	107 (53·8%)
Other‡	26 (12·6%)	26 (13·1%)

By central independent review at the time of final overall survival analysis. *n=655 for docetaxel plus nintedanib; n=659 for docetaxel plus placebo. †Odds ratio (OR; by logistic regression adjusted for baseline Eastern Cooperative Oncology Group [ECOG] performance status) for disease control in overall population was 1·68 (95% CI 1·35–2·09); p<0·0001. ‡Other includes patients with stable disease within 6 weeks and non-evaluable responses. §n=322 for docetaxel plus nintedanib; n=336 for docetaxel plus placebo. ¶OR (by logistic regression adjusted for baseline ECOG performance status) for disease control in patients with adenocarcinoma was 1·93 (95% CI 1·42–2·64); p<0·0001. ‖n=206 for docetaxel plus nintedanib; n=199 for docetaxel plus placebo. **OR (by logistic regression adjusted for baseline ECOG performance status) for objective response in patients with adenocarcinoma and time since start of first-line therapy of less than 9 months was 3·54 (95% CI 1·06–16·03); p=0·0393. ††OR (by logistic regression adjusted for baseline ECOG performance status) for disease control in patients with adenocarcinoma and time since start of first-line therapy of less than 9 months was 2·90 (95% CI 1·94–4·38); p<0·0001.

Table 2: **Confirmed best tumour response and disease control according to modified Response Evaluation Criteria in Solid Tumors version 1.0[18]**

Discussion

Docetaxel plus nintedanib significantly improved PFS independently of histology in patients with advanced recurrent NSCLC who had progressed following first-line chemotherapy, and significantly prolonged overall survival of patients with adenocarcinoma, including patients with poor prognosis (ie, those who had progressed within 9 months of start of first-line therapy). Adverse events that were substantially more common in the docetaxel plus nintedanib group than the docetaxel plus placebo group were diarrhoea, increased alanine aminotransferase, and increased aspartate aminotransferase. 35 (5·4%) fatal adverse events possibly unrelated to disease progression occurred in the docetaxel plus nintedanib group compared with 25 (3·8%) in the docetaxel plus placebo group.

	Docetaxel plus nintedanib (n=652)					Docetaxel plus placebo (n=655)				
	All grades	Grade 1–2	Grade 3	Grade 4	Grade 5	All grades	Grade 1–2	Grade 3	Grade 4	Grade 5
Any serious adverse event	224 (34·4%)	20 (3·1%)	48 (7·4%)	49 (7·5%)	107 (16·4%)	206 (31·5%)	31 (4·7%)	58 (8·9%)	39 (6·0%)	77 (11·8%)
Any adverse event*	610 (93·6%)	145 (22·2%)	138 (21·2%)	220 (33·7%)	107 (16·4%)	609 (93·0%)	188 (28·7%)	139 (21·2%)	205 (31·3%)	77 (11·8%)
Diarrhoea	276 (42·3%)	233 (35·7%)	39 (6·0%)	3 (0·5%)	1 (0·2%)	143 (21·8%)	126 (19·2%)	16 (2·4%)	1 (0·2%)	0
Decreased neutrophils	242 (37·1%)	33 (5·1%)	59 (9·0%)	150 (23·0%)	0	235 (35·9%)	39 (6·0%)	57 (8·7%)	139 (21·2%)	0
Fatigue	198 (30·4%)	161 (24·7%)	32 (4·9%)	4 (0·6%)	1 (0·2%)	176 (26·9%)	151 (23·1%)	21 (3·2%)	3 (0·5%)	0
Increased ALT	186 (28·5%)	135 (20·7%)	51 (7·8%)	0	0	55 (8·4%)	49 (7·5%)	6 (0·9%)	0	0
Decreased white blood cell count	160 (24·5%)	53 (8·1%)	75 (11·5%)	32 (4·9%)	0	160 (24·4%)	60 (9·2%)	73 (11·1%)	27 (4·1%)	0
Nausea	158 (24·2%)	153 (23·5%)	5 (0·8%)	0	0	118 (18·0%)	112 (17·1%)	6 (0·9%)	0	0
Increased AST	147 (22·5%)	125 (19·2%)	22 (3·4%)	0	0	43 (6·6%)	40 (6·1%)	3 (0·5%)	0	0
Decreased appetite	145 (22·2%)	136 (20·9%)	7 (1·1%)	2 (0·3%)	0	102 (15·6%)	94 (14·4%)	7 (1·1%)	0	1 (0·2%)
Dyspnoea	124 (19·0%)	92 (14·1%)	14 (2·1%)	3 (0·5%)	15 (2·3%)	110 (16·8%)	75 (11·5%)	21 (3·2%)	2 (0·3%)	12 (1·8%)
Vomiting	110 (16·9%)	105 (16·1%)	4 (0·6%)	1 (0·2%)	0	61 (9·3%)	58 (8·9%)	3 (0·5%)	0	0
Alopecia	107 (16·4%)	106 (16·3%)	1 (0·2%)	0	0	119 (18·2%)	118 (18·0%)	0	0	0
Cough	99 (15·2%)	93 (14·3%)	5 (0·8%)	0	1 (0·2%)	110 (16·8%)	106 (16·2%)	4 (0·6%)	0	0
Neutropenia	90 (13·8%)	11 (1·7%)	21 (3·2%)	58 (8·9%)	0	94 (14·4%)	15 (2·3%)	19 (2·9%)	60 (9·2%)	0
Pyrexia	83 (12·7%)	78 (12·0%)	3 (0·5%)	2 (0·3%)	0	98 (15·0%)	96 (14·7%)	2 (0·3%)	0	0
Decreased haemoglobin	73 (11·2%)	64 (9·8%)	7 (1·1%)	2 (0·3%)	0	79 (12·1%)	65 (9·9%)	12 (1·8%)	2 (0·3%)	0
Constipation	35 (5·4%)	35 (5·4%)	0	0	0	76 (11·6%)	73 (11·1%)	3 (0·5%)	0	0
Asthenia	58 (8·9%)	43 (6·6%)	13 (2·0%)	0	2 (0·3%)	64 (9·8%)	54 (8·2%)	8 (1·2%)	1 (0·2%)	1 (0·2%)
Chest pain	56 (8·6%)	46 (7·1%)	4 (0·6%)	3 (0·5%)	2 (0·3%)	62 (9·5%)	48 (7·3%)	10 (1·5%)	4 (0·6%)	0
Febrile neutropenia	48 (7·4%)	2 (0·3%)	17 (2·6%)	29 (4·4%)	0	32 (4·9%)	1 (0·2%)	14 (2·1%)	17 (2·6%)	0
Anaemia	35 (5·4%)	28 (4·3%)	5 (0·8%)	2 (0·3%)	0	49 (7·5%)	39 (6·0%)	8 (1·2%)	1 (0·2%)	1 (0·2%)
Pneumonia	33 (5·1%)	13 (2·0%)	14 (2·1%)	3 (0·5%)	3 (0·5%)	36 (5·5%)	14 (2·1%)	14 (2·1%)	0	8 (1·2%)
Hypokalaemia	27 (4·1%)	17 (2·6%)	6 (0·9%)	4 (0·6%)	0	20 (3·1%)	10 (1·5%)	9 (1·4%)	1 (0·2%)	0
Increased GGT	26 (4·0%)	16 (2·5%)	10 (1·5%)	0	0	6 (0·9%)	5 (0·8%)	1 (0·2%)	0	0
Leucopenia	26 (4·0%)	7 (1·1%)	13 (2·0%)	6 (0·9%)	0	34 (5·2%)	18 (2·7%)	12 (1·8%)	4 (0·6%)	0
Hyperglycaemia	24 (3·7%)	17 (2·6%)	7 (1·1%)	0	0	30 (4·6%)	20 (3·1%)	10 (1·5%)	0	0
Hyponatraemia	22 (3·4%)	8 (1·2%)	12 (1·8%)	2 (0·3%)	0	13 (2·0%)	2 (0·3%)	10 (1·5%)	1 (0·2%)	0
Pleural effusion	15 (2·3%)	7 (1·1%)	5 (0·8%)	1 (0·2%)	2 (0·3%)	19 (2·9%)	10 (1·5%)	6 (0·9%)	1 (0·2%)	2 (0·3%)
Increased hepatic enzyme	10 (1·5%)	3 (0·5%)	6 (0·9%)	1 (0·2%)	0	0	0	0	0	0

ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=gamma-glutamyltransferase. *Reported as adverse events of all grades occurring in at least 10% of patients in either treatment group or adverse events of grade 3 or 4 occurring in more than 1% of patients.

Table 3: **Overview of adverse events, classified by Common Terminology Criteria for Adverse Events (version 3.0) in all patients who received at least one dose of study drug**

More than 15 second-line phase 3 studies have been done in the past decade (appendix pp 7–9). Taken together, except for the BR.21 trial[4] investigating erlotinib versus placebo and the TAX 317 trial[5] investigating docetaxel versus best supportive care, none of these studies have shown a significant improvement in overall survival, either for the total population of patients or for any of the major histological subtypes, such as adenocarcinoma or squamous-cell carcinoma. This lack of success includes studies of targeted agents in combination with standard second-line therapy, such as ZODIAC,[19] VITAL,[20] BETA,[21] and SUN1087[22] (appendix pp 7–9).

As far as we are aware, the present study is the first trial in the second-line setting combining a targeted agent with chemotherapy to show a survival benefit, with median overall survival surpassing 1 year in patients with adenocarcinoma NSCLC versus an active comparator (panel; appendix pp 7–9). The median overall survival for the docetaxel plus placebo group of 10·3 months in the adenocarcinoma population is much the same as that reported for patients in the docetaxel control group in the ZODIAC study (10 months),[19] VITAL study (10·4 months),[20] JMEI study (7·9 months),[23] or the TAX317 study (7·5 months).[5] Moreover, the post-study treatments in the two groups in the present study were balanced in the total study population, in the total adenocarcinoma population, in patients with adenocarcinoma and time since start of first-line treatment of less than 9 months (appendix p 14), and in patients with squamous-cell carcinoma histology, suggesting that the recorded prolongation of median overall survival is attributable to a treatment effect of nintedanib in combination with docetaxel and not to an underperforming control group or to post-study treatments. EGFR biomarker testing was not standard clinical practice at the time that the study was done. The small group of Asian patients (18%) was

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similarly distributed between the groups and there was no imbalance of subsequent treatment with EGFR inhibitors between the groups.

The improvement in overall survival for patients with adenocarcinoma in the present study was consistent among most analysed subgroups. Furthermore, the predefined sensitivity analysis of overall survival confirmed the robustness of the results (appendix p 13). To the best of our knowledge, none of the antiangiogenic compounds that have been tested in the second-line setting, such as vandetanib,[18,24] sunitinib,[21] or aflibercept,[19] have shown a significant overall survival benefit, despite PFS improvements. Other trials assessing antiangiogenic compounds in the first-line setting, such as sorafenib,[25,26] cediranib,[27] or motesanib,[28] in combination with chemotherapy have also failed to show any effect on overall survival in advanced NSCLC, either in the main study population or histological subtypes. Up to now, bevacizumab was the only antiangiogenic drug shown to prolong overall survival in advanced NSCLC, when combined with chemotherapy (paclitaxel or carboplatin) in the first-line setting.[29]

Our understanding of NSCLC has improved substantially in recent years. Nowadays, NSCLC is no longer viewed as one disease entity but as a cluster of different disease variants that can be identified by histological subtyping or genetic characterisation of tumours harbouring specific mutations.[30,31] Although we noted improvement in PFS in the total population, independent of histology, improved overall survival was noted only in patients with adenocarcinoma, not in patients with squamous-cell carcinoma, possibly due to the different genetic background of squamous-cell carcinoma compared with adenocarcinoma.[28,30]

In the present study there is evidence of efficacy of nintedanib in patients with adenocarcinoma with a poor prognosis who were either refractory to first-line therapy or had a response of very short duration. In these patients, who progressed within 9 months after starting first-line treatment, PFS was significantly longer in the docetaxel plus nintedanib group than in the docetaxel plus placebo group, which translated to an improvement in overall survival. Consistent with this finding, in patients with adenocarcinoma who had only progressive disease as best response to first-line therapy, there was a significant improvement in median overall survival. Up to now, only the TITAN trial[32] has been done in a similar population of rapidly progressing or platinum-refractory patients. In that study, however, erlotinib in comparison with chemotherapy (docetaxel or pemetrexed) did not improve PFS (6·3 *vs* 8·6 weeks with chemotherapy) or overall survival (5·3 *vs* 5·5 months).

The assessment of outcomes in specific subgroups of patients suggests a better response from docetaxel plus nintedanib in the never-smoker population; however, despite these numerical differences, statistical analyses failed to show a significant interaction between smoking and treatment outcome, raising the possibility that this finding might be attributable to chance. The biological rationale underlying this difference is not known at this time, but from a pharmacological perspective, there was no evidence of substantial differences in pharmacokinetics or pharmacodynamics between the groups.

Although objective response by central review for the total population did not differ between the two groups, significantly more patients with adenocarcinoma and with time since start of first-line therapy of less than 9 months achieved an objective response with docetaxel plus nintedanib than with docetaxel plus placebo. However, significantly more responses were not expected on the basis of the mechanism of action of nintedanib as compared with EGFR inhibitors in patients with EGFR activating mutations. Objective responses based on investigator assessment of imaging scans were noted in 68 (10·4%) of 655 patients with docetaxel plus nintedanib and 50 (7·6%) of 659 patients in the docetaxel plus placebo (appendix p 6). These results are much the same as those reported in the JMEI[22] (8·8% in the docetaxel group) and the TAX317[5] studies (5·5% in the intention-to-treat population and 7·1% in evaluable patients).

In addition to previously noted angiokinases (VEGFR1–3, FGFR1–3, PDGFR α and β), nintedanib also inhibits RET. Although the potential contribution of this mechanism has been considered, RET biomarker testing was not done in the present study. In the scientific literature, KIF5B-RET fusion has been reported in a small proportion (about 1%) of patients with

***Panel:* Research in context**

Systematic review

We searched PubMed using the keywords "NSCLC", "adenocarcinoma", "squamous-cell carcinoma", and the clinically evaluated antiangiogenic compounds: "vandetanib", "bevacizumab", "sunitinib", "sorafenib", "motesanib", "aflibercept", "pazopanib", "axitinib", and "cediranib" to delineate which antiangiogenic compounds had been studied in NSCLC in either the first-line setting, second-line setting, or maintenance setting. We further examined second-line treatment by searching for the names of compounds currently registered for NSCLC in this setting ("docetaxel", "pemetrexed", "erlotinib"), which helped to confirm that there was a great unmet need for refractory patients with NSCLC. We did not find any available evidence suggesting that any therapy substantially extends overall survival versus an active comparator in patients with adenocarcinoma or squamous-cell carcinoma, or significantly improves PFS in patients with squamous-cell carcinoma. Encouraging preclinical and phase 1 and 2 clinical activity with nintedanib and a tolerability profile that favoured the combination with docetaxel and allowed the inclusion of patients with squamous-cell carcinoma provided further support to do this trial.

Interpretation

Docetaxel plus nintedanib improved PFS for patients with refractory NSCLC compared with docetaxel plus placebo, irrespective of histological subtypes, and improved overall survival for patients with adenocarcinoma. The combination of nintedanib and docetaxel seems to be especially beneficial in adenocarcinoma patients with poor prognosis, for whom there is a high unmet need, such as patients with progressive disease in the first-line setting, or patients who progress within 9 months after the initiation of first-line therapy.

adenocarcinoma NSCLC in both Asians and non-Asians.[33,34] It would be unlikely that this small fraction of patients would account for the treatment effect seen with nintedanib, but a potential contribution of this mode of action cannot be fully excluded.

In future studies, it will be important to do correlative biomarker analyses and to try to identify the biological rationale underpinning the response to nintedanib in combination with docetaxel in NSCLC, in particular for patients with adenocarcinoma refractory to first-line therapy. The results in these patients might be correlated to the biology of rapidly progressing tumours. Such tumours might contain a large fraction of proliferating cells and need high levels of oxygen and nutrients to sustain biosynthetic processes. If so, they would be more likely to be dependent on the development of new blood vessels and contain a higher fraction of immature, growth factor-dependent vessels, which would render them more sensitive to treatment with nintedanib. One limitation of this study is that tumour samples have not been collected that would have allowed us to search for molecular markers. However, currently there is no validated biomarker available to predict the efficacy of antiangiogenic compounds.

Docetaxel plus nintedanib had a manageable safety profile. The adverse event profile with nintedanib was as expected from phase 1/2 monotherapy and combination studies.[7–10] Notably, there was a low incidence of class effects typically associated with antiangiogenic agents, such as hypertension, bleeding, perforation, and thromboembolism, which have been noted with other antiangiogenic agents in NSCLC.[35] The recorded pattern of adverse events leading to dose reductions of nintedanib was as expected from previous phase 1 and phase 2 studies in patients with NSCLC.[8,10] The frequency of patients with adverse events leading to dose reductions of docetaxel was in the range of what has been previously reported for docetaxel in the second-line setting.[19,36] The dose intensity of docetaxel was much the same between both groups, suggesting that the addition of nintedanib to docetaxel did not reduce the planned dose of docetaxel.

In conclusion, nintedanib plus docetaxel is an effective second-line option for patients with advanced NSCLC previously treated with one line of platinum-based therapy, especially for patients with adenocarcinoma.

Contributors

MR, RK, and BG-M contributed to the conception and design of the study. MR, AM, J-YD, SO, MK, JvP, MG, IB, ML, and SN were involved in the provision of study material or patients or data acquisition. MR, RK, C-NG, JB, and BG-M were involved in data analysis and interpretation. Appendix pp 26–28 list all investigators who participated in the LUME-Lung 1 study.

Conflicts of interest

RK, C-NG, JB, and BG-M are employees of Boehringer Ingelheim. RK and BG-M have patents for Boehringer Ingelheim. MR and AM have participated in advisory board meetings for Boehringer Ingelheim. J-YD has received fees from Boehringer Ingelheim for participation in data review or monitoring boards. JvP has received fees for consultancy from Boehringer Ingelheim. SO, MK, MG, IB, ML, and SN declare that they have no conflicts of interest.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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WEB APPENDIX

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Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomized controlled trial

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Supplementary methods

Unmasking/unblinding procedures before final database lock

For the purpose of the independent Data Monitoring Committee (DMC) reviews, the safety data were unmasked into two treatment arms (Arm A and Arm B), but was still blinded as to the treatment identity of each arm. A pre-planned futility analysis was performed by the independent DMC after 50% of the events for the primary progression-free survival (PFS) analysis had been observed (~356 events). The futility analysis was performed by the independent DMC for the purpose of advising the sponsor as to whether or not the study should continue as planned. The sponsor was blinded to the results of this analysis. At the timepoint of the futility analysis, the DMC statistician had access to the treatment allocation to each arm. All data and analyses were restricted to the committee members. For exceptional treatment-essential safety reasons, the treating physician could call the Interactive Voice Response System to find out the identity of the treatment for a specific patient who would then discontinue the investigational agent.

Additional details on the statistical analyses of the primary and key secondary efficacy endpoints

Timing of final overall survival (OS) analysis

The analysis of the primary endpoint centrally assessed PFS of LUME-Lung 1 was performed prior to the independent validation of the hypothesis using the final OS data of LUME-Lung 1 and at the same time when the LUME-Lung 2 trial was stopped due to the futility analysis based on investigator-assessed PFS. To minimise any potential bias resulting from the interim evaluation of OS at the time of the primary PFS analysis and to ensure the integrity of the ongoing LUME-Lung 1 trial, the interim analysis of OS was performed by a limited group of individuals who were not involved in overseeing the day-to-day conduct of the study. These individuals were held to strict confidentiality. The study team responsible for data collection and day-to-day operation of the clinical trial remained blinded. The sponsor also decided not to include the OS data in the Clinical Trial Report for the primary PFS analysis of the LUME-Lung 1 trial. In addition, the sponsor decided not to publish any of the results of analyses of the LUME-Lung 1 and 2 data before the read out for final OS of the LUME-Lung 1 trial.

Sensitivity analyses

Pre-planned sensitivity analyses were undertaken to assess the robustness of statistical model assumptions and study conduct (i.e. image collection) of the primary analysis of PFS (four sensitivity analyses). Sensitivity analysis performed for the primary PFS analysis were a Cox

proportional hazards model fitting the four stratification factors as covariates, a stepwise variable selection method to identify covariates that might be relevant to efficacy, an analysis replacing actual tumour imaging dates with the originally scheduled dates of radiological assessments, and a sensitivity analysis using an interval-censoring approach. A stepwise variable selection method was used to obtain the best fitting model to test the effect of nintedanib *vs* placebo at the nominal two-sided level of 0·05. Treatment effect was included in all stages of the model selection process. Pre-defined baseline factors were included as covariate in the modelling process: factors were excluded from the final model if they did not improve the model fit according to a pre-defined algorithm. Regarding the four stratification factors, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and tumour histology at randomisation were fitted as stratification factors and were not removed from the model, whereas bevacizumab pre-treatment and brain metastases were included in the modelling process, as covariates and could be removed through the model selection process. The critical value for inclusion and exclusion from the model was significance at the 10% level.

Two sensitivity analyses using Cox proportional hazards models were performed for OS to assess the robustness of statistical model assumptions. One model included the stratification factors used at randomisation as covariates, and the second model included both the stratification factors and the baseline sum of the longest diameters (SLD) of the target lesions (mm) as covariates.[1]

Subgroup analyses

HRs were produced in order to investigate the consistency of the treatment effect for each level of pre-defined baseline characteristics. HRs were obtained from models fitted for each level of the baseline covariate, e.g. for the baseline characteristic of sex, one model was produced for males and one for females. All models were stratified by the stratification factors used in randomisation, and were fitted using identical methodology, as described in the Statistical analyses section of the manuscript. However, in cases where the stratification factor is the baseline covariate that was investigated, this was not included in the strata statement of the models. Patients from strata combinations with no events did not contribute to the stratified test.[2] In order to provide a statistical framework for interpretation of the consistency of the treatment effect, interaction p values were created. The interaction p value formally tested the hypothesis of whether the HR (treatment effect) was different in the two levels of the baseline characteristic. Interaction p values were created using a modelling procedure that assumed proportionality on a global basis (within and between strata). Models were fitted to include the factors used to stratify the randomisation as covariates. Models were fitted with

and without treatment by covariate interactions and the models compared using the log likelihood ratio statistic.[3]

Statistical analyses of other secondary efficacy endpoints

Statistical analysis of investigator-assessed PFS was conducted in the same manner as described for the primary endpoint of independently reviewed PFS. Tumour response (objective response, defined as confirmed complete response [CR] and partial response [PR]) and disease-control, defined as confirmed CR, confirmed PR, and/or confirmed stable disease (SD), were analysed with a logistical regression adjusted for the baseline ECOG PS. Analysis of variance was used to explore differences in tumour shrinkage, defined as the best percentage change from baseline in the sum of the longest diameters of the target lesions, between the two groups, with randomisation stratification factors included as covariate. The p value of the comparison of nintedanib *vs* placebo and the adjusted (least squares) means for the change in tumour size in each treatment group was presented.

Supplementary results

The primary endpoint was defined by a cut-off date of Nov 2, 2010 when 714 PFS events had occurred (there were two events on the cut-off date) with 1134 patients randomised, and the cut-off for all secondary endpoints (including OS) and safety analysis was Feb 15, 2013 when 1121 OS events had occurred with 1314 patients randomised.

Interim analysis of OS and confirmation of PFS

There were no significant differences in the interim analysis of OS carried out at the time of the primary PFS endpoint analysis when 423 deaths had occurred. PFS by independent review at the time of the key secondary endpoint (final OS) analysis was significantly improved with nintedanib in the overall patient population (N=1314) compared with placebo (median PFS 3·5 [95% CI 3·0 to 4·0] *vs* 2·7 [95% CI 2·6 to 2·8] months, HR, 0·85 [95% CI, 0·75 to 0·96]; p=0·0070). At the time of final OS analysis, the PFS for patients with adenocarcinoma (median PFS 4·2 [95% CI 3·6 to 4·4] *vs* 2·8 [95% CI 2·6 to 3·2] months, HR, 0·84 [95% CI, 0·71 to 1·00]; p=0·0485) was also significantly longer with docetaxel/nintedanib compared with docetaxel/placebo. There was a trend for PFS improvement in patients with squamous-cell carcinoma (median PFS 3·0 [95% CI 2·8 to 3·6] *vs* 2·6 [95% CI 1·7 to 2·7] months, HR, 0·83 [95% CI, 0·69 to 1·01]; p=0·0566) at the time of final OS analysis.

Sensitivity analyses of the primary endpoint

The results of these sensitivity analyses were very similar to the results of the primary PFS analysis and generally confirmed the robustness of the primary PFS analysis (table S4).

Other secondary analyses

Investigator assessment of PFS at the analysis of the primary endpoint (PFS by central independent review) also showed a significant improvement with docetaxel/nintedanib in all patients, independent of histology. In the overall population, the median PFS was 4·2 [95% CI 3·9 to 4·4] months in the docetaxel/nintedanib arm *vs* 3·1 [95% CI 2·8 to 3·8] months in the docetaxel/placebo arm (HR 0·80 [95% CI, 0·69 to 0·93]; p=0·0034). In patients with adenocarcinoma, the HR was 0·78 (95% CI, 0·62 to 0·97); p=0·0246 and in patients with squamous-cell carcinoma, the HR was 0·80 (95% CI, 0·64 to 1·00); p=0·05.

There was a trend towards a better confirmed best objective by investigator review at the time of the final OS analysis in patients in the nintedanib arm (68/655 patients [10·4%] *vs* 50/659 patients [7·6%], odds ratio [OR] 1·41 [95% CI, 0·96 to 2·08]; p=0·076). Moreover, disease control was significantly higher with docetaxel/nintedanib compared with docetaxel/placebo (415/655 patients [63·4%] *vs* 339/659 patients [51·4%], OR 1·64 [95% CI, 1·31 to 2·05]; p<0·0001).

At the time of the final OS analysis, there was a statistically significant difference in the adjusted mean of the best percentage change in sum of the longest diameters of target lesions from baseline in the docetaxel/nintedanib *vs* the docetaxel/placebo arm in all patients (–4·87% [95% CI, –6·62 to –3·12%] *vs* +0·58% [95% CI, –1·19 to +2·35%], respectively; p<0·0001). This effect was more pronounced for the overall adenocarcinoma subpopulation (–7·76% [95% CI, –10·25 to –5·26%] *vs* –0·97% [95% CI, –3·48 to +1·55%], respectively; p=0·0002), and the population of patients with adenocarcinoma histology and time since first-line treatment <9 months (–7·52% [95% CI, –10·64 to –4·41%] *vs* +3·70% [95% CI, +0·39 to +7·01%], respectively; p<0·0001) (figure S3).

SUPPLEMENTARY TABLES

Table S1: **Efficacy outcomes in patients with NSCLC in the second-line setting according to tumour histology (where available); selected published phase 3 trials**

Study	Treatment	HR for PFS	Median PFS (months)	HR for OS	Median OS (months)
Tax 320[4]	Docetaxel (n=125, D100 mg/m^2) *vs* ifofosfamide or vinorelbine (n=123)		2·0 *vs* 1·8 (TTP), p=0·044		5·5 *vs* 5·6, n.s.
(N=373)	Docetaxel (n=125, D75 mg/m^2) *vs* ifofosfamide or vinorelbine (n=123)		2·0 *vs* 1·8 (TTP), n.s.		5·7 *vs* 5·6, p=0·025
Tax 317[5]	Docetaxel (n=49, D100 mg/m^2) *vs* BSC (n=100)		2·4 (D75 mg plus D100 mg) *vs*		5·9 *vs* 4·6, n.s.
(N=204)	Docetaxel (n=55, D75 mg/m^2) *vs* BSC (n=100)		1·5 (TTP), p=0·001		7·5 *vs* 4·6, p=0·01
JMEI[6,7]	Pemetrexed* *vs* docetaxel	0·97, n.s.	2·9 *vs* 2·9	0·99, n.s.	8·3 *vs* 7·9
(N=571, 1:1)	Adenocarcinoma (n=302)	0·83, n.s.	3·5 *vs* 3·5	0·92, n.s.	9·0 *vs* 9·2
	Squamous-cell carcinoma (n=172)	1·4, p=0·046	2·3 *vs* 2·7	1·56, p=0·018	6·2 *vs* 7·4
BR·21[8]	Erlotinib *vs* placebo	0·61, p<0·001	2·2 *vs* 1·8	0·70, p<0·001	6·7 *vs* 4·7
(N=731, 2:1)	Adenocarcinoma (n=365)			0·70, p=0·008	
	Squamous-cell carcinoma (n=222)			0·67, n.s.	
ISEL[9]	Gefitinib *vs* placebo	0·82 (TTTF)	3·0 *vs* 2·6 (TTTF)	0·89, n.s.	5·6 *vs* 5·1
(N=1692, 2:1)	Adenocarcinoma (n=767)			0·84, n.s.	6·3 *vs* 5·4
	Squamous-cell carcinoma (n=586)				
INTEREST[10]	Gefitnib *vs* docetaxel	1·04, n.s.	2·2 *vs* 2·7	1·02, n.s.	7·6 *vs* 8·0
(N=1466; 1:1)†	Adenocarcinoma (n=830)			n.s.	8·5 *vs* 8·9
	Non-adenocarcinoma (n=636)			n.s.	6·4 *vs* 6·9

ZODIAC[11]	Vandetanib plus docetaxel *vs* docetaxel	0·79, p<0·0001	4.0 *vs* 3·2	0·91, n.s.	10·6 *vs* 10.0
(N=1391, 1:1)	Adenocarcinoma (n=829)	0·80, p<0·05		0·89, n.s.	
	Squamous-cell carcinoma (n=344)	0·79, n.s		0·98, n.s.	
ZEAL[12]	Vandetanib plus pemetrexed *vs* pemetrexed	0·86, n.s.	4·1 *vs* 2·8	0·86, n.s.	10·5 *vs* 9·2
(N=534, 1:1)	Adenocarcinoma (n=336)	0·80, n.s.		0·82, n.s.	
	Squamous-cell carcinoma (n=114)	1·04, n.s.		1·08, n.s.	
ZEST[13]	Vandetanib *vs* erlotinib	0·98, n.s.	2·6 *vs* 2·0	1·01, n.s.	6·9 *vs* 7·8
(N=1240,1:1)	Adenocarcinoma (n=749)	1·0, n·s		0·99, n.s.	
	Squamous-cell carcinoma (n=272)	1·09, n·s		1·25, n.s.	
VITAL[14]	Aflibercept plus docetaxel *vs* docetaxel	0·82, p=0·0035	5·2 *vs* 4·1	1·01, n.s.	10·1 *vs* 10·4
(N=913,1:1)	Adenocarcinoma (n=761)				
	Other (n=152)				
BETA[15]	Bevacizumab plus erlotinib *vs* erlotinib	0·62, n.s.	3·4 *vs* 1·7	0·97, n.s.	9·3 *vs* 9·2
(N=636, 1:1)	Adenocarcinoma (n=477)			1·07, n.s.	
	Squamous-cell carcinoma (n=28)			0·91, n.s.	
TAILOR[16]	Docetaxel *vs* erlotinib, non-EGFR mutations	0·69, p=0·014	3·4 *vs* 2·4		Not reached
(N=222, 1:1)	Non-squamous-cell carcinoma (n=222)				
TITAN[17]	Docetaxel/pemetrexed *vs* erlotinib, fast progressors	1·19, n.s.	2·0 *vs* 1·4	0·96, n.s.	5·5 *vs* 5·3
(N=424, 1:1)	Adenocarcinoma (n=210)			0·95, n.s.	
	Squamous-cell carcinoma (n=154)			0·86, n.s.	
SUN1087[18]	Sunitinib plus erlotinib *vs* erlotinib	0·807, p=0·0023	3·6 *vs* 2·0	0·922, n.s.	9·0 *vs* 8·5
(N=960, 1:1)	Non-squamous-cell carcinoma (n=568)	0·859		0·943, n.s.	
	Squamous-cell carcinoma (n=270)	0·797		0·935, n.s.	

Vinflunine[19]	Vinflunine *vs* docetaxel	1·004	2·3 *vs* 2·3	0·973	6·7 *vs* 7·2
(N=551, 1:1)	Adenocarcinoma (n=235)				
	Squamous-cell carcinoma (n=194)				
Topotecan[20]	Oral topotecan *vs* docetaxel	1·20, p=0·02	2·5 *vs* 3·0 (TTP)	1·23, p=0·0568	6·4 *vs* 7·1
(N=829, 1:1)	Adenocarcinoma (n=345)	(TTP)			
	Squamous-cell carcinoma (n=336)				
DELTA[21]	Erlotinib *vs* docetaxel (60 mg/m^2),				
(N=301, 1:1)	unselected for EGFR mutations	1·22, n.s.	2·0 *vs* 3·2	0·91, n.s.	14·8 *vs*12·2
	Adenocarcinoma (n=207)	1·14, n.s.			
	Non-adenocarcinoma (n=94)	1·60, n.s.			
	EGFR wild-type	1·44, p=0·013	1·3 *vs* 2·9	0·98, n.s.	9·0 *vs* 9·2

BSC=best supportive care. EGFR=epidermal growth factor receptor. HR=hazard ratio; n.s.=not significant. NSCLC=non-small-cell lung cancer; OS=overall survival. PFS=progression-free survival. TTTF=time to treatment failure. TTP=time to progression.

*Pemetrexed only registered for non-squamous-cell carcinoma patients.

[†]237 patients had received more than one previous line of therapy.

Table S2: **Inclusion and exclusion criteria**

Inclusion criteria
• Male or female patient aged 18 years or older • Histologically or cytologically confirmed, locally advanced and/or metastatic NSCLC of stage IIIB or IV or recurrent NSCLC • Relapse or failure of one first line prior chemotherapy • At least one target tumour lesion that has not been irradiated within the past 3 months and that can accurately be measured • Life expectancy of at least 3 months • ECOG PS of 0 or 1 • Patient has given written informed consent
Exclusion criteria
• More than one prior chemotherapy regimen for advanced and/or metastatic or recurrent NSCLC • More than one chemotherapy treatment regimen (either neoadjuvant or adjuvant or neoadjuvant plus adjuvant) prior to first-line chemotherapy • Previous therapy with other VEGFR inhibitors (other than bevacizumab) or docetaxel for treatment of NSCLC • Persistence of clinically relevant therapy related toxicities from previous chemotherapy and/or radiotherapy • Treatment with other investigational drugs or other anti-cancer therapy, or treatment in another clinical trial within the past 4 weeks before start of therapy or concomitantly with this trial • Radiotherapy (except extremities and brain) within the past 3 months prior to baseline imaging • Active brain metastases or leptomeningeal disease • Radiographical evidence of cavitary or necrotic tumours • Centrally located tumours with radiographical evidence (CT or MRI) of local invasion of major blood vessels • History of clinically significant haemoptysis within the past 3 months • Therapeutic anticoagulation (except low dose heparin) or antiplatelet therapy • History of major thrombotic or clinically relevant major bleeding event in the past 6 months • Known inherited predisposition to bleeding or thrombosis • Significant cardiovascular diseases

- Inadequate safety laboratory parameters
- Significant weight loss (>10 %) within the past 6 weeks
- Current peripheral neuropathy greater than CTCAE grade 2 except due to trauma
- Pre-existing ascites and/or clinically significant pleural effusion
- Major injuries and/or surgery within the past 10 days prior to randomisation with incomplete wound healing
- Serious infections requiring systemic antibiotic therapy
- Decompensated diabetes mellitus or other contraindication to high-dose corticosteroid therapy
- Gastrointestinal disorders or abnormalities that would interfere with absorption of the study drug
- Active or chronic hepatitis C and/or B infection
- Serious illness or concomitant non-oncological disease or laboratory abnormality that may increase the risk associated with study participation or study drug administration
- Patients who are sexually active and unwilling to use a medically acceptable method of contraception during the trial and for at least 12 months after end of active therapy
- Pregnancy or breast feeding
- Psychological, familial, sociological, or geographical factors potentially hampering compliance with the study protocol and follow-up schedule
- Patients unable to comply with the protocol
- Active alcohol or drug abuse
- Other malignancy within the past 3 years other than basal cell skin cancer, or carcinoma *in situ* of the cervix
- Any contraindications for therapy with docetaxel
- History of severe hypersensitivity reactions to docetaxel or other drugs formulated with polysorbate 80 (Tween 80)
- Hypersensitivity to nintedanib and/or the excipients of the trial drugs
- Hypersensitivity to contrast media

CT=computerised (or computed) tomography. CTCAE=Common Toxicity Criteria for Adverse Events. ECOG PS=Eastern Cooperative Oncology Group Performance Status. MRI=magnetic resonance imaging. NSCLC=non-small-cell lung cancer. VEGFR=vascular endothelial growth factor receptor.

***Table S3*: Dose-reduction schemes for nintedanib and docetaxel**

Dose-reduction schemes
• Two dose-reduction schemes were allowed for nintedanib (from 200 to 150 mg twice daily, and from 150 to 100 mg twice daily) following: liver enzyme increases; diarrhoea, nausea, or vomiting not responding to supportive treatment; or any non-haematological, drug-related AE CTCAE grade ≥3 – nintedanib had to be discontinued if there were any additional episodes of these AEs that required further dose reduction • According to the label, one dose reduction was permitted for docetaxel: from 75 to 60 mg per square meter • Docetaxel had to be discontinued in case of CTCAE grade ≥3 peripheral neuropathy, severe hypersensitivity, or an AE requiring a second dose reduction • Patients who discontinued docetaxel for reasons other than progression could continue with nintedanib/placebo monotherapy if they had received ≥4 cycles of combination treatment • Similarly, patients who discontinued nintedanib/placebo could continue with docetaxel monotherapy
AE=adverse event. CTCAE=Common Toxicity Criteria for Adverse Events.

Table S4: **Pre-specified sensitivity analyses of the primary and key secondary endpoints in the overall patient population**

Endpoint	Sensitivity analyses	HR (95% CI)	p value
Primary: PFS (central review)	**Primary analysis**	**0·79 (0·68 to 0·92)**	**0·0019**
	Proportional hazards modelling*	0·77 (0·67 to 0·89)	0·0005
	Stepwise selection model†	0·76 (0·66 to 0·89)	0·0004
	Replacing actual image dates with scheduled dates‡	0·78 (0·67 to 0·91)	0·0011
	Interval-censored analysis§	n.a.	0·0008
Key secondary: OS	**Primary analysis**	**0·94 (0·83 to 1·05)**	**0·2720**
	Proportional hazards modelling*	0·92 (0·82 to 1·04)	0·1832
	Proportional hazards modelling adjusting for baseline sum of longest diameters¶	0·88 (0·78 to 0·99)	0·0365

CI=confidence interval. HR=hazard ratio. PFS=progression-free survival. n.a.=not assessed.
HRs, CIs, and p values were obtained:

*From a proportional−hazards model with stratification factors fitted as covariates.

†From a model selected using a stepwise selection procedure. The model was stratified by Eastern Cooperative Oncology Group Performance Status and tumour histology.

‡From a proportional−hazards model stratified by stratification factors. The endpoint PFS was derived by using the scheduled images dates. Scheduled dates are based upon those described in the protocol study plan. Images are mandated by the protocol every 6 weeks after the start of therapy.

§P value was calculated from the generalised log-rank test proposed by Zhao and Sun.[22]

¶From proportional−hazards model with stratification factors and baseline sum of longest diameters fitted as covariates.[1]

Table S5: **Post-study therapy**

	Overall		Adenocarcinoma		Adenocarcinoma <9 months since start of first-line treatment		Squamous-cell carcinoma	
	Docetaxel plus nintedanib (n=655)	**Docetaxel plus placebo (n=659)**	**Docetaxel plus nintedanib (n=322)**	**Docetaxel plus placebo (n=336)**	**Docetaxel plus nintedanib (n=206)**	**Docetaxel plus placebo (n=199)**	**Docetaxel plus nintedanib (n=276)**	**Docetaxel plus placebo (n=279)**
Any systemic therapy	345 (52·7%)	351 (53·3%)	179 (55·6%)	188 (56·0%)	108 (52·4%)	110 (55·3%)	134 (48·6%)	131 (47·0%)
Any chemotherapy	246 (37·6%)	251 (38·1%)	123 (38·2%)	136 (40·5%)	67 (32·5%)	77 (38·7%)	97 (35·1%)	93 (33·3%)
Pemetrexed	78 (11·9%)	78 (11·8%)	52 (16·1%)	62 (18·5%)	22 (10·7%)	32 (16·1%)	10 (3·6%)	5 (1·8%)
Docetaxel	32 (4·9%)	27 (4·1%)	15 (4·7%)	13 (3·9%)	8 (3·9%)	8 (4·0%)	13 (4·7%)	13 (4·7%)
Other chemotherapy	187 (28·5%)	199 (30·2%)	90 (28·0%)	101 (30·1%)	50 (24·3%)	54 (27·1%)	82 (29·7%)	83 (29·7%)
EGFR tyrosine kinase inhibitor	178 (27·2%)	172 (26·1%)	98 (30·4%)	105 (31·3%)	65 (31·6%)	64 (32·2%)	67 (24·3%)	53 (19·0%)
Anti-angiogenesis agent	9 (1·4%)	5 (0·8%)	6 (1·9%)	2 (0·6%)	4 (1·9%)	2 (1·0%)	1 (0·4%)	2 (0·7%)
Investigational agent	25 (3·8%)	9 (1·4%)	18 (5·6%)	5 (1·5%)	11 (5·3%)	4 (2·0%)	7 (2·5%)	4 (1·4%)

EGFR=epidermal growth factor receptor.

Table S6: **Confirmed best tumour response and disease control in patients with squamous-cell carcinoma, according to modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1·0 (central independent review) at the timepoint of the final overall survival analysis**

	Squamous-cell carcinoma	
	Docetaxel plus nintedanib (n=276)	**Docetaxel plus placebo (n=279)**
Objective response	13 (4·7%)	7 (2·5%)
Disease control	136 (49·3%)*	99 (35·5%)
Confirmed best tumour response		
Complete response	0	1 (0·4%)
Partial response	13 (4·7%)	6 (2·2%)
Stable disease	123 (44·6%)	92 (33·0%)
Progressive disease	90 (32·6%)	134 (48·0%)
Other†	50 (18·1%)	46 (16·5%)

*Odds ratio (by logistic regression adjusted for baseline performance status) for disease control with docetaxel plus nintedanib *vs* docetaxel plus placebo in patients with squamous-cell carcinoma (based on central review) was 1·78 (95% confidence interval, 1·26 to 2·51; p=0·0009).

†Other includes patients with stable disease within <6 weeks and non-evaluable responses.

Table S7: **AEs associated with VEGF inhibition in all treated patients**

	Docetaxel plus nintedanib (n=652)		Docetaxel plus placebo (n=655)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Bleeding	92 (14·1%)	15 (2·3%)	76 (11·6%)	12 (1·8%)
Gastrointestinal perforation	3 (0·5%)	1 (0·2%)	3 (0·5%)	3 (0·5%)
Thrombolic events	33 (5·1%)	14 (2·1%)	30 (4·6%)	20 (3·1%)
Venous thromboembolism	18 (2·8%)	8 (1·2%)	10 (1·5%)	7 (1·1%)
Arterial thromboembolism	4 (0·6%)	3 (0·5%)	9 (1·4%)	4 (0·6%)
Hypertension	23 (3·5%)	4 (0·6%)	6 (0·9%)	1 (0·2%)

AE=adverse event. VEGF=vascular endothelial growth factor.
AEs were categorised into special search categories by pooling Medical Dictionary for Regulatory Activities (MedDRA) preferred terms using standardised MedDRA queries (SMQ) and individually tailored searches.

Table S8: **AEs leading to death possibly unrelated to disease progression**

	Docetaxel plus nintedanib (n=652)	Docetaxel plus placebo (n=655)
Any AE leading to death possibly unrelated to disease progression	35 (5·4%)	25 (3·8%)
Sepsis	5 (0·8%)	1 (0·2%)
Respiratory failure	4 (0·6%)	0
Lower respiratory tract infection	2 (0·3%)	0
Pneumonia	2 (0·3%)	7 (1·1%)
Septic shock	2 (0·3%)	0
Death	2 (0·3%)	1 (0·2%)
Dyspnoea	1 (0·2%)	2 (0·3%)
Haemorrhage	1 (0·2%)	2 (0·3%)
Disseminated intravascular coagulation	1 (0·2%)	0
Cardiac arrest	1 (0·2%)	0
Cardiopulmonary failure	1 (0·2%)	1 (0·2%)
Myocardial infarction	1 (0·2%)	0
Diverticulum intestinal	1 (0·2%)	0
Large intestine perforation	1 (0·2%)	1 (0·2%)
Asthenia	1 (0·2%)	0
Chest pain	1 (0·2%)	0
Multi-organ failure	1 (0·2%)	1 (0·2%)
Cellulitis	1 (0·2%)	0
Infectious pleural effusion	1 (0·2%)	0
Lung abscess	1 (0·2%)	0
Neutropenic infection	1 (0·2%)	0
Dehydration	1 (0·2%)	0
Coma	1 (0·2%)	0
Ischaemic stroke	1 (0·2%)	0
Loss of consciousness	1 (0·2%)	0
Acute respiratory distress syndrome	1 (0·2%)	0
Chronic obstructive pulmonary disease	1 (0·2%)	0

Haemoptysis	1 (0·2%)	0
Obstructive airways disorder	1 (0·2%)	0
Venous thrombosis	1 (0·2%)	0
Pulmonary embolism	0	3 (0·5%)
Alcohol poisoning	0	1 (0·2%)
Anaemia	0	1 (0·2%)
Angina pectoris	0	1 (0·2%)
Cardio-respiratory arrest	0	1 (0·2%)
Cerebrovascular accident	0	1 (0·2%)
Chest discomfort	0	1 (0·2%)
Coronary artery disease	0	1 (0·2%)
General physical health deterioration	0	1 (0·2%)
Opportunistic infection	0	1 (0·2%)
Pulmonary haemorrhage	0	1 (0·2%)
Respiratory tract infection bacterial	0	1 (0·2%)
Streptococcal infection	0	1 (0·2%)
AE=adverse event.		

Table S9: **Overview of AEs, classified by CTCAE version 3·0 in patients with adenocarcinoma histology**

	Docetaxel plus nintedanib (n=320)		Docetaxel plus placebo (n=333)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE leading to death	56 (17·5%)		32 (9·6%)	
Related to disease progression	36 (11·3%)		24 (7·2%)	
Unrelated to disease progression	20 (6·3%)		8 (2·4%)	
Any AE leading to permanent discontinuation of last study medication	67 (20·9%)	57 (17·8%)	59 (17·7%)	43 (12·9%)
Any AE leading to dose reduction of nintedanib/placebo	69 (21·6%)	41 (12·8%)	22 (6·6%)	19 (5·7%)
Any AE leading to dose reduction of docetaxel	53 (16·6%)	41 (12·8%)	41 (12·3%)	32 (9·6%)
Any serious AE	111 (34·7%)	100 (31·3%)	107 (32·1%)	92 (27·6%)
Any AE*	308 (96·3%)	243 (75·9%)	314 (94·3%)	228 (68·5%)
Diarrhoea	139 (43·4%)	20 (6·3%)	82 (24·6%)	12 (3·6%)
Neutrophil count decreased	131 (40·9%)	116 (36·3%)	135 (40·5%)	116 (34·8%)
ALT increased	121 (37·8%)	37 (11·6%)	31 (9·3%)	3 (0·9%)
Fatigue	99 (30·9%)	15 (4·7%)	98 (29·4%)	14 (4·2%)
AST increased	97 (30·3%)	13 (4·1%)	24 (7·2%)	2 (0·6%)
Nausea	91 (28·4%)	3 (0·9%)	59 (17·7%)	2 (0·6%)
White blood cell count decreased	89 (27·8%)	63 (19·7%)	94 (28·2%)	61 (18·3%)
Decreased appetite	75 (23·4%)	4 (1·3%)	52 (15·6%)	5 (1·5%)
Vomiting	62 (19·4%)	4 (1·3%)	41 (12·3%)	2 (0·6%)

Alopecia	56 (17·5%)	1 (0·3%)	68 (20·4%)	0
Dyspnoea	54 (16·9%)	15 (4·7%)	52 (15·6%)	20 (6·0%)
Neutropenia	44 (13·8%)	38 (11·9%)	51 (15·3%)	45 (13·5%)
Cough	42 (13·1%)	3 (0·9%)	63 (18·9%)	2 (0·6%)
Pyrexia	39 (12·2%)	2 (0·6%)	47 (14·1%)	1 (0·3%)
Stomatitis	36 (11·3%)	4 (1·3%)	26 (7·8%)	1 (0·3%)
Haemoglobin decreased	35 (10·9%)	3 (0·9%)	46 (13·8%)	7 (2·1%)
Constipation	22 (6·9%)	0	39 (11·7%)	1 (0·3%)

AE=adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CTCAE=Common Terminology Criteria for Adverse Events.
*Reported as AEs of 'all grades' occurring in at least 10% of the patients in either treatment arm.

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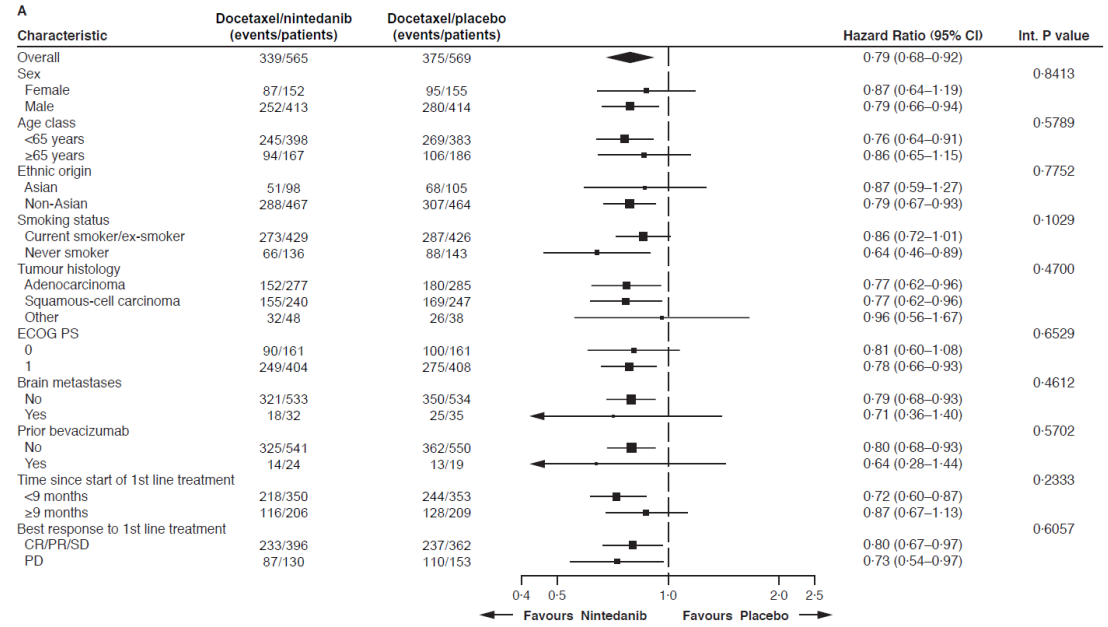
SUPPLEMENTARY FIGURES

Figure S1: **Hazard ratios and 95% CIs of centrally reviewed progression-free survival at the timepoint of the primary analysis (A), and overall survival at the timepoint of final analysis (B) by patients' baseline characteristics in the overall population**

CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group Performance Status. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. The bubble size reflects the number of events.



B

Characteristic	Docetaxel/nintedanib (events/patients)	Docetaxel/placebo (events/patients)	Hazard ratio (95%CI)	Int. P value
Overall	564/655	557/659	0·94 (0·83–1·05)	
Sex				0·4244
Female	147/179	150/180	0·86 (0·68–1·09)	
Male	417/476	407/479	0·97 (0·85–1·12)	
Age class				0·5482
<65 years	392/455	379/445	0·91 (0·79–1·05)	
≥65 years	172/200	178/214	0·98 (0·79–1·22)	
Ethnic origin				0·4471
Asian	98/118	102/124	1·00 (0·75–1·33)	
Non-Asian	466/537	455/535	0·92 (0·81–1·05)	
Smoking status				0·1213
Current smoker/ex-smoker	437/490	424/498	1·00 (0·87–1·14)	
Never smoker	127/165	133/161	0·78 (0·60–0·99)	
Tumour histology				0·1194
Adenocarcinoma	259/322	276/336	0·83 (0·70–0·99)	
Squamous cell carcinoma	254/276	240/279	1·01 (0·85–1·21)	
Other	51/57	41/44	1·31 (0·84–2·03)	
ECOG PS				0·1673
0	159/187	154/189	1·06 (0·85–1·33)	
1	405/468	403/470	0·89 (0·78–1·03)	
Brain metastases				0·3670
No	528/617	524/621	0·92 (0·82–1·04)	
Yes	36/38	33/38	1·15 (0·70–1·87)	
Prior bevacizumab				0·1207
No	544/628	536/636	0·95 (0·84–1·07)	
Yes	20/27	21/23	0·61 (0·32–1·17)	
Time since start of 1st line treatment				0·5705
<9 months	371/418	357/406	0·89 (0·77–1·03)	
≥9 months	186/228	195/245	0·95 (0·77–1·17)	
Best response to 1st line treatment				0·2895
CR/PR/SD	405/476	373/445	0·95 (0·83–1·10)	
PD	116/127	125/139	0·84 (0·65–1·10)	

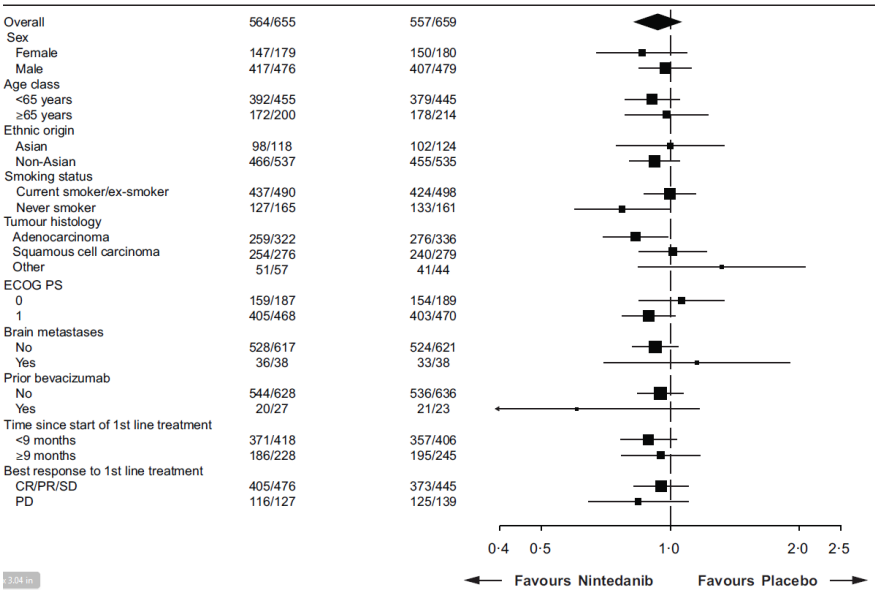


Figure S2: **Kaplan–Meier curves for OS in patients with squamous-cell carcinoma at the timepoint of the final OS analysis**

CI=confidence interval. HR=hazard ratio. OS=overall survival. Patients without documented death were censored at the date of last contact when the patient was known to be alive.

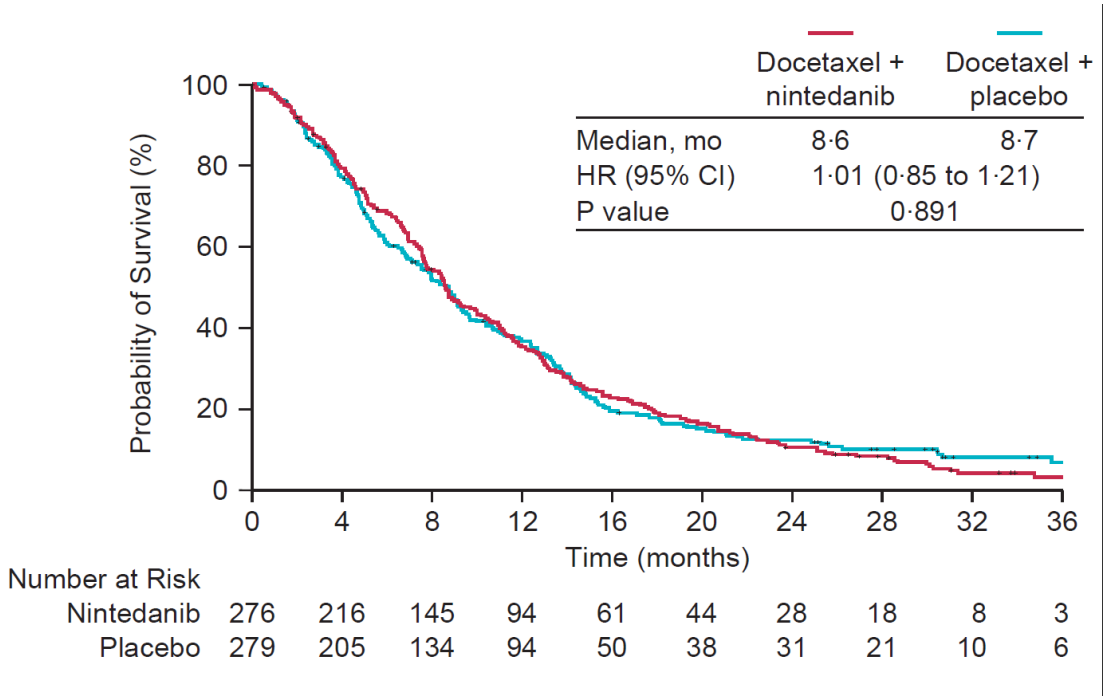
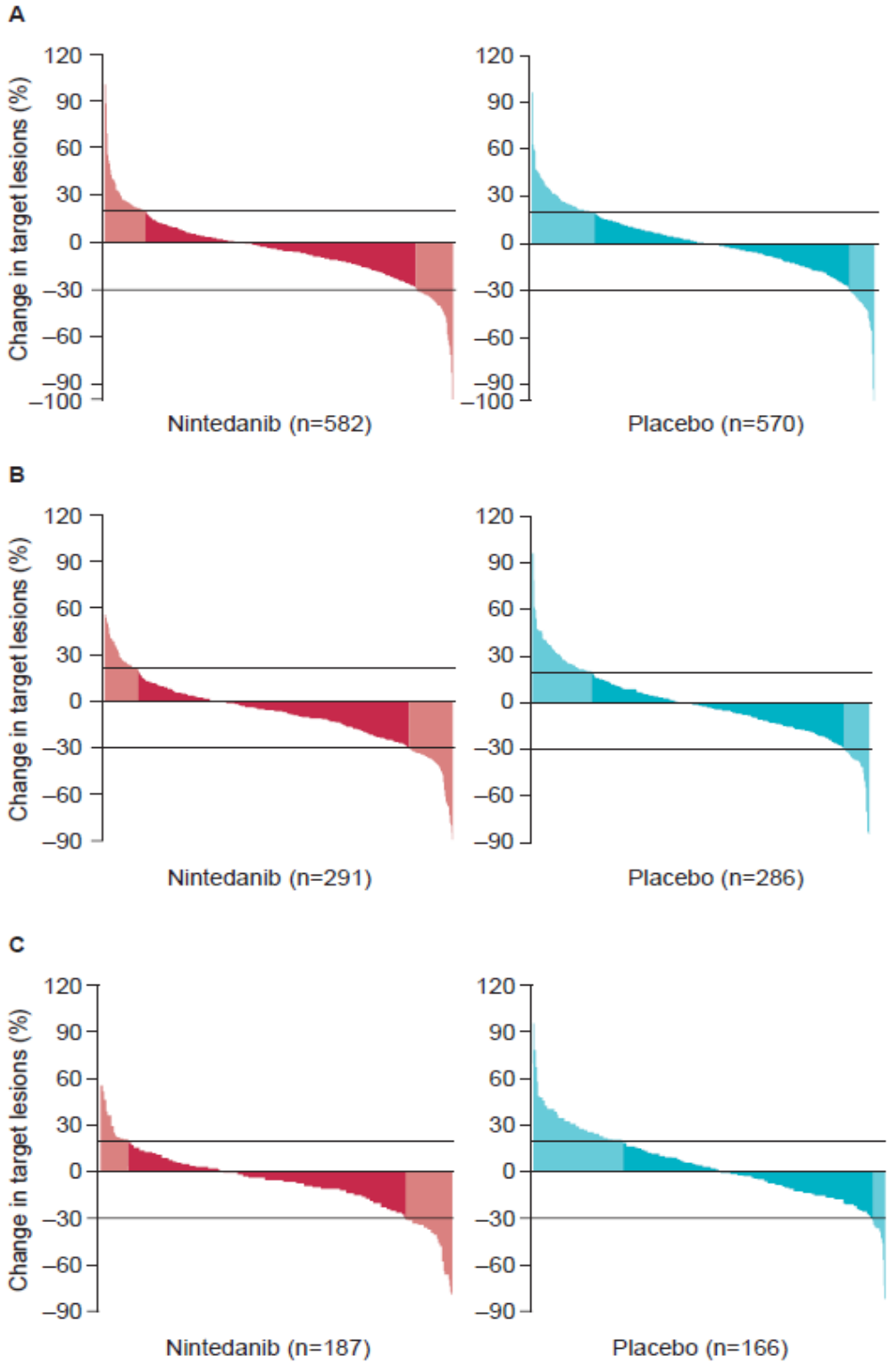


Figure S3: **Waterfall plot of maximum percentage change in the sum of the longest diameters of the target lesions in the overall population (A), patients with adenocarcinoma histology (B), and patients with adenocarcinoma histology and time since first-line treatment <9 months (C) at the time of final overall survival analysis**



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Portugal — Teresa Almodovar, António Araujo, Fernando Barata, João Cunha, António Meleiro, Barbara Parente, Henrique Queiroga, and Encarnação Teixeira

Romania — Cristina Cebotaru, Mircea Dediu, Dumitru Filip, Doina-Elena Ganea-Motan, Ioan-Catalin Iacob, Iuliu Ionas, Lucian Miron, Cristina Oprean, Emilia-Mariana Popescu, Lucian Vata, and Constantin Volovat

Russia — Zinaida Akishina, Vasily Borisov, Irina Bulavina, Nina Chekha, Valeriy Demchenko, Viktoriya Dvornichenko, Oleg Gladkov, Rustem Khasanov, Igor Kiselev, Dmitry Komov, Evgeny Kulikov, Mikhail Leonov, Vladimir Lubennikov, Alexander Luft, Georgy Manikhas, Vladimir Moiseyenko, Viktor Mus, Sergey Orlov, Ekaterina Solovieva, Dmitriy Udovitsa, Alexander Vitsin, and Vladimir Vladimirov

Slovakia — Ludovit Jurga and Juraj Mazal

South Africa — Jacobus Erhardus Bouwer, Lydia Mary Dreosti, Louis Henri Dupper, Gregory Landers, Riaz Mall, Johan Raats, Bernardo Rapoport, and Paul Ruff

Spain — Jose Enrique Alés, Inmaculada Fernández, Alfonso Gurpide, Susana Hernando, Berta Hernández, Amelia Insa, Ulpiano Jiménez, Oscar Juan, Natividad Martinez, Miguel Muñoz, Ramon María Pérez, and Nuria Viñolas

Switzerland — Clemens Caspar and Lukas v.Rohr

Ukraine — Igor Bondarenko, Tetyana Danilova, Igor Drobner, Oleksandr Dudnichenko,
Igor Galaychuk, Yevhen Hotko, Volodymyr Komisarenko, Natalia Lisovska, Sergii Matviychuk, Petro Odarchenko, Sergiy Prokhoda, Roman Senyutovich, and Grygori Ursol

United Kingdom — Adam Dangoor, Neville Davidson, Tom Geldart, Virginia Laurence, Gary Middleton, Elaine Rankin, Riyaz Shah, and Paul Taylor

LUME-Lung 1 investigators by patients recruited

Site Code	Site Name	PI	# Patients Entered (act)
Germany	Asklepios Klinik, 82131 Gauting, Robert-KoSwitzerlandAllee 2	von Pawel, Joachim	45
Ukraine	Dnipropetrovsk State Medical Acadamy	Bondarenko, Igor	40
Russia	GUZ Leningradskaya Regional Clin. Hospital, St. Petersburg	Luft, Alexander	35
Russia	Blokhin Cancer Research Centre, RAMS, Moscow	Komov, Dmitry	29
Ukraine	Vinnytsya Regional Oncological Centre	Odarchenko, Petro	23
Poland	Specialist Hospital, Chemotherapy Department	Serwatowski, Piotr	22
Germany	Klinik, Löwenstein	Fischer, Jürgen Richard	20
China	Jilin Province Cancer Hospital	Cheng, Ying	18
Romania	Institute of Oncology 'Prof. Dr. Alexandru Trestioreanu'	Dediu, Mircea	17
Poland	Institute of Tuberculosis & Pulmonology, III. Dept., Olsztyn	Kazarnowicz, Andrzej	16
Poland	Wielkopolski Center Pulmonology+Tuberculosis PortugalIII, Poznan	Ramlau, Rodryg	16
Russia	Clinical Oncology Dispensary	Manikhas, Georgy	16
Denmark	Herlev Hospital, Onkologisk afd.	Mellemgaard, Anders	15
France	HOP Laennec, Pneumo, St Herblain	Bennouna, Jaafar	15
Italy	Ospedale S. Luigi Gonzaga - Clinica Malattie Respiratorie	Scagliotti, Giorgio	15
China	Jiangsu Cancer Hospital	Feng, Jifeng	15
Germany	Zentralklinik Bad Berka GmbH	Bonnet, Reiner	14
China	First Hospital of Jilin University	Li, Wei	14
Germany	LungenClinic, Grosshansdorf	Heigener, David	13
France	Institut PaolItalyCalmettes, Onco, Marseille	Madroszyk, Anne	13
India	Shatabdi Superspeciality Hospital	Shailesh, Bondarde	13

India	SEAROC cancer center,S.K.soni Hospital	Maru, Anish	13
India	City Cancer Centre, Cancer Hospital & Research	GopiChand, Mamillapalli	13
Poland	Mazowieckiego Centrum	Szczesna, Aleksandra	13
China	Zhejiang Cancer Hospital	Zhang, Yiping	13
Russia	GLPU Cheliabinsky	Gladkov, Oleg	13
Russia	GOU VPO Med. University n.a. I.P. Pavlov, St. Petersburg	Orlov, Sergey	13
Romania	Centrul de Oncologie Medicala	Volovat, Constantin	13
Ukraine	Ternopil regional communal clinical oncology centre	Galaychuk, Igor	13
Georgia	National Centre of Oncology	Gagua, Revaz	12
Ukraine	Kryvorizskyi regional communal clinical oncology centre	Komisarenko, Volodymyr	12
Greece	General Hospital of Thessaloniki "Papanikolaou"	Zarogoulidis, Kostas	11
Poland	Institute Maria SklodowskAustriaCurie Memorial	Krzakowski, Maciej	11
China	First Affiliated Hospital of Dalian Medical University	Liu, Jiwei	11
Romania	Oncomed SRL	Oprean, Cristina	11
South Korea	Seoul Veterans Hospital	Kim, Bong Seog	11
Ukraine	Kharkiv Medical Acadamy of Postgraduate education	Dudnichenko, Oleksandr	11
Germany	Universitätsklinikum Heidelberg, Amalienstraße 5	Thomas, Michael	10
Belarus	Public Health Inst. Minsk City Clinical Oncology Dispensary	Prokharau, Aliaksandr	10
Spain	Hospital Universitario de Elche	Martinez, Natividad	10
France	Sainte Anne Training hospital for the armies	Bérard, Henri	10
Georgia	Chemotherapy & Immunotherapy Clinic 'Medulla', Tbilisi	Tabagari, David	10
Israel	Meir Medical Center	Gottfried, Maya	10
India	KIDWAI memoraial Institute of oncology	Lakshmaiah, Kuntegowdenahalli C.	10
China	Sun Yat-Sen University Cancer Center	Zhang, Li	10

Belarus	Scientific Research Minsk	Zhavrid, Edvard	9
Israel	Hadassah medical organization, Jerusalem 91120	Peylan-Ramu, Nili	9
India	B. P .Poddar Hospital & Medical Research Ltd.	Goswami, Chanchal	9
China	Zhongshan Hospital Fudan University	BAI, Chun Xue	9
China	West China Hospital Sichuan University	Lu, You	9
China	Fujian Provincial Tumor Hospital	Huang, Cheng	9
Romania	Institutul Oncologic "Prof. Dr. Ion Chiricuta"	Cebotaru, Cristina	9
Ukraine	Odesa Regional Oncological Centre	Prokhoda, Sergiy	9
Belgium	Liège - UNIV CHU Sart Tilman - Pneumo	Bosquée, Léon	8
Belarus	Brest Regional Clinical	Shelepen, Konstantin	8
Croatia	Clinic for Lung Diseases 'Jordanovac', Zagreb	Samarzija, Miroslav	8
Lithuania	Vilniaus Universiteto	Zablockis, Rolandas	8
China	Fudan University Shanghai Cancer Center	Chang, Jianhua	8
China	Guangdong General Hospital	Wu, Yilong	8
China	Shanghai Chest Hospital	Liao, MeItalyLin	8
China	307 Hospital of PLA	Liu, Xiao-Qing	8
Ukraine	Donetsk Regional Antitumor Centre	Lisovska, Natalya	8
Ukraine	Chernigiv Regional Oncology Centre	Matviychuk, Sergii	8
Bulgaria	District Oncology Dispensary Plovdiv	Petrov, Petar	7
Belarus	Gomel Regional Clinical	Beliakouski, Vasili	7
Israel	Assaf Harofeh Medical Center, Zerifin 70300	Cyjon, Arnold	7
Portugal	IPO Lisboa Francisco Gentil, EPE, Pneumology Dep.	Almodovar, Teresa	7
Portugal	IPO Porto Francisco Gentil, EPE, Oncology Dep.	Soares da Rocha, Marta	7
China	Shanghai Pulmonary Hospital	Zhou, Caicun	7

China	Southwest Hospital	Liang, Houjie	7
China	The Third Affiliated Hospital of Harbin Medical University	Chen, Gong-Yan	7
Romania	Onesti County Hospital	Ionas, Iuliu	7
Ukraine	Uzhgorod National University, Oncology Centre	Hotko, Yevhen	7
Germany	Städisches Krankenhaus MarthAustriaMaria, Halle/Saale	Schütte, Wolfgang	6
Germany	Universitätsklinikum Freiburg, Hugstetter Straße 55	Waller, Cornelius F.	6
Germany	Johannes-Gutenberg-Universitätsklinik, Mainz, Langenbeckstr.	Fischer, Berthold	6
Belgium	Liège - HOSP CHR de la Citadelle - Emergency	Bustin, Frédérique	6
Bulgaria	Specialized Hospital for Active Treatment in Oncolcogy	Damyanov, Danail	6
Spain	Hospital Clinic I Provincial de Barcelona	Viñolas, Nuria	6
Great Britain	Wythenshawe Hospital, North West Lung Centre	Taylor, Paul	6
Greece	Papageorgiou Hospital, 1st Cardiological Cl., Thessaloniki	Fountzilas, George	6
India	Sir Gangaram Hospital	Aggarwal, Shyam	6
India	Tata Memorial Centre	Menon, Hari	6
India	Birla Cancer Centre	Malhotra, Hemant	6
India	Jawaharlal Nehru Cancer Hospital & Research Centre	Tarini, Prasad Sahoo	6
India	Bhagwan Mahaveer Cancer Hospital & Research Center, Jawahar	Somani, Naresh	6
Portugal	CHLN, EPE - Hospital de Santa Maria,Pneumology Dep.	Teixeira, Encarnacao	6
China	the 81th Hospital of PLA	Qin, Shukui	6
South Africa	GVI oncology Medi Clinic	Jacobs, Conrad	6
Germany	HELIOS-Kliniken Emil von Behring, Berlin	Kollmeier, Jens	5
Germany	Praxis Dr. Gessner, Leipzig	Geßner, Christian	5
Belarus	Vitebsk Regional Clinical Oncology Dispensary	Tomchina, Anzhelika	5
Czech Republic	District Hospital Liberec	Chalupa, Jiri	5

Italy	Hospital University Corporation - Genaral Hospital	Melotti, Barbara	5
Italy	Ospedale "Niguarda"	Siena, Salvatore	5
India	Regional Cancer Center	Sivanandan, Choondal Devan	5
India	Vedanta Institute of Medical Sciences	Desai, Chirag Jyotirker	5
Romania	Baia Mare Emergency County Hospital	Filip, Dumitru	5
Romania	Emergency Clinical County Hospital "Sf Spiridon", Iasi	Miron, Lucian	5
South Korea	Kangnam St.Mary's Hospital	Kang, Jin-Hyoung	5
South Korea	Gachon University Gil Hospital	Cho, Eun Kyung	5
Ukraine	Chmelnytskyi Oblasnnyi Oncologichnyi Tsentr	Drobner, Igor	5
Germany	Krankenhaus Nordwest, Frankfurt/Main	Jäger, Elke	4
Germany	Städtisches Krankenhaus Ffm.-Höchst, Frankfurt/Main	Derigs, Hans Günter	4
Germany	Allgemeines Krankenhaus Harburg, 21075 Hamburg	Eschbach, Corinna	4
Germany	Evangelische Lungenklinik Berlin	Grohé, Christian	4
Austria	AKH d. Stadt Linz, Pulmologie	Kropfmüller, Roland	4
Bulgaria	District Oncology Dispensary Shumen	Markova, Hristina	4
Denmark	Odense Universitetshospital, Onkologisk afd.	Sørensen, Peter	4
Spain	Hospital Universitario de la Princesa	Jiménez, Ulpiano	4
France	HOP Civil, Med A, Strasbourg	Quoix, Elisabeth	4
India	Apollo Hospital	Mohapatra, Ranjan Kumar	4
Lithuania	Hospital of Lithuanian Univ. of Health Services, Pulmonology	Sakalauskas, Raimundas	4
Portugal	Centro Hospitalar São João, EPE, Pneumology Dep.	Queiroga, Henrique	4
Portugal	IPO Porto Francisco Gentil, EPE, Oncology Dep.	Barata, Fernando	4
Poland	Regional Complex Hospital	RyniewiCzech RepublicZander, Iwona	4
Poland	Regional Specialist Hospital	Kwiatkowski, Ryszard	4

Russia	GUZ Kurskiy Regional Oncology Dispensary	Kiselev, Igor	4
South Africa	Parklands Hospital	Landers, Gregory	4
South Africa	Wits Donald Gordon Clinical Trial Site	Ruff, Paul	4
Germany	Städt. Krankenhaus, München-Bogenhausen	Gallenberger, Sebastian	3
Germany	St. Hildegardiskrankenhaus, Mainz	Kortsik, Cornelius	3
Germany	Dr. Horst-Schmidt-Kliniken, Wiesbaden	Frickhofen, Norbert	3
Germany	Kllinikum Kassel GmbH	Wolf, Martin	3
Bulgaria	Univ.Multiprofile Hospital "Dr. Georgy Stranski" EAD, Pleven	Ivanova, Nina	3
Switzerland	Kantonsspital Baden AG	Caspar, Clemens	3
Czech Republic	District Hospital Pribram, Oncology Centrum	Karasova, Elena	3
Spain	Servicio de Oncologia Radiotherapica	Insa, Amelia	3
France	Oncology Institute of the Loire	Fournel, Pierre	3
France	HOP Lyon Sud, Pneumo, Lyon	Souquet, PierrSpainJean	3
France	CHU de Rouen - Hôpital de Bois Guillaume	Muir, Jean-François	3
Greece	Athens Hospital of Chest Diseasea "SOTIRIA"	Toumbis, Michalis	3
Italy	Fondazione Poliambulanza - Dip.to di Neurologia - BRESCIA	Zaniboni, Alberto	3
Italy	Istituto Scientifico Romagnolo Meldola	Amadori, Dino	3
Israel	Chaim Sheba Medical Center	Onn, Amir	3
Israel	Sourasky Medical Center, Tel-Aviv	Merimsky, Ofer	3
India	Rajalakshmi Multispeciality Hospital	Ganesha, Dev Vashishta	3
India	Jehangir Hospital Oncology Department	Nag, Shona	3
India	King George Hospital	Mohan, Ravi	3
Portugal	CHS, EPE - Hospital de São Bernardo, Oncology Dep.	Meleiro, António	3
China	The Second Affiliated Hospital of Dalian Medical University	Zhang,, Yang	3

Russia	GUZ "Regional Clinical Oncology Dispensary"	Kulikov, Evgeny	3
Russia	GUZ Sverdlovsky Regional Oncology Dispensary	Bulavina, Irina	3
Russia	GUZ Pyatigorsky Oncological Dispensary	Vladimirov, Vladimir	3
Russia	GUZ Arkhangelsk Regional Clinical Oncology Dispensary	Solovieva, Ekaterina	3
Romania	Emergency County Hospital "Sf.loan cel Nou"	GaneAustriaMotan, DoinAustriaElena	3
Romania	Spitalul Clinic Judetean de Urgenta Brasov	Iacob, Ioan-Catalin	3
South Africa	Langenhoven Drive Oncology Centre	Dupper, Henri Louis	3
Germany	Universitätsklinik links der Isar, München, Ziemssenstr. 1	Huber, Rudolf Maria	2
Germany	Evangelisches Krankenhaus, Witten	Höfeler, Herbert	2
Germany	Klinikum rechts der Isar TU, München, Ismaninger Str. 22	Schneller, Folker	2
Germany	EberharGermanyKarls-Universität, Tübingen, OtfrieGermanyMüller-Str. 10	Spengler, Werner	2
Czech Republic	Institut onkologie a rehabilitace Na Plesi s.r.o.	Vydra, Jan	2
Spain	Hospital Quiron Madrid	Pérez, Ramón María	2
Spain	Fundación Instituto Valenciano de Oncologia	Munoz, Miguel	2
Spain	Hospital Jerez de la Frontera	Fernandez, Inmaculada	2
Great Britain	Bristol Haematology and Oncology Centre	Dangoor, Adam	2
Georgia	National Centre of Oncology	Abesadze, Ioseb	2
Georgia	Amtel Hospital first Clinical LLC	Katsarava, Vakhtang	2
Greece	University Hospital of Heraklio	Georgoulias, Vasilios	2
Italy	Fondazione Salvatore Maugeri	Pavesi, Lorenzo	2
India	Rajiv Gandhi Cancer Institute and Clinical Research	Doval, Dinesh Chandra	2
Lithuania	Siauliu ligonine, Siauliai	Zlabiene, Augenija	2
China	SIR RUN RUN SHAW HOSPITAL	Pan, Hongming	2

Russia	GUZ Regional Oncology Dispensary, Magnitogorsk	Chekha, Nina	2
Russia	Research Institute of Oncology n.a. Petrov, Dept.Bioth.& BMT	Protsenko, Svetlana	2
Russia	GUZ Kazansky Oncology Dispensary, Kazan	Khasanov, Rustem	2
Romania	County Hospital 'Dr. Alex Simionescu', Hunedoara	Vata, Lucian	2
South Africa	Medical Oncology Centre of Rosebank	Rapoport, Bernardo	2
Germany	Universitätsklinikum Benjamin Franklin, Berlin	Keilholz, Ulrich	1
Germany	Universitätsklinik Lübeck, Ratzenburger Allee, 23538 Lübeck	Dalhoff, Klaus	1
Germany	Universität, Leipzig, Johannisallee 32	Wirtz, Hubert	1
Germany	Pius-Hospital, Oldenburg	Griesinger, Frank	1
Germany	Universitätsklinikum Schleswig-Holstein	Gahn, Benedict	1
Germany	Gemeinschaftspraxis für Hämatologie und Onkologie, Köln	Schmitz, Stephan	1
Germany	Gemeinschaftspraxis Dr. Brudler / Dr. Heinrich	Heinrich, Bernhard	1
Austria	KH St. Vinzenz, Zams, Int. Abtlg.	Zabernigg, August	1
Bulgaria	Interdistrict Oncology Dispensary, Ruse	Guenova, Katerina	1
Bulgaria	Multiprofile Hospital for Active Treatment	Baeva, Blaga	1
Belarus	Bobruisk Inter-distict	Bogdan, Vadim	1
Switzerland	Kantonsspital Aarau	Mamot, Christoph	1
Czech Republic	St. Anna Hospital, 2nd Internal Department	Coupkova, Helena	1
Czech Republic	University Hospital Brno, Internal Dept.	Skrickova, Jana	1
Spain	Hospital Arnau de Vilanova	Juan, Oscar	1
Great Britain	Broomfield Hospital, Medical Oncology Dept.	Davidson, Neville	1
Great Britain	Royal Bournemouth Hospital, Oncology Department	Geldart, Tom	1
Great Britain	Poole General Hospital, Dorset Cancer Centre	Laurence, Virginia	1
Greece	Iaso General Hospital	Tzannes, Spiros	1

Croatia	University Hospital 'Sestre Milosrdnice', Zagreb	Kusic, Zvonko	1
Italy	A.O. Santa Maria della Misericordia	Crinò, Lucio	1
Italy	Centro di riferimento oncologico	Bearz, Alessandra	1
Italy	Azienda Ospedaliera Careggi - U.O. Clin. Urolgica ItalyFIRENZE	Di Costanzo, Francesco	1
Italy	Ospedale di IVREA - ASL	Bretti, Sergio	1
Israel	E. Wolfson Medical Center, Holon 58100	Brenner, Joseph	1
India	Kasturba Medical College and Hospital	Prasad, Krishna	1
Portugal	Centro Hospitalar de Vila Nova Gaia/Espinho, Pneumology Dep.	Parente, Barbara	1
Poland	Pulmonology Center in Bydgoszcz	Jagiello, Grazyna	1
China	Tongji Hospital	Yu, Shiying	1
Russia	GUZ Irkutsk Regional Oncology Dispensary	Dvornichenko, Viktoriya	1
Russia	GUZ "Oncological Dispesary #2"	Udovitsa, Dmitriy	1
Slovakia	Faculty Hospital Trnava	Jurga, Ludovit	1
Ukraine	Bukovynsk State Medical University	Senyutovich, Roman	1
South Africa	Wilgers oncology	Bouwer, J. Erhardus	1
South Africa	Pretoria Academic Hospital	Dreosti, Lydia Mary	1