

RESEARCH ARTICLE

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Nintedanib plus docetaxel as second-line therapy in patients with non-small-cell lung cancer: a network meta-analysis

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ABSTRACT Background: Nintedanib plus docetaxel has proven an overall survival benefit over docetaxel monotherapy in second-line treatment of non-small-cell lung cancer of adenocarcinoma histology in the LUME-Lung 1 pivotal trial. No published trials have previously compared nintedanib plus docetaxel with agents – other than docetaxel – that are approved second-line treatments for non-small-cell lung cancer. **Methods:** The relative efficacy of nintedanib plus docetaxel versus second-line agents was evaluated by conducting a network meta-analysis of progression-free survival and overall survival. **Results:** Nine suitable studies were identified. The estimated probability of nintedanib plus docetaxel being the best treatment with regard to overall survival was 70% (versus 16% for pemetrexed, 10% for docetaxel and 3% for erlotinib). Results for progression-free survival were similar. **Conclusion:** In patients with advanced non-small-cell lung cancer of adenocarcinoma histology, results suggest that nintedanib plus docetaxel offers clinical benefit compared with docetaxel alone, when used as second-line treatment, and suggests that this combination may also add clinical benefit compared with erlotinib in this patient group.

Improved understanding of lung cancer, such as the role of histology in treatment selection and recognition of distinct subgroups of non-small-cell lung cancer (NSCLC) that respond differently to treatment, has improved median survival times to beyond 12 months for first-line therapy in patients with advanced disease [1]. However, approximately 25% of patients show disease progression during first-line chemotherapy and nearly all patients eventually progress; second-line therapy is recommended for good performance status relapsed patients [2,3]. For patients without known treatable oncogenic alterations (the majority of patients with NSCLC), limited treatment options are available in the second-line setting. Currently approved treatment options include monotherapy with docetaxel, erlotinib or pemetrexed (non-squamous NSCLC) [3,4]. Pemetrexed has been shown to be superior to docetaxel for both progression-free survival (PFS) and overall survival (OS) in non-squamous histology NSCLC when used as first-line treatment [5] and is, thus, frequently used as a first-line treatment option in patients with adenocarcinoma [6]. Combination regimens in second-line therapy investigated to date have failed to demonstrate improvements in OS [4].

Nintedanib is a potent, orally available, angiokinase inhibitor with proven preclinical antiangiogenic and antitumor activity, that targets all subtypes of VEGF receptor, PDGF receptor and FGF

KEYWORDS

- adenocarcinoma
- chemotherapy
- nintedanib • NSCLC
- second-line treatment

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receptor [7], as well as RET and FLT3. Nintedanib in combination with docetaxel has recently been evaluated in previously treated patients with advanced or recurrent NSCLC in the Phase III LUME-Lung 1 trial (ClinicalTrials.gov NCT00805194; LUME-Lung 1, 1199.13) [8]. In this study, nintedanib combined with docetaxel significantly improved centrally reviewed PFS regardless of histology (hazard ratio [HR] = 0.79, $p = 0.0019$) and significantly prolonged OS in patients with adenocarcinoma histology (HR = 0.83, $p = 0.0359$). LUME-Lung 1 represents the first trial in the second-line setting to show a clinically meaningful survival benefit of an add-on treatment versus an active comparator in patients with NSCLC of adenocarcinoma histology.

While nintedanib plus docetaxel has been compared with docetaxel alone, no published trials to date have been conducted to compare the efficacy of this combination to other approved agents in this setting, namely pemetrexed and erlotinib. In the absence of randomized controlled trials (RCTs) involving a direct comparison of all treatments of interest, indirect treatment comparisons and network meta-analysis (NMA; also known as multiple treatments meta-analysis or mixed treatment comparisons meta-analysis) provide a method for estimating the best treatment option and an estimate of the potential relative effects [9]. A NMA combines both direct and indirect evidence to create a network of trials that allows comparison of different treatments that have not been directly compared – something that is not possible with traditional meta-analyses. As NMA uses relative treatment effects, such as HRs, this method has advantages over naive indirect comparisons by not breaking randomization and avoiding biases due to differences in the study population between treatments [10].

Here, we report the findings from a NMA to evaluate the comparative efficacy of nintedanib plus docetaxel with docetaxel, pemetrexed, erlotinib and gefitinib for the second-line treatment of patients with advanced or metastatic NSCLC of adenocarcinoma histology.

Methods

• Literature identification

A systematic review was undertaken to identify all relevant RCTs conducted to evaluate the efficacy and safety of second-line treatments for advanced or metastatic NSCLC. EMBASE,

MedLine (including Medline [R] In-Process), the Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Reviews were searched using relevant search criteria to identify all relevant trials. Clinicaltrials.gov, the National Guidelines Clearinghouse and conference proceedings from the American Society of Clinical Oncology and the European Society for Medical Oncology were also searched to identify additional studies. Searches were limited to English language publications published since 2000 (full publications) or 2011 (conference abstracts) and before 11 March 2014. Full search syntax is given in **Supplementary Appendix 1** (see online: <http://www.futuremedicine.com/doi/full/10.2217/FON.14.290>).

Studies identified by the systematic review were reviewed according to the following inclusion criteria: patient population: relapsed or refractory NSCLC – histologically or cytologically confirmed, locally advanced and/or metastatic NSCLC of stage IIIB or IV (according to American Joint Committee on Cancers) or recurrent NSCLC (all histologies); intervention: any second-line chemotherapy or targeted therapy used alone or in combination; comparator: chemotherapy, targeted therapy, placebo or best supportive care; outcomes: included data on OS and PFS; study type: RCTs, although systematic literature reviews and meta-analyses were identified and checked to ensure that no relevant trials were missed.

• Selection of trials for inclusion in networks

Following the initial literature search to identify potential clinical trials for inclusion in the network, trials of studies without a common comparator that could connect them via a network to nintedanib plus docetaxel were excluded, as were trials investigating interventions not licensed for second-line treatment of patients with NSCLC. Studies were further screened to only include trials conducted exclusively in adenocarcinoma patients, trials that reported results for a subgroup of patients with adenocarcinoma histology or trials where $\geq 75\%$ of patients had adenocarcinoma at baseline that did not report subgroup data for adenocarcinoma patients.

One trial (TITAN [11]) was identified in which physicians could choose docetaxel or pemetrexed as chemotherapy. As results from this trial could not be combined in a network with trials in which patients were randomized to docetaxel or pemetrexed, two networks were

constructed; a base case network and a scenario network (Figure 1). In the base case network the efficacy of docetaxel and pemetrexed was not assumed to be equal. In this analysis any trials in which patients were not randomly assigned to treatment with docetaxel or pemetrexed (i.e., treatment was based on physician’s choice) were excluded. The scenario network assumed equal efficacy between docetaxel and pemetrexed for the second-line treatment of NSCLC. In this analysis, any trials including docetaxel and/or pemetrexed were included as one node on the network regardless of whether patients were randomized to docetaxel or pemetrexed or

physician’s choice of docetaxel or pemetrexed (Figure 1). In this analysis any trials that directly compared docetaxel and pemetrexed were excluded.

The assumption of similarity of populations across these studies is necessary in order to allow for a NMA; however, clinical heterogeneity was evaluated to identify potential effect modifiers. This evaluation highlighted that some identified trials had a high percentage of patients with known EGF receptor (EGFR) mutation-positive NSCLC at baseline or used clinical criteria to include patients with a higher likelihood of EGFR mutation-positive NSCLC.

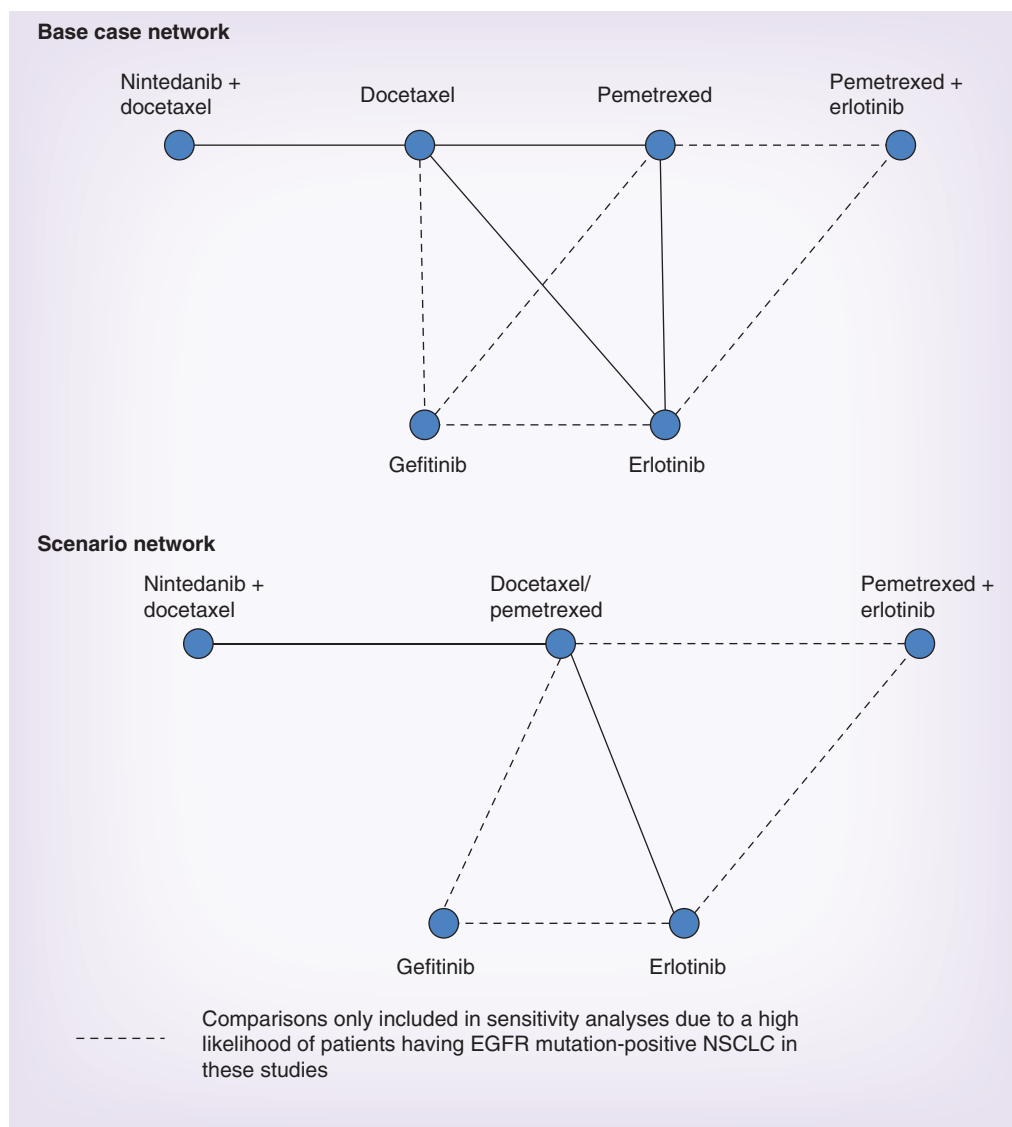


Figure 1. Networks of second-line studies for the treatment of non-small-cell lung cancer used in the base case and scenario analyses.

EGFR: EGF receptor; NSCLC: Non-small-cell lung cancer.

EGFR mutation status is known to impact on patients' outcomes in NSCLC [12,13], which could add heterogeneity of data across trials, especially if patients receive treatment with EGFR-targeted tyrosine kinase inhibitors. As such, trials with a high proportion of EGFR mutation-positive patients or trials that targeted EGFR mutation-positive patients using clinical characteristics known to be associated with EGFR mutation-positive disease (e.g., Asian race, female gender or non-smoking status [14]) were excluded from the base case analysis. These studies were, however, included in the sensitivity analyses.

Outcomes included in the NMA were OS and PFS, with OS considered the primary outcome of interest. Data extraction was performed by one researcher and validated by a second to ensure accuracy of data reporting; any discrepancies were resolved by consensus. Unadjusted data were used where possible; however, adjusted data were also included when unadjusted data were unavailable. Where HRs were not reported, data from Kaplan–Meier curves were extracted to calculate HRs using the Parmar method [15].

• Statistical analyses

The statistical analysis combined direct and indirect evidence simultaneously to obtain estimates of the relative effectiveness of each of the treatments evaluated across multiple RCTs. Data were analyzed using a Bayesian meta-analysis approach [16,17], conducted using OpenBUGS 3.2.2 software that provides estimates of the relative effectiveness of each treatment comparison as HRs, as well as an estimation of the underlying probabilities of treatments being the most effective. The posterior distributions of the treatment effect (i.e., relative risk reduction in mortality as expressed by the HR) were summarized with mean and 95% credible intervals to reflect the range of the true underlying effect with 95% probability. Based on the posterior distributions of relative treatment effects the probability that a certain intervention was more efficacious than another was calculated based on ranking. Both fixed-effects and random-effects models were used, although random-effects models were only possible when sufficient data were available to estimate a random-effects coefficient (i.e., when there is more than one trial per comparison). Random-effects analyses used vague (essentially non-informative) priors for study and treatment

effects. Estimated probabilities were calculated from the random effects model when both models were used.

The results of all analyses were based on a sample of 50,000 simulations after a burn-in period of 50,000 simulations had been discarded (after assessing convergence of the model with the Brooks–Gelman–Rubin diagnostic in OpenBUGS).

Sensitivity analyses were performed to confirm the robustness of results from both the base case (primary) and scenario analysis and included analysis of OS and PFS data, including trials with a high likelihood of containing patients with EGFR mutation-positive NSCLC. As such, sensitivity analyses examined the effects of including these patients in the comparisons.

Results

• Identification of trials for inclusion in the NMA

The search of the published literature identified 337 full-text articles that were assessed for eligibility; 61 studies, reported in 86 publications, were identified as having been conducted in the second-line treatment setting in NSCLC patients with any histology (Figure 2). Of the 61 studies identified, 18 publications reported results from nine trials in patients treated with second-line pharmacotherapy for NSCLC and in which >75% of patients had adenocarcinoma histology or reported data for the subgroup of patients with adenocarcinoma histology [5,8,11,18–24].

The patient characteristics of the identified studies are presented in Table 1. Four trials were eligible for inclusion on the base case analysis [5,8,21–22,24] and four trials were excluded from the base case analysis but were eligible for inclusion in the sensitivity analysis [18–20,23]. One trial (TITAN [11]) was excluded from the base case analysis as physicians could choose docetaxel or pemetrexed as chemotherapy treatment; this trial was included in the scenario analyses. The reported HRs for OS and PFS for each of the trials included in the NMA are shown in Table 2; all studies reported data on OS and PFS, with the exception of TITAN, which, for the adenocarcinoma subgroup, only reported OS. The network of evidence formed by the included trials in each analysis is shown in Figure 1.

• Base case NMA

The estimated HRs for OS and PFS from the base case NMA are shown in Figure 3; these

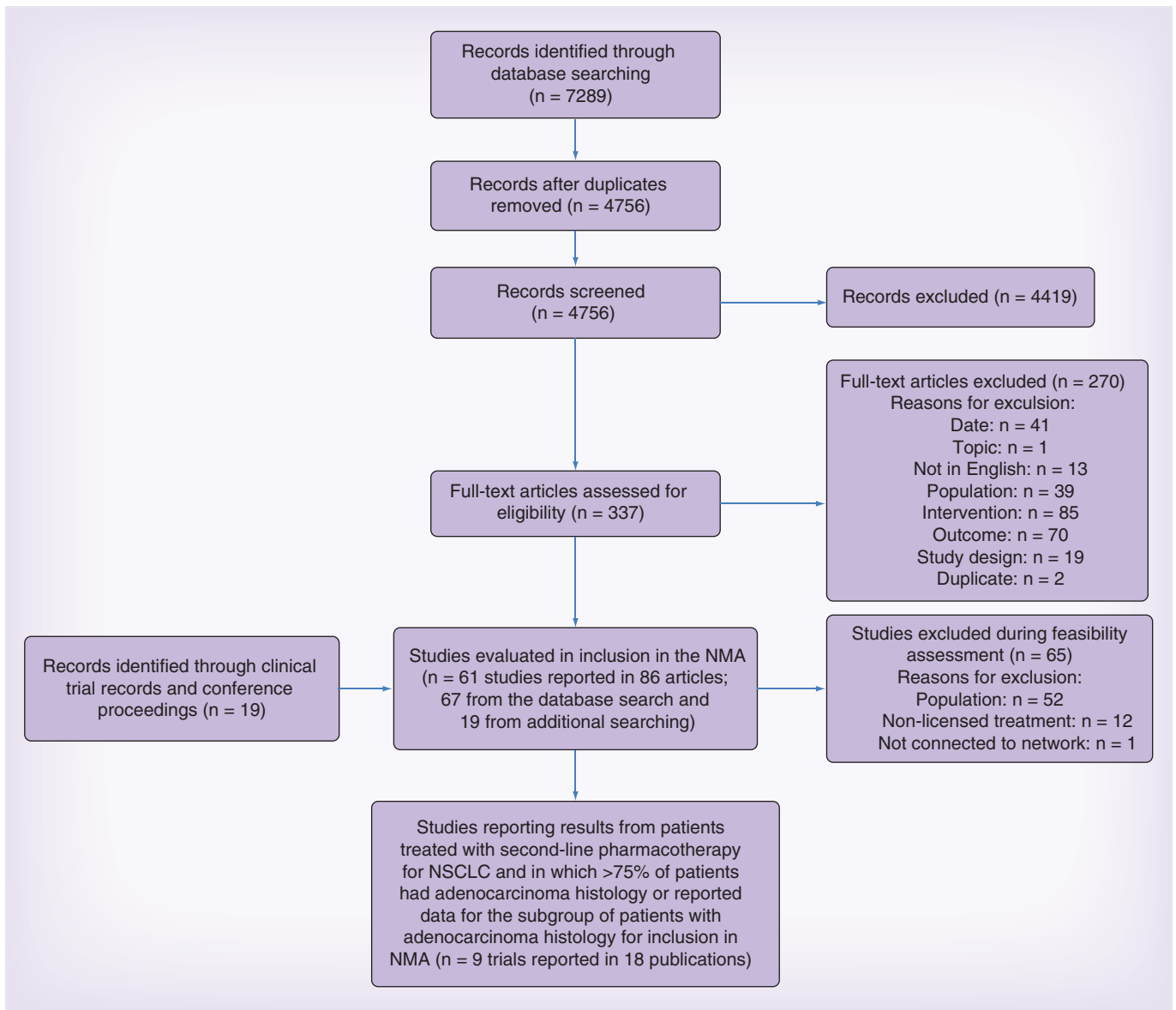


Figure 2. Flow chart outlining systematic literature review to identify trials for inclusion in network meta-analysis.

NMA: Network meta-analysis; NSCLC: Non-small-cell lung cancer.

results are from the fixed-effects model as there was no more than one trial per comparison. There was general consistency between this indirect evidence and the direct evidence from the controlled trials.

For analysis of OS, nintedanib plus docetaxel showed a statistically significant advantage in prolonging OS compared with docetaxel alone or erlotinib alone. The estimated HR for OS favored nintedanib plus docetaxel compared with pemetrexed, but this comparison did not reach statistical significance. The estimated probability of nintedanib plus docetaxel being the best treatment with regard to OS was 70.4%

compared with 16.4% for pemetrexed and 9.8% for docetaxel. There was a 3.3% probability of erlotinib being the best treatment.

For analysis of PFS, nintedanib plus docetaxel showed a statistically significant advantage in prolonging PFS compared with docetaxel alone or erlotinib. As for OS, HRs indicated that nintedanib plus docetaxel prolonged PFS compared with pemetrexed but the difference was not statistically significant. The estimated probability of nintedanib plus docetaxel being the best treatment with regard to PFS was 69.7% compared with 18.5% for pemetrexed, 6.8% for erlotinib and 5.0% for docetaxel.

Table 1. Characteristics of patients enrolled in trials included in the meta-analysis.

Treatment (number of patients randomized)	Adeno-carcinoma (%)	Median age (range; years)	White (%)	Female (%)	EGFR mutation status		Smoking status: never smoker (%)	Trial name	Ref.
					Mutation-positive (%)	Wild type (%)			
Trials included in base case									
Nintedanib plus docetaxel (n = 655)	49.2 [†]	60 (53–67)	81.4	27.3	–	–	25.2	Reck <i>et al.</i> 2013 (LUME-Lung 1)	[8]
Docetaxel plus placebo (n = 659)	51 [†]	60 (54–66)	80.4	27.3	–	–	24.4		
Pemetrexed (n = 283)	54.4 [†]	59 (22–81)	–	31.4	–	–	–	Hanna <i>et al.</i> 2004 (JMEI)	[5,21]
Docetaxel (n = 288)	49.3 [†]	57 (28–87)	–	24.7	–	–	–		
Erlotinib (n = 109)	63 [†]	66 (40–81)	99	29	0	100	17	Garassino <i>et al.</i> 2013 (TAILOR)	[22]
Docetaxel (n = 110)	75 [†]	67 (35–83)	99	34	0	100	27		
Erlotinib (n = 61)	100	54.3 (30–74)	– [‡]	34.4	0	100	24.6	Li <i>et al.</i> 2014 (WSY001)	[25]
Pemetrexed (n = 62)	100	55.1 (33–75)	– [‡]	37.1	0	100	27.4		
Trials included in sensitivity analysis									
Gefitinib (n = 71)	100	58 (40–77)	– [‡]	85.3	23.5	22.1	100	Sun <i>et al.</i> 2012 (KCSG-LU08-01)	[19]
Pemetrexed plus placebo (n = 70)	100	64 (30–78)	– [‡]	85.1	25.4	23.9	100		
Gefitinib (n = 245)	78.4	56.3% ≤64	– [‡]	38.4 [§]	–	–	29.0 [§]	Maruyama <i>et al.</i> 2008 (V-15-32)	[20]
Docetaxel (n = 244)	77.0	55.3% ≤64	– [‡]	38.1 [§]	–	–	35.7 [§]		
Gefitinib (n = 48)	91.7	60 (37–83)	– [‡]	85.4	43	–	91.7	Kim <i>et al.</i> 2012	[18]
Erlotinib (n = 48)	89.6	56 (32–81)	– [‡]	85.4	29	–	95.8		
Erlotinib plus pemetrexed (n = 78)	92.3	55.8	– [‡]	74.4	–	–	100	Lee <i>et al.</i> 2013 (S103)	[23]
Erlotinib (n = 82)	92.7	53.9	– [‡]	65.9	–	–	100		
Pemetrexed (n = 80)	96.3	55.9	– [‡]	56.3	–	–	100		
Erlotinib (n = 203)	47 [†]	59 (36–80)	85	20.6	3.4	36.9	14.7	Ciuleanu <i>et al.</i> 2012 (TITAN)	[11]
Docetaxel or pemetrexed (n = 221)	52 [†]	59 (22–79)	86	27.6	1.8	33.5	19.9		

[†]Eligible for inclusion as results reported for subgroup of patients with adenocarcinoma.
[‡]Not reported, although this trial was conducted in Asia.
[§]Data for total population, which included patients treated in first- and second-line setting.
 –: Not reported.
 EGFR: EGF receptor.

• **Base case NMA sensitivity analyses including trials with a high likelihood of containing patients with EGFR mutation-positive NSCLC**

Results of random and fixed-effects sensitivity analyses of the base case, which included trials with a high likelihood of containing patients with EGFR mutation-positive NSCLC, are shown in **Supplementary Figure 1**. Inclusion of these additional trials (n = 4) resulted in the addition of two further treatments to the network: gefitinib and erlotinib plus pemetrexed. In the random-effects model, no comparisons were statistically significant owing to wide credible intervals (**Supplementary Figure 1A**). Sensitivity analysis did not change the conclusions of the base case analysis for OS; nintedanib plus docetaxel was associated with the greatest probability of being the best treatment for prolonging OS (49.2%) followed by erlotinib plus pemetrexed (37.2%); all other agents had a low probability (<6%) of being the best treatment. For PFS, erlotinib plus pemetrexed had the greatest probability of being the best treatment (62.0%), with nintedanib plus docetaxel ranked second (25.0%), followed by gefitinib (12.2%). All other treatments were

associated with extremely low probabilities of being the best treatment with regard to PFS (each <1% chance).

The fixed-effects sensitivity analysis (**Supplementary Figure 1B**) did not change the conclusions of the base case analysis for comparison of nintedanib plus docetaxel versus docetaxel alone or erlotinib, for either OS or PFS, although the comparison of nintedanib plus docetaxel versus pemetrexed reached significance for both OS and PFS. Of the new comparisons permitted in this sensitivity analysis, nintedanib plus docetaxel showed a statistically significant advantage in prolonging OS compared with gefitinib, gefitinib showed a statistically significant advantage in prolonging PFS compared with docetaxel or pemetrexed and erlotinib plus pemetrexed showed a statistically significant advantage in prolonging PFS compared with either docetaxel or pemetrexed.

• **Scenario NMA**

The estimated HRs for OS and PFS from the scenario NMA, in which equal efficacy of docetaxel and pemetrexed was assumed, are shown in **Figure 4** for both the random-effects

Table 2. Hazard ratios for progression-free survival and overall survival from individual studies included in the network meta-analysis.

Treatments		PFS	OS	Study	Ref.
Gefitinib	Erlotinib	1.17 (95% CI: 0.81–1.7) [†]	0.47 (95% CI: 0.22–0.99) [†]	Kim <i>et al.</i> 2012	[18]
Gefitinib	Pemetrexed plus placebo	0.54 (95% CI: 0.37–0.79; p = 0.0006, two-sided p = 0.0013)	0.80 (95% CI: 0.50–1.30; p = 0.37)	Sun <i>et al.</i> 2012 (KCSG-LU08–01)	[19]
Nintedanib plus docetaxel	Docetaxel plus placebo	0.77 (95% CI: 0.62–0.96; p = 0.0193)	0.83 (95% CI: 0.70–0.99; p = 0.0359)	Reck <i>et al.</i> 2013 (LUME-Lung 1)	[8]
Erlotinib	Docetaxel or pemetrexed	–	0.95 (95% CI: 0.70–1.29)	Ciuleanu <i>et al.</i> 2012 (TITAN)	[11]
Gefitinib	Docetaxel or Pemetrexed	–	1.2 (95% CI: 0.94–1.51)	Maruyama <i>et al.</i> 2008 (V-15–32)	[20]
Pemetrexed	Docetaxel	0.83 (95% CI: 0.65–1.06; p = 0.135)	0.92 (95% CI: 0.69–1.22; p = 0.551)	Hanna <i>et al.</i> 2004 (JMEI)	[5,21]
Docetaxel	Erlotinib	0.76 (95% CI : 0.54–1.05; p = NR)	0.67 (95% CI : 0.48–0.95; p = NR)	Garassino, <i>et al.</i> 2013 (TAILOR)	[22]
Erlotinib plus pemetrexed	Erlotinib	0.57 (95% CI: 0.40–0.81; p = 0.002)	1.08 (95% CI: 0.69–1.67; p = 0.747)	Lee <i>et al.</i> 2013 (S103)	[23]
Erlotinib plus pemetrexed	Pemetrexed	0.58 (95% CI: 0.39–0.85; p = 0.005)	0.75 (95% CI: 0.49–1.13; p = 0.168)		
Erlotinib	Pemetrexed	0.99 (95% CI: 0.70–1.40; p = 0.959)	1.44 (95% CI: 0.94–2.21; p = 0.094)		
Erlotinib	Pemetrexed	0.92 (95% CI: 0.62–1.37; p = 0.683)	1.01 (95% CI: 0.66–1.54; p = 0.970)	Li <i>et al.</i> 2014 (WSY001)	[25]

[†]Calculated as described in methods.
NR: Not reported; OS: Overall survival; PFS: Progression-free survival.

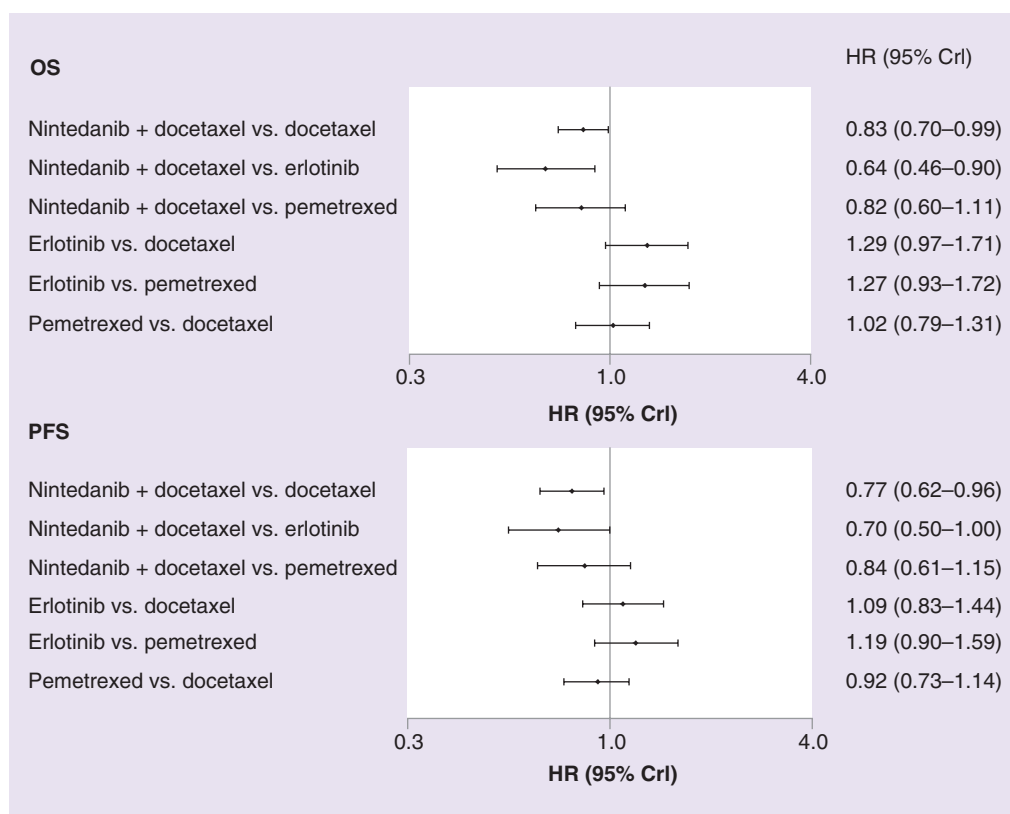


Figure 3. Base case network meta-analysis results for overall survival and progression-free survival, results from fixed-effects model.

CrI: Credible interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival.

and fixed-effects models. In the random-effects model, no comparisons were statistically significant owing to the wide credible intervals. The estimated probability of nintedanib plus docetaxel being the best treatment with regard to OS was 79% compared with 14% for docetaxel/pemetrexed and 7% for erlotinib, while the estimated probability of nintedanib plus docetaxel being the best treatment with regard to PFS was 84% compared with 9% for docetaxel/pemetrexed and 8% for erlotinib. Results from the fixed-effects scenario analysis indicated that nintedanib plus docetaxel showed a statistically significant advantage in prolonging both OS and PFS compared with patients who received docetaxel/pemetrexed alone or erlotinib.

Sensitivity analyses, including trials with a high likelihood of containing patients with EGFR mutation-positive NSCLC, are shown in [Supplementary Figure 2](#). As for other random-effects model analyses, no comparisons were statistically significant owing to the wide credibility intervals. Fixed-effects sensitivity analysis did not change the conclusions of the original

fixed-effects scenario analysis for comparison of nintedanib plus docetaxel versus docetaxel or pemetrexed, for either OS or PFS, although the comparison of nintedanib plus docetaxel versus erlotinib only remained significant in the PFS analysis. Of the new comparisons permitted in this sensitivity analysis, nintedanib plus docetaxel showed a statistically significant advantage in prolonging OS compared with gefitinib, while erlotinib plus pemetrexed and gefitinib significantly prolonged PFS compared with docetaxel/pemetrexed.

Discussion

The addition of nintedanib to docetaxel has been shown to improve both OS and PFS in patients with refractory NSCLC of adenocarcinoma histology compared with docetaxel alone in the LUME-Lung 1 trial [8]. Findings from this NMA suggest that nintedanib plus docetaxel is also potentially superior to monotherapy with erlotinib in terms of OS and PFS in this patient population. Analyzing the relative treatment effects by means of HRs indicated

that nintedanib plus docetaxel had the highest probability of being the best treatment with regard to both OS and PFS, compared with docetaxel alone and erlotinib in the base case analysis; a finding that was supported in the sensitivity analyses of OS that included patients with a high likelihood of having EGFR mutation-positive NSCLC. Sensitivity analyses, which resulted in additional treatment comparisons, also indicated that nintedanib plus docetaxel offered improvements in OS and PFS compared with pemetrexed monotherapy and improvements in OS compared with gefitinib. Scenario analysis, which assumed equivalent efficacy of docetaxel and pemetrexed, did not change the main findings that nintedanib plus docetaxel had the highest probability of being the best treatment for improving OS and PFS.

A primary assumption in all NMAs is that the clinical studies included in the analysis

are sufficiently clinically and methodologically homogeneous to be quantitatively combined. As such, differences in patient baseline characteristics between studies must be considered when interpreting the findings, as significant differences between trials can influence the results and subsequent conclusions. Differences in the percentage of patients with EGFR mutation-positive NSCLC were controlled by excluding studies with a high likelihood of containing these patients, or studies known to contain patients with EGFR mutation-positive NSCLC, from the base case analysis. As such, the base case analysis is considered the most appropriate network for indirect treatment comparisons as the trials included in this network are likely to have the most comparable patient populations. While excluding these trials did reduce heterogeneity, it also resulted in only one trial contributing

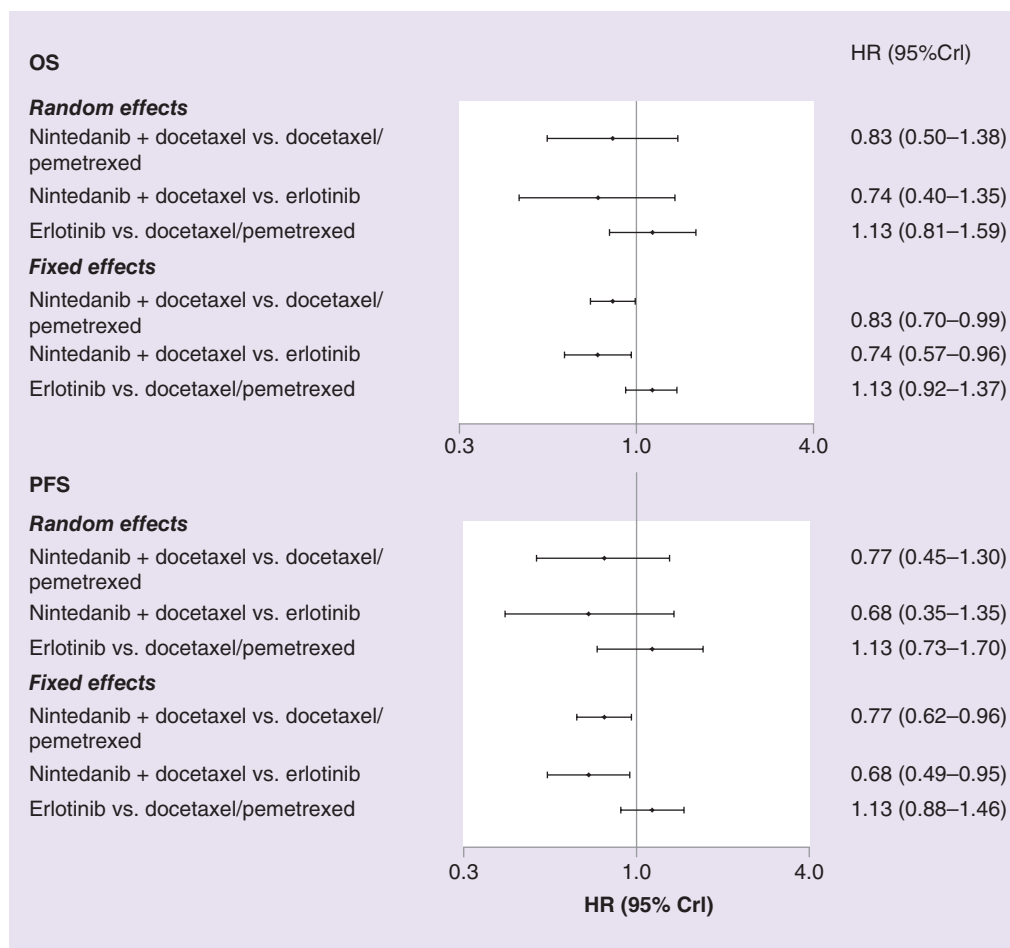


Figure 4. Scenario network meta-analysis results for overall survival and progression-free survival, results from the random- and fixed-effects model.

CrI: Credible interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival.

to each treatment comparison in the base case analysis; this should be considered as a limitation. Additionally, as this network did not assume equivalent efficacy of docetaxel and pemetrexed, results from the TITAN study [11] were excluded. This is a consideration as the TITAN study found no differences in efficacy between erlotinib and standard chemotherapy (docetaxel or pemetrexed), and inclusion of these results would have influenced comparisons across the entire network and was the reason for conducting scenario analyses. Importantly, key findings from the sensitivity analyses, despite representing a broader patient population than the base case analysis, were not significantly different from the base case analysis. Additional heterogeneity was noted within trials included in the sensitivity analysis as some studies were known to have a higher percentage of patients with known EGFR mutations [18,19].

A further source of heterogeneity between studies is the fact that not all patients in the trials had adenocarcinoma histology; a cutoff of 75% of patients with adenocarcinoma was used to maximize the evidence base available for the comparison. Furthermore, studies that did not report the number of patients with adenocarcinoma histology were excluded, despite the fact that a significant proportion of patients with non-squamous NSCLC typically have adenocarcinoma. While the results from the recently reported REVEL trial [25] were not available at the time these analyses were conducted, REVEL would not have met the criteria for inclusion as the percentage of patients with adenocarcinoma was not reported. One of the strengths of this analysis is that rigorous inclusion and exclusion criteria were employed in order to select the most appropriate studies for inclusion; however, this also resulted in only a few trials being available for specific treatment comparisons (e.g., data for nintedanib plus docetaxel came from a single study) and this should be considered a limitation. While the results from a Phase III trial (LUME-Lung 2) comparing the combination of nintedanib with pemetrexed versus placebo plus pemetrexed have been reported, this study was not included in the network as the results have not yet been reported in full, the study was stopped prematurely and the combination of nintedanib plus pemetrexed is not the approved treatment combination [26]. An additional limitation of

this analysis is the fact that the relative tolerability of treatments was not compared. While we believe NMA provides the most robust methodology for evaluating the comparative efficacy of nintedanib plus docetaxel to other second-line treatment options, simple indirect comparisons based on the Bucher methodology agreed with findings from the NMA that nintedanib plus docetaxel offers advantages in OS and PFS compared with erlotinib monotherapy (Supplementary Appendix 2).

Conclusion

NMA provides a useful source of information on the comparative benefits of different treatments for healthcare decision makers when direct head-to-head trials have not been conducted. Results of this NMA support the conclusions of the LUME-Lung 1 trial [8], that nintedanib plus docetaxel offers clinical benefit compared with docetaxel alone for the second-line treatment of patients with advanced NSCLC of adenocarcinoma histology, and suggest that this combination may also add clinical benefit compared with erlotinib when used in this patient group.

Future perspective

Nintedanib in combination with docetaxel recently received marketing authorization by the EMA for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumor histology after first-line chemotherapy. As such, nintedanib in combination with docetaxel will be an available treatment option for these patients and analyses such as this can help clinicians decide the most appropriate treatment based on the available data. Recent data from clinical trials [22,27] and meta-analyses [28] suggest that the EGFR tyrosine kinase inhibitors erlotinib and gefitinib may not be the most appropriate second-line treatment choice in patients with EGFR wild-type NSCLC. Analyses such as ours provide additional information to guide treatment choice in this patient group. Growing clinical experience with the combination with nintedanib plus docetaxel will help establish the value of this treatment option in clinical practice.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

Background

- Nintedanib in combination with docetaxel is a new treatment option for patients with locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma tumor histology after first-line chemotherapy.
- This network meta-analysis compared relative efficacy of second-line agents that had not been directly compared.

Methods

- A systematic literature review was conducted to identify relevant randomized clinical trials evaluating the efficacy of second-line treatments for advanced or metastatic non-small-cell lung cancer between January 2000 and March 2014.
- Statistical analysis was used to combine direct and indirect evidence simultaneously to obtain estimates of the relative effectiveness of each of the treatments evaluated across the multiple randomized controlled trials identified.

Results

- The estimated overall survival hazard ratio (95% credible interval) for nintedanib plus docetaxel was 0.83 (0.70–0.99) compared with docetaxel, 0.64 (0.46–0.90) compared with erlotinib and 0.82 (0.60–1.11) compared with pemetrexed in the base case.
- Nintedanib plus docetaxel had the highest probability of being the best treatment with regard to overall survival.
- Sensitivity analysis did not change the findings of the base case analysis for these comparisons. Results for progression-free survival were similar.

Conclusion

- This network meta-analysis suggest that nintedanib plus docetaxel offers clinical benefit compared with docetaxel alone, when used as second-line treatment, and suggests that this combination offers clinical benefit compared with erlotinib in these patients.

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