# Nintedanib in combination with pemetrexed and cisplatin for chemotherapy-naive patients with advanced malignant pleural mesothelioma (LUME-Meso): a double-blind, randomised, placebo-controlled phase 3 trial

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## Summary

**Background** Nintedanib targets VEGF receptors 1–3, PDGF receptors α and β, FGF receptors 1–3, and Src and Abl kinases, which are all implicated in malignant pleural mesothelioma pathogenesis. Here, we report the final results of the phase 3 part of the LUME-Meso trial, which aimed to investigate the efficacy and safety of pemetrexed plus cisplatin combined with nintedanib or placebo in unresectable malignant pleural mesothelioma.

**Methods** This double-blind, randomised, placebo-controlled phase 3 trial was done at 120 academic medical centres and community clinics in 27 countries across the world. Chemotherapy-naive adults (aged ≥18 years) with unresectable epithelioid malignant pleural mesothelioma and ECOG performance status 0–1 were randomly assigned 1:1 via an independently verified random number-generating system to receive up to six 21-day cycles of pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) on day 1, then nintedanib (200 mg twice daily) or matched placebo on days 2–21. Patients without disease progression after six cycles received nintedanib or placebo maintenance on days 1–21 of each cycle. The primary endpoint was progression-free survival (investigator-assessed according to mRECIST) in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of their assigned study drug. This study is registered with ClinicalTrials.gov, number NCT01907100.

**Findings** Between April 14, 2016, and Jan 5, 2018, 541 patients were screened and 458 were randomly assigned to either the nintedanib group (n=229) or the placebo group (n=229). Median treatment duration was 5·3 months (IQR 2·8–7·3) in the nintedanib group and 5·1 months (2·7–7·8) in the placebo group. After 250 events, progression-free survival was not different between the nintedanib group (median 6·8 months [95% CI 6·1–7·0]) and the placebo group (7·0 months [6·7–7·2]; HR 1·01 [95% CI 0·79–1·30], p=0·91). The most frequently reported grade 3 or worse adverse event in both treatment groups was neutropenia (73 [32%] in the nintedanib group *vs* 54 [24%] in the placebo group). Serious adverse events were reported in 99 (44%) patients in the nintedanib group and 89 (39%) patients in the placebo group. The only serious adverse event occurring in at least 5% of patients in either group was pulmonary embolism (13 [6%] *vs* seven [3%]).

**Interpretation** The primary progression-free survival endpoint of the phase 3 part of LUME-Meso was not met and phase 2 findings were not confirmed. No unexpected safety findings were reported.

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## Introduction

Malignant pleural mesothelioma is an uncommon but aggressive disease associated with poor prognosis.[1] A major risk factor for this disease is exposure to asbestos. Regulation of commercial asbestos use has reduced occupational exposure in some countries, but asbestos exposure continues relatively unchecked in others, particularly in low-income and middle-income countries, potentially giving rise to an increase in malignant pleural mesothelioma cases.[2] The burden of this disease is exacerbated because it is usually diagnosed at an advanced stage, at which point most patients have unresectable disease or are no longer eligible for surgery.[1–3]

For patients with unresectable malignant pleural mesothelioma, the main component of treatment is systemic chemotherapy. Pemetrexed combined with cisplatin is the only globally approved first-line treatment,[1–3] although raltitrexed combined with cisplatin is used in several European countries as first-line treatment on the basis of the results of a phase 3 trial.[4] Pemetrexed with cisplatin is associated with a median overall survival of approximately 1 year[5] and despite substantial clinical

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## Research in context

### Evidence before this study

The original protocol for this study was finalised in 2013 and based on consideration of relevant data available at the time, which were identified through literature searches in PubMed and data presented at major oncology congresses, including the American Society of Clinical Oncology annual meeting, the European Society for Medical Oncology annual meeting, and the International Association for the Study of Lung Cancer World Conference on Lung Cancer. We used no publication date or language restrictions in our search. At this time, signalling via the VEGF pathway was known to play an important role in the pathophysiology of mesothelioma, but other signalling pathways inhibited by nintedanib, such as signalling via PDGF, FGF, and Src/Abl were also thought to be involved. Nintedanib was also known to have a manageable safety profile in combination with chemotherapy, making it suitable for administration in combination with pemetrexed and cisplatin, which is the standard of care in unresectable malignant pleural mesothelioma. This knowledge provided the rationale for the LUME-Meso study.

### Added value of this study

The LUME-Meso study confirmed that treatment with nintedanib in combination with pemetrexed plus cisplatin was well tolerated in patients with unresectable malignant pleural mesothelioma, with a tolerability profile consistent with the known safety profile of these drugs.

### Implications of all the available evidence

Phase 3 of the LUME-Meso study did not meet the primary objective of showing significantly improved progression-free survival with the addition of nintedanib to standard-of-care pemetrexed plus cisplatin in patients with histologically confirmed unresectable malignant pleural mesothelioma of epithelioid histology. The phase 3 results did not confirm the findings from the phase 2 part of the study. Our study adds to the existing evidence that supports the prognostic value of baseline platelet count in malignant pleural mesothelioma and suggests that this baseline variable might also have a role in predicting treatment outcome, at least for nintedanib. However, this finding needs prospective confirmation. The study also showed that concordance between investigator-assessed progression-free survival and centrally reviewed progression-free survival is possible in a patient population with malignant pleural mesothelioma.

research, a plateau in malignant pleural mesothelioma treatment has been reached since this combination became the first-line standard of care.

Angiogenesis plays an established role in the pathogenesis of malignant pleural mesothelioma, contributing to a favourable microenvironment for tumour growth. In vitro inhibition of vascular endothelial growth factor (VEGF) and VEGF-C has been shown to produce synergistic inhibition of mesothelioma cell growth.[6] Preclinical data also indicate that VEGF is an autocrine growth factor in malignant mesothelioma.[7] In line with these observations, increased levels of VEGF has been associated with more advanced disease and poor prognosis.[8] Tumour angiogenesis in malignant pleural mesothelioma also involves signalling via other pathways. Expression patterns of platelet-derived growth factor (PDGF) indicate that PDGF also functions as an autocrine growth stimulator in the pathogenesis of malignant mesothelioma.[9,10] Preclinical studies have implicated fibroblast growth factor (FGF) in malignant pleural mesothelioma pathogenesis, pointing to its role in cell proliferation and migration; FGF receptor 1, FGF2, and FGF18 are overexpressed in mesothelioma cell lines.[11]

Data from the phase 3 Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS), which investigated the addition of bevacizumab to pemetrexed with cisplatin (with maintenance bevacizumab), showed a significant improvement in overall survival compared with pemetrexed with cisplatin alone (median overall survival 18·8 [95% CI 15·9–22·6] *vs* 16·1 months [14·0–17·9]; hazard ratio [HR] 0·77 [0·62–0·95], p=0·017),[12] supporting the concept of VEGF inhibition as a rational approach in malignant pleural mesothelioma. Targeting more than one antiangiogenic pathway might have the potential for increased efficacy. Nintedanib is an oral triple angiokinase inhibitor targeting VEGF receptors 1–3, PDGF receptors α and β, and FGF receptors 1–3.[13] In addition, nintedanib also inhibits Src and Abl kinases, which promote mesothelioma cell migration,[13,14] making this pathway an additional therapeutic target in malignant pleural mesothelioma.[15]

The LUME-Meso study[16] was a global phase 2–3, randomised, double-blind, placebo-controlled study in chemotherapy-naive patients with unresectable malignant pleural mesothelioma. It investigated the efficacy and safety of nintedanib or placebo combined with pemetrexed with cisplatin followed by nintedanib or placebo maintenance therapy. Results from the phase 2 part of the trial showed that nintedanib prolonged progression-free survival versus placebo (HR 0·56 [95% CI 0·34–0·91], p=0·017; median 9·4 months [6·7–11·2] *vs* 5·7 months [5·5–7·0]). Median overall survival was 18·3 months (95% CI 15·2–28·8) versus 14·2 months (12·3–20·9; HR 0·77 [95% CI 0·46–1·29], p=0·319).[16] The clinical benefit of nintedanib was also evident in the subgroup of patients with epithelioid histology (median progression-free survival 9·7 months [95% CI 7·2–12·4] with nintedanib *vs* 5·7 months [5·5–7·0] with placebo; HR 0·51

[0·30–0·86], p=0·010; and median overall survival 20·6 months [16·2–28·8] *vs* 15·2 months [12·2–23·6]; HR 0·70 [0·40–1·21], p=0·197).[16] In light of the phase 2 results, the trial was formally amended to include a confirmatory phase 3 part, which enrolled patients with epithelioid histology only. Here, we report these phase 3 results.

## Methods

### Study design and participants

This double-blind, randomised, placebo-controlled phase 3 trial was done at 120 academic medical centres and community clinics in 27 countries across the world. Eligible patients were aged 18 years or older, with histologically confirmed, unresectable malignant pleural mesothelioma of epithelioid subtype, measurable disease according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST) for mesothelioma,[17] life expectancy of at least 3 months, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had not received previous systemic chemotherapy for malignant pleural mesothelioma. Histological diagnosis was done according to the treating centre; a central pathological review was not conducted. Complete eligibility criteria are in the protocol (appendix p 8).

The trial followed the principles of the Declaration of Helsinki and was done in accordance with good clinical practice and local laws and regulations. The protocol was approved by health authorities and independent ethics committees or institutional review boards in each country or centre. All patients provided written informed consent.

### Randomisation and masking

Patients were randomly assigned 1:1 to pemetrexed plus cisplatin either with nintedanib or placebo by a validated random number-generating system at Boehringer Ingelheim. Randomisation was verified by an independent statistician and implemented centrally via an interactive voice-based or web-based response system. Separate randomisation lists were generated for each phase of the study. Individuals directly involved in the conduct and analysis of the trial did not have access to the randomisation schedule. Randomisation was done in blocks of four without stratification for this phase 3 part of the trial.

Patients, treating physicians, and representatives of the study funder were masked to study treatment assignment. Nintedanib and placebo were supplied in identical blister packs with unique identifiers and had identical storage requirements.

### Procedures

Patients received combination treatment of up to six 21-day cycles of 500 mg/m² pemetrexed plus 75 mg/m² cisplatin (sourced locally) by intravenous infusion on day 1, plus 200 mg nintedanib orally twice daily (Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim, Germany) or matched placebo on days 2–21. After six cycles, patients who had not progressed received nintedanib or placebo maintenance therapy on days 1–21 of each cycle until disease progression, undue toxicity, withdrawal of consent, or death. Patients who had disease progression were eligible to receive nintedanib or placebo beyond the point of progression if they had clinical benefit, as established by the investigator. Dose reduction of study treatments and treatment delays were permitted according to predefined criteria to manage tolerability and adverse events.

Tumour response assessment by computed tomography or magnetic resonance imaging was done at baseline (≤4 weeks before first treatment) and then every 6 weeks (±1 week) and continued until disease progression or start of subsequent anticancer therapy. Tumour response was assessed by investigators using mRECIST.[17] Tumour images were collected for subsequent independent central review. Health-related quality of life was assessed using the mesothelioma version of the Lung Cancer Symptom Scale (LCSS-Meso)[18] at baseline and before every chemotherapy administration until the first follow-up visit after the end of treatment. Each LCSS-Meso scale (and items) was scored from 0 to 100, with 0 representing no symptom distress, no interference with activity level, or best possible health-related quality of life.

See Online for appendix

Safety was assessed throughout the study using the US National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Adverse events of interest were categorised by medical concept using standardised Medical Dictionary for Regulatory Activities.

### Outcomes

The primary endpoint was investigator-assessed progression-free survival according to mRECIST. The key secondary endpoint was overall survival. Other secondary endpoints were objective response and disease control. Other endpoints were health-related quality of life, best overall response, time to objective response, and duration of disease control (not reported).

### Statistical analysis

The assumed treatment effect in this phase 3 trial was based on results from the phase 2 part of the trial. This phase 3 trial had 90% power to detect a statistically significant (one-sided α of 2·5%) and clinically meaningful improvement in progression-free survival (assumed HR 0·63) after 199 events of progression or death. Additionally, 279–346 overall survival events were needed to detect an improvement in overall survival (assumed HR 0·71–0·74) with 80% power (one-sided α of 2·5%). The final number of overall survival events for the first overall survival analysis was to be established at the time of the primary progression-free survival analysis, with the final statistical analysis using the weighted inverse normal method.[19] The calculated sample size was 450 patients.

Progression-free survival and overall survival were analysed according to a hierarchical testing strategy:

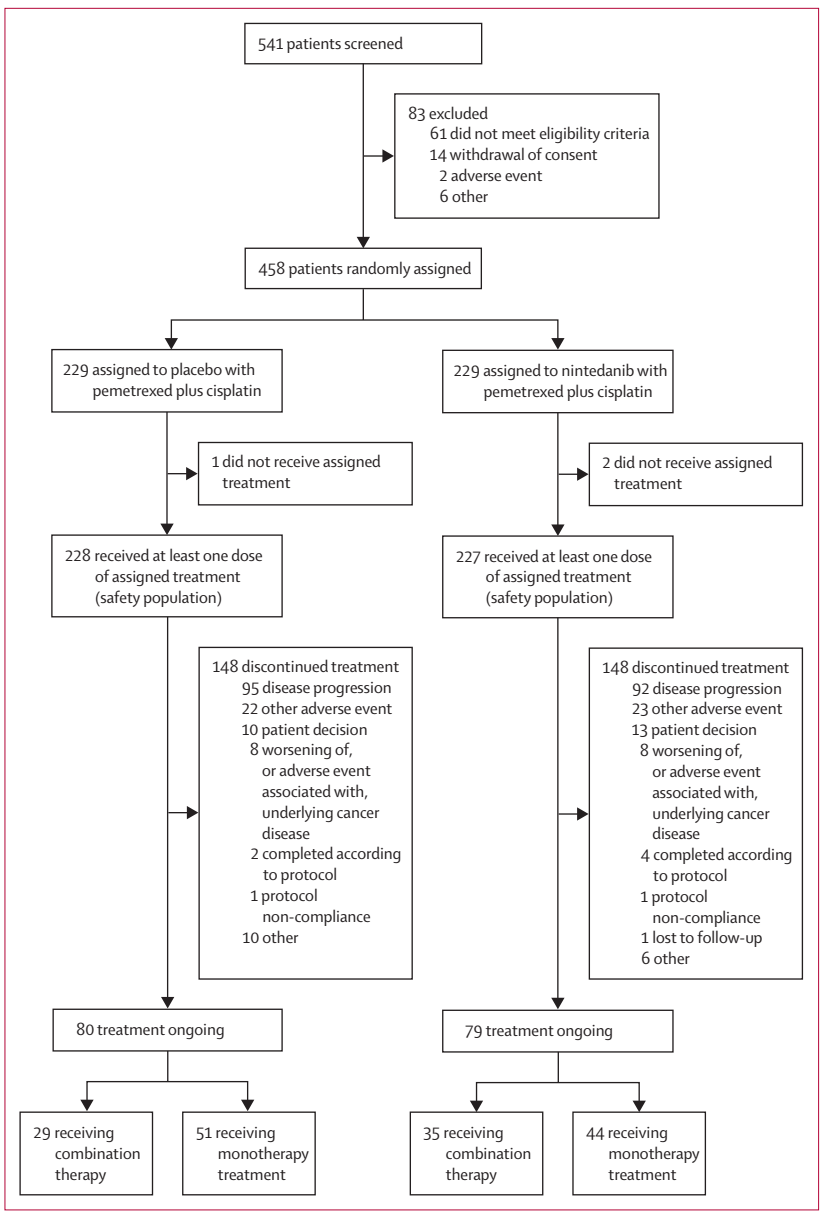



***Figure 1:*** **Trial profile**

formal statistical testing for overall survival would be done only if the difference in the primary endpoint was significant. At the time of the primary progression-free survival analysis, an interim analysis for overall survival was to be done with an α level according to the O'Brien and Fleming spending function. Progression-free survival and overall survival were analysed using the Kaplan–Meier method. HRs and corresponding 95% CIs were estimated using Cox proportional hazards models. The proportionality assumption was confirmed using log cumulative hazard plots. p values were obtained from a one-sided log-rank test without stratification. One-sided p values were needed for the weighted inverse normal method, although two-sided p values were also calculated and are used throughout this manuscript. Proportions of patients achieving an objective response or disease control were compared between treatment groups using logistic regression models.

For progression-free survival and overall survival, consistency of treatment effect was investigated in prespecified subgroups, namely sex (male *vs* female), race (Asian *vs* other), age (<65 years *vs* ≥65 years), ECOG performance status (0 *vs* 1), previous asbestos exposure (yes *vs* no or unknown), smoking status (current smoker or ex-smoker *vs* never smoker), previous surgery (yes *vs* no), lactate dehydrogenase at baseline (equal to or less than upper limit of normal [ULN] *vs* more than ULN), region (north Africa or South Africa *vs* Asia *vs* Australia, New Zealand, Europe, or North America *vs* Central America or South America); histology (epithelioid *vs* biphasic), white blood cell count at baseline (low [$<15\cdot5\times10^9$ cells per L] *vs* high [$\geq15\cdot5\times10^9$ cells per L]), haemoglobin at baseline (low [<146 g/L] *vs* high [≥146 g/L]), and platelet count at baseline (low [$<400\times10^9$ cells per L] *vs* high [$\geq400\times10^9$ cells per L]).[20] Each subgroup was investigated using a single proportional hazards model adjusted for treatment, subgroup, and treatment-by-subgroup interaction; HR and 95% CI of the treatment effect were calculated as well as the interaction p values.

Changes in LCSS-Meso scores over time were assessed using mixed-effects growth curve models with the average longitudinal profile for each score being described by a piecewise linear model. The estimated area under the curve (AUC) up to the median follow-up time was calculated for each treatment group; AUC divided by the median follow-up time was interpreted as the mean score over time. Treatment effect was estimated as the difference between the mean scores in each treatment group. Symptom improvement was defined as an at least ten-point decrease from baseline at any time during the trial. If a patient had not improved, symptom worsening was defined as a ten-point increase in score at any time during the trial. Otherwise, a patient was considered stable. A logistic regression model, adjusted for treatment, was used for status-change analyses. Dose intensity was calculated from the first dose of medication to the last dose and was defined as the amount of medication received over this time divided by the amount of medication that would have been administered had the protocol-specified dose been received. Post-hoc exploratory analyses were done, including Kaplan–Meier analyses for overall survival and progression-free survival, for analyses by selected baseline characteristics.

Efficacy analyses included all patients randomly assigned to a group according to the intention-to-treat principle, whether they had received treatment or not. Patients with biphasic histology (who were enrolled before the protocol amendment) were included in the efficacy

assessments. Safety analyses included all patients who received at least one dose of study treatment. Patients from the phase 2 part of the trial were not included in the phase 3 analyses presented here. An independent data-monitoring committee was responsible for periodic assessment of safety and efficacy data in the study.

All statistical analyses were done using SAS, version 9.4. The study is registered with ClinicalTrials.gov, number NCT01907100.

### Role of the funding source

The trial was collaboratively designed by the study Steering Committee and the funder. The funder was responsible for the collection and analysis of the data and had a role in data interpretation and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between April 14, 2016, and Jan 5, 2018, 541 patients were screened, of whom 83 were excluded and the remaining 458 randomly assigned to either the nintedanib group (n=229) or the placebo group (n=229; figure 1). Demographic and baseline disease characteristics were generally well balanced between the treatment groups (table 1). At data cutoff on March 16, 2018, 159 patients were still receiving treatment. At the time of analysis, median duration of follow-up was 9·2 months (IQR 5·2–13·1) in the nintedanib group and 9·7 months (5·4–13·9) in the placebo group.

227 (99%) of 229 patients in the nintedanib group and 228 (>99%) of 229 in the placebo group received at least one dose of study treatment. Median treatment duration was 5·3 months (IQR 2·8–7·3) in the nintedanib group and 5·1 months (2·7–7·8) in the placebo group and the mean dose intensity was 95·3% (SD 11·5) for nintedanib and 98·1% (6·5) for placebo. Nintedanib dose reductions were required in 67 (30%) of 227 patients, and 16 (7%) required a second dose reduction. Placebo dose reduction was required in 22 (10%) of 228 patients, and five (2%) required a second dose reduction. 180 (79%) patients in the nintedanib group and 171 (75%) in the placebo group received at least four cycles of cisplatin and pemetrexed. The median number of pemetrexed and cisplatin cycles was five (IQR 4–6) with nintedanib and six (4–6) with placebo. The mean dose intensity for pemetrexed was 96·4% (SD 7·4) in the nintedanib group and 98·5% (SD 5·7) in the placebo group; the mean dose for cisplatin was 96·2% (7·1) in the nintedanib group and 97·9% (6·3) in the placebo group. Pemetrexed dose was reduced in 53 (23%) patients who received nintedanib and 20 (9%) who received placebo, whereas cisplatin dose was reduced in 57 (25%) patients treated with nintedanib and 31 (14%) who received placebo.

142 (63%) patients in the nintedanib group and 140 (61%) patients in the placebo group received nintedanib or placebo maintenance treatment after completion of chemotherapy. Treatment duration during the monotherapy maintenance phase was similar between treatment groups (median 2·8 months [IQR 1·5–5·0] for nintedanib *vs* 3·0 months [1·4–4·8] for placebo; mean 3·8 months [SD 3·1] *vs* 3·6 months [3·0]). Most patients who went on to receive nintedanib or placebo monotherapy had received at least four cycles of

| | Nintedanib group (n=229) | Placebo group (n=229) |
|---|---|---|
| Age, years | 66 (58–70) | 66 (58–70) |
| Sex | | |
| Male | 165 (72%) | 169 (74%) |
| Female | 64 (28%) | 60 (26%) |
| Race | | |
| White | 185 (81%) | 180 (79%) |
| American Indian or Alaska native | 12 (5%) | 14 (6%) |
| Asian | 14 (6%) | 16 (7%) |
| Other | 2 (<1%) | 0 |
| Missing* | 16 (7%) | 19 (8%) |
| ECOG performance status | | |
| 0 | 99 (43%) | 98 (43%) |
| 1 | 130 (57%) | 131 (57%) |
| Smoking history | | |
| Never smoker | 92 (40%) | 89 (39%) |
| Ex-smoker | 113 (49%) | 122 (53%) |
| Current smoker | 24 (10%) | 18 (8%) |
| Previous exposure to asbestos | | |
| Yes | 141 (62%) | 150 (66%) |
| No | 68 (30%) | 53 (23%) |
| Unknown | 20 (9%) | 26 (11%) |
| Time since first histological diagnosis, months | 1·3 (0·9–2·0) | 1·2 (0·8–1·8) |
| Histology | | |
| Epithelioid | 220 (96%) | 223 (97%) |
| Biphasic† | 9 (4%) | 6 (3%) |
| Tumour stage at screening (UICC or AJCC)‡ | | |
| I | 12 (5%) | 15 (7%) |
| II | 15 (7%) | 17 (7%) |
| III | 89 (39%) | 90 (39%) |
| IV | 113 (49%) | 105 (46%) |
| Missing | 0 | 2 (<1%) |
| Pleural effusion | 13 (6%) | 23 (10%) |
| Previous radiotherapy | 11 (5%) | 13 (6%) |
| Previous surgery (pleurectomy, decortication, or extrapleural pneumonectomy) | 16 (7%) | 16 (7%) |

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. UICC=Union Internationale Contre le Cancer. AJCC=American Joint Committee on Cancers (6th or 7th edition). *Race was only recorded where allowed by local regulations. †Patients with biphasic histology were enrolled before the protocol amendment. ‡Patients with stage I or II disease were all considered to have unresectable disease according to the investigating clinician.

***Table 1:*** **Demographic and clinical characteristics of the patients at baseline**

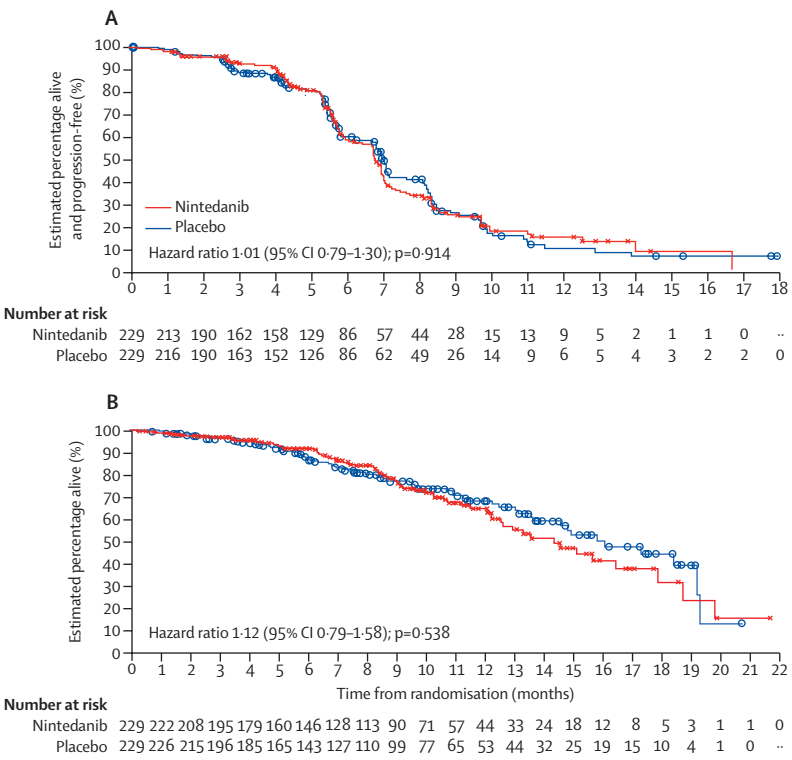



***Figure 2:*** **Kaplan–Meier curves**
Progression-free survival by investigator assessment (A) and overall survival (B).

| | Nintedanib group (n=229) | Placebo group (n=229) |
|---|---|---|
| Any | 69 (30%) | 81 (35%) |
| Radiotherapy | 6 (3%) | 12 (5%) |
| Systemic therapy | | |
| Any | 67 (29%) | 78 (34%) |
| Pemetrexed and cisplatin | 1 (<1%) | 8 (3%) |
| Pemetrexed and carboplatin | 10 (4%) | 27 (12%) |
| Pemetrexed monotherapy | 6 (3%) | 4 (2%) |
| Pemetrexed and other systemic anticancer therapy | 5 (2%) | 3 (1%) |
| Immunotherapy | 9 (4%) | 11 (5%) |
| Bevacizumab and other systemic anticancer therapy | 5 (2%) | 3 (1%) |
| Other subsequent systemic anticancer therapy | 42 (18%) | 36 (16%) |
| Investigational drug | 3 (1%) | 5 (2%) |

Patients could have more than one subsequent anticancer therapy. Post-study treatments refer to any anticancer treatments that the patient received after discontinuation of study medication in this trial.

***Table 2:*** **Post-study therapy**

pemetrexed plus cisplatin (133 [94%] in the nintedanib group and 133 [95%] in the placebo group).

At the time of the primary analysis, 126 (55%) of 229 patients in the nintedanib group and 124 (54%) of 229 patients in the placebo group had had a progression-free survival event. Progression-free survival by investigator assessment was not different between treatment groups (median 6·8 months [95% CI 6·1–7·0] in the nintedanib group *vs* 7·0 months [6·7–7·2] in the placebo group; HR 1·01 [95% CI 0·79–1·30], p=0·914; figure 2A).

Results for progression-free survival by independent central review were consistent with findings from investigator assessment (median 6·8 months [5·7–7·0] *vs* 6·8 months [5·8–7·0]; HR 0·99 [95% CI 0·77–1·28], p=0·963 (appendix p 1). Concordance between investigator assessment and independent central review was high (>80% in both treatment groups). Based on these results, the study was stopped as per the protocol.

127 (28%) patients died—64 (28%) of 229 patients in the nintedanib group and 63 (28%) of 229 patients in the placebo group. Median overall survival was 14·4 months (95% CI 12·2–17·9) in the nintedanib group versus 16·1 months (13·7–19·3) in the placebo group, with an HR of 1·12 (95% CI 0·79–1·58, p=0·538; figure 2B).

After progression, 69 (30%) patients in the nintedanib group and 81 (35%) patients in the placebo group went on to receive post-study therapy (table 2).

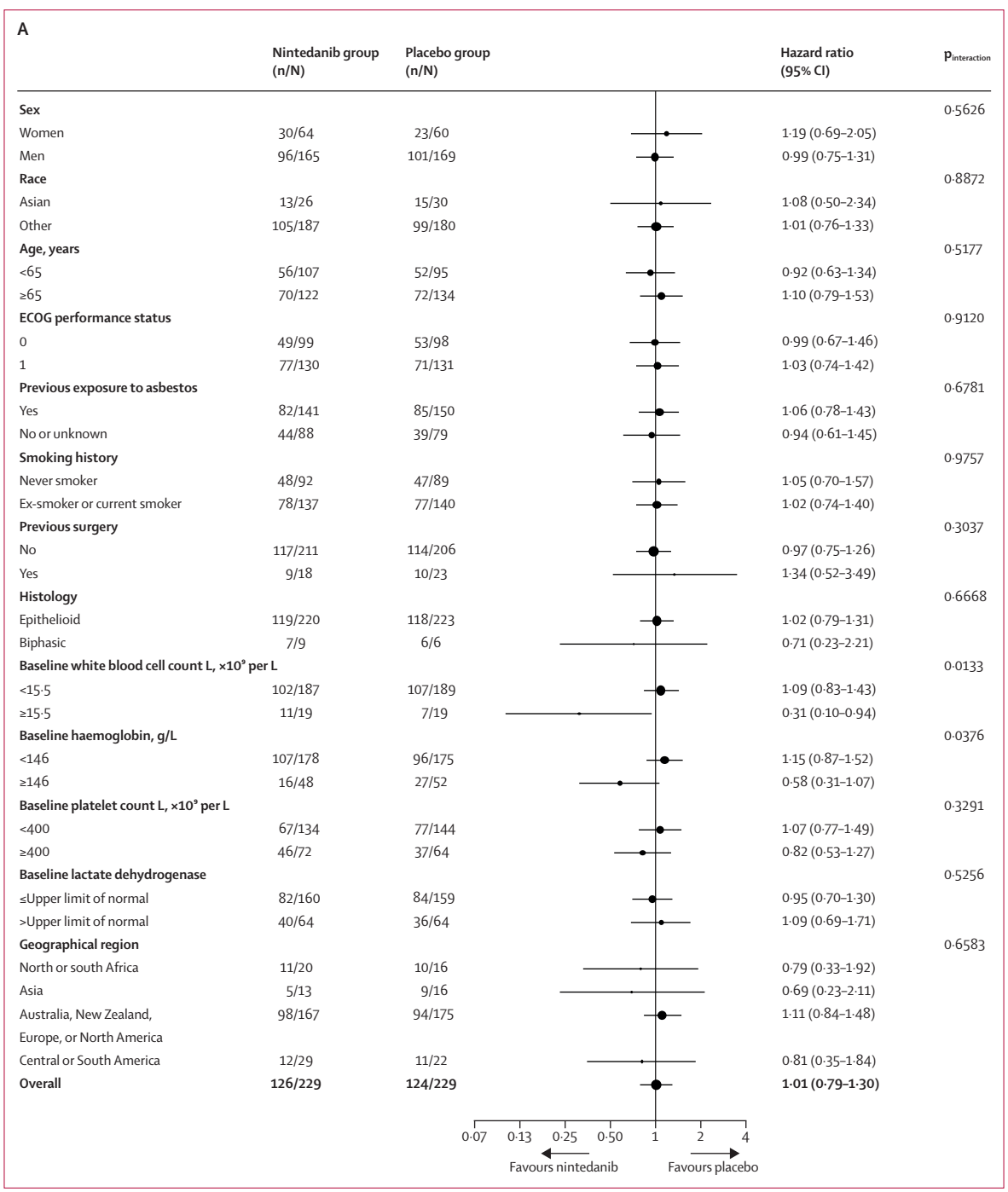
Objective response according to investigator assessment was achieved in 103 (45%) patients receiving nintedanib, all of whom had confirmed partial responses, and 98 (43%) patients in the placebo group, one of which was a confirmed complete response and the rest were partial response. Most objective responses occurred during the chemotherapy phase. The median time to confirmed response was 1·4 (IQR 1·3–2·7; mean 2·1 [SD 1·3]) months in the nintedanib group and 1·5 (1·3–2·8; mean 2·2 [1·2]) months in the placebo group. Disease control was achieved in 208 (91%) patients receiving nintedanib and 212 (93%) patients receiving placebo.

LCSS-Meso scores (treatment difference –1·2 [95% CI –3·2 to 0·7]) and average symptom burden index scores (–1·1 [–3·0 to 0·9]) were not significantly different between the groups but slightly favoured nintedanib, as did the LCSS-Meso global scales activity level and symptom distress scores and all individual symptoms scale scores except appetite loss (appendix p 2). The odds ratios for status change (improved *vs* not improved) favoured nintedanib over placebo for activity level (1·67; p=0·0087) and symptom distress (1·58; p=0·019).

Progression-free survival by investigator assessment was generally consistent across prespecified subgroups; only baseline haemoglobin and white blood cell count had a $p_{interaction}$ of 0·1 or less (figure 3A). For overall survival subgroup analysis, previous known exposure to asbestos, baseline white blood cell count, and baseline platelet count showed a $p_{interaction}$ of 0·1 or less (figure 3B). The strongest treatment effect interaction was observed for platelet count at baseline for overall survival ($p_{interaction}$=0·00052).

Analysis of outcome according to baseline platelet count suggested that this might be a potential predictive factor for treatment benefit with nintedanib. However, given these analyses were exploratory, we could not include formal statistical testing. For overall survival,

exploratory analyses suggest that the treatment effect is positive for patients with a high platelet count at baseline (HR 0·53 [95% CI 0·30–0·92]) but negative for patients with low platelet count (2·04 [1·21–3·45]; appendix p 4). For progression-free survival, the predictive potential of platelet count at baseline was less pronounced, with a slight advantage for nintedanib-treated patients in the high (0·82 [0·53–1·27]) but not in the low platelet count group (1·07 [0·77–1·49]; appendix p 4). Of note, baseline characteristics were generally balanced between treatment groups in the subgroups with low and high baseline platelet counts, although more patients with a high platelet count than those with a low platelet count at baseline had an ECOG performance status of 1. Baseline




(Figure 3 continues on next page)

B

| | Nintedanib group (n/N) | Placebo group (n/N) | Hazard ratio (95% CI) | $p_{interaction}$ |
|---|---|---|---|---|
| **Sex** | | | | 0·9870 |
| Women | 14/64 | 11/60 | 1·22 (0·55–2·70) | |
| Men | 50/165 | 52/169 | 1·13 (0·76–1·66) | |
| **Race** | | | | 0·8133 |
| Asian | 6/26 | 6/30 | 1·03 (0·33–3·21) | |
| Other | 53/187 | 52/180 | 1·10 (0·75–1·62) | |
| **Age, years** | | | | 0·5927 |
| <65 | 28/107 | 27/95 | 1·01 (0·59–1·71) | |
| ≥65 | 36/122 | 36/134 | 1·20 (0·75–1·91) | |
| **ECOG performance status** | | | | 0·5212 |
| 0 | 18/99 | 18/98 | 1·35 (0·70–2·62) | |
| 1 | 46/130 | 45/131 | 0·98 (0·65–1·49) | |
| **Previous exposure to asbestos** | | | | 0·0245 |
| Yes | 50/141 | 39/150 | 1·44 (0·95–2·20) | |
| No or unknown | 14/88 | 24/79 | 0·61 (0·31–1·20) | |
| **Smoking history** | | | | 0·6904 |
| Never smoker | 23/92 | 23/89 | 1·33 (0·73–2·42) | |
| Ex-smoker or current smoker | 41/137 | 40/140 | 1·08 (0·70–1·68) | |
| **Previous surgery** | | | | 0·4079 |
| No | 59/211 | 58/206 | 1·08 (0·75–1·55) | |
| Yes | 5/18 | 5/23 | 1·71 (0·48–6·09) | |
| **Histology** | | | | 0·1316 |
| Epithelioid | 56/220 | 59/223 | 1·03 (0·71–1·48) | |
| Biphasic | 8/9 | 4/6 | 2·75 (0·71–10·63) | |
| **Baseline white blood cell count L, ×10⁹ per L** | | | | 0·0373 |
| <15·5 | 50/187 | 47/189 | 1·27 (0·85–1·90) | |
| ≥15·5 | 7/19 | 9/19 | 0·32 (0·11–0·91) | |
| **Baseline haemoglobin, g/L** | | | | 0·8885 |
| <146 | 56/178 | 57/175 | 1·12 (0·77–1·62) | |
| ≥146 | 7/48 | 6/52 | 1·36 (0·45–4·08) | |
| **Baseline platelet count L, ×10⁹ per L** | | | | 0·00052 |
| <400 | 36/134 | 23/144 | 2·04 (1·21–3·45) | |
| ≥400 | 21/72 | 33/64 | 0·53 (0·30–0·92) | |
| **Baseline lactate dehydrogenase** | | | | 0·1834 |
| ≤Upper limit of normal | 43/160 | 38/159 | 1·27 (0·82–1·97) | |
| >Upper limit of normal | 18/64 | 24/64 | 0·79 (0·43–1·46) | |
| **Geographical region** | | | | 0·4885 |
| North or south Africa | 7/20 | 7/16 | 0·72 (0·25–2·06) | |
| Asia | 2/13 | 2/16 | 1·11 (0·16–7·96) | |
| Australia, New Zealand, Europe, or North America | 50/167 | 48/175 | 1·27 (0·85–1·89) | |
| Central or South America | 5/29 | 6/22 | 0·64 (0·19–2·12) | |
| **Overall** | **64/229** | **63/229** | **1·12 (0·79–1·58)** | |

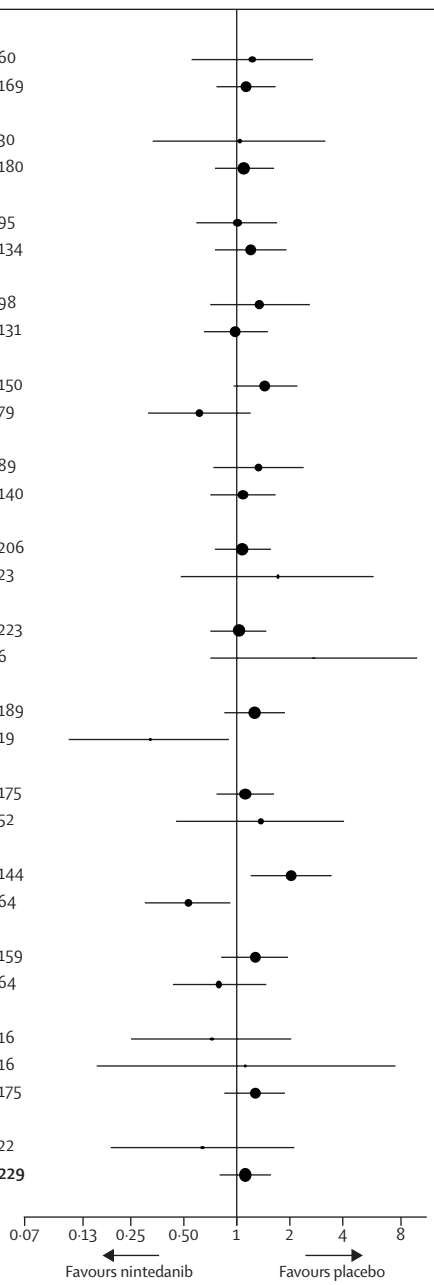



***Figure 3:*** **Subgroup analyses**
Progression-free survival (A) and overall survival (B). ECOG=Eastern Cooperative Oncology Group. n=number of events. N=group size. Size of dots represents numbers of patients.

platelet count also predicted treatment benefit with nintedanib for other endpoints, including health-related quality-of-life endpoints (data not shown).

Overall, 223 (98%) of 227 patients who received nintedanib and 225 (99%) of 228 patients who received placebo had an adverse event. Adverse events were treatment related in 204 (90%) patients who received nintedanib and 190 (83%) patients who received placebo.

The most frequent adverse events of any grade were nausea and fatigue in both treatment groups and

diarrhoea in the nintedanib treatment group (table 3). The most frequent grade 3 or worse adverse event in both groups was neutropenia (73 [32%] for nintedanib *vs* 54 [24%] for placebo), although complications such as febrile neutropenia were scarce (five [2%] *vs* six [3%]). Some adverse events (group terms) commonly associated with antiangiogenic drugs were reported, namely bleeding (30 [13·2%] in the nintedanib group *vs* 20 [8·8%] in the placebo group), gastrointestinal perforation (three [1·3%] *vs* one [0·4%]), venous thromboembolism (20 [8·8%] *vs* 16 [7·0%]), and arterial thromboembolism (five [2·2%] *vs* two [0·9%]).

Serious adverse events were reported in 99 (44%) patients who received nintedanib and 89 (39%) patients who received placebo (appendix p 5). Pulmonary embolism was the only serious adverse event present in at least 5% of patients in either group (13 [6%] patients receiving nintedanib *vs* seven [3%] receiving placebo). 26 (6%) of 455 patients died during the study because of adverse events (nine [4%] in the nintedanib group and 17 [7%] in the placebo group); ten (2%) patients died because of progressive disease or underlying cancer (four [2%] and six [3%]). 16 (4%) patients died because of adverse events not associated with disease progression, including five (2%) in the nintedanib group (one each of cardiorespiratory arrest, intestinal obstruction, peripheral ischaemia, pneumonia, and death) and 11 (5%) in the placebo group (one each of acute kidney injury, anaemia, cardiorespiratory arrest, death, dehydration, and mucosal inflammation; two respiratory failure; one abdominal pain and general physical health deterioration; one neutropenia and pneumonia; and one enteritis and sepsis). 52 (23%) patients in the nintedanib group and 22 (10%) patients in the placebo group had adverse events requiring a dose reduction of nintedanib or placebo.

The most common adverse events leading to dose reduction of nintedanib or placebo were diarrhoea (17 [7%] in the nintedanib group *vs* five [2%] in the placebo group), nausea (13 [6%] *vs* five [2%]), and vomiting (ten [4%] *vs* eight [4%]) in both treatment groups. Adverse events leading to discontinuation of last study drug (nintedanib, placebo, pemetrexed, or cisplatin) were reported by 25 (11%) patients in the nintedanib group versus 22 (10%) patients in the placebo group. Adverse events leading to discontinuation of nintedanib or placebo were reported by 37 (16%) versus 28 (12%) patients. Adverse events that led to discontinuation in more than one patient were pulmonary embolism and vomiting (each in four [2%] patients); asthenia, diarrhoea, and nausea (each in three [1%]); and abdominal pain, acute kidney injury, and decreased appetite (each in two [1%]) in the nintedanib group and neutropenia (three [1%] patients), deterioration in general physical health, increased blood creatinine, renal failure, and nausea (each in two [1%]) in the placebo group.

| | Nintedanib group (n=227) | | Placebo group (n=228) | |
|---|---|---|---|---|
| | Any grade | Grades 3–5 | Any grade | Grades 3–5 |
| All adverse events | 221 (97%) | 153 (67%) | 220 (97%) | 127 (56%) |
| Nausea | 159 (70%) | 12 (5%) | 135 (59%) | 15 (7%) |
| Fatigue | 125 (55%) | 24 (11%) | 126 (55%) | 17 (7%) |
| Diarrhoea | 121 (53%) | 18 (8%) | 53 (23%) | 7 (3%) |
| Neutropenia | 116 (51%) | 73 (32%) | 109 (48%) | 54 (24%) |
| Vomiting | 99 (44%) | 6 (3%) | 70 (31%) | 10 (4%) |
| Infection | 84 (37%) | 14 (6%) | 84 (37%) | 13 (6%) |
| Anaemia | 79 (35%) | 17 (7%) | 101 (44%) | 33 (14%) |
| Electrolyte imbalance | 68 (30%) | 15 (7%) | 59 (26%) | 13 (6%) |
| Liver related investigation | 61 (27%) | 27 (12%) | 32 (14%) | 2 (1%) |
| Peripheral neuropathies | 50 (22%) | 5 (2%) | 63 (28%) | 5 (2%) |
| Mucositis | 50 (22%) | 3 (1%) | 56 (25%) | 5 (2%) |
| Rash | 40 (18%) | 1 (<1%) | 40 (18%) | 1 (<1%) |
| Increased alanine aminotransferase | 38 (17%) | 9 (4%) | 10 (4%) | 1 (<1%) |
| Abdominal pain | 36 (16%) | 7 (3%) | 24 (11%) | 3 (1%) |
| Increased aspartate aminotransferase | 35 (15%) | 7 (3%) | 9 (4%) | 1 (<1%) |

Events were graded according to Common Terminology Criteria for Adverse Events.

***Table 3:*** **Adverse events by worst grade occurring in at least 15% of patients in either treatment group or adverse events of grade 3 or worse occurring in more than 5% of patients**

## Discussion

Making significant improvements in the systemic therapy for malignant pleural mesothelioma has proven to be quite challenging. Despite promising data from the phase 2 part of the LUME-Meso study, the primary endpoint (progression-free survival) was not met in the phase 3 part. The addition of nintedanib to pemetrexed plus cisplatin did not improve progression-free survival compared with chemotherapy with placebo in patients with unresectable malignant pleural mesothelioma. The progression-free survival results by investigator assessment were confirmed by independent central review, with high concordance between the two assessments. Secondary efficacy outcomes, including interim analysis of overall survival (the key secondary endpoint) and objective response, also showed no difference between treatment groups. The safety profile of nintedanib in combination with chemotherapy was consistent with the known profile of these drugs.

The LUME-Meso study was originally designed as an exploratory, proof-of-concept phase 2 trial, which was extended to include a confirmatory phase 3 part on the basis of the phase 2 results. In trying to understand the difference in outcomes between the two parts of the trial, several potential factors were considered. No major changes were made to the trial design or patient populations that could account for the differences. Both parts of the trial were randomised, double-blind, placebo-controlled, and, with the exception of inclusion of patients with epithelioid histology only in phase 3 in view of the phase 2 results, no major changes were made to inclusion criteria. Patient baseline characteristics were

broadly similar between the two parts of the trial, with only minor imbalances in variables associated with poor prognosis in malignant pleural mesothelioma.[20] A higher proportion of patients in phase 3 had an ECOG performance status of 1 than in phase 2 (57% in phase 3 *vs* 47% in phase 2) and a minor imbalance was reported in high platelet count at baseline (30% *vs* 25%), but these differences are considered unlikely to have been sufficient to account for the absence of treatment effect in phase 3. Also, no major imbalances were present in baseline patient characteristics or prognostic factors between treatment groups in phase 3 that would account for the study findings or suggest sampling bias within the trial. As such, we could not identify any factors that, individually or in combination, could account for why there might be differences in outcome between the phase 2 and phase 3 parts of the studies. Although uncommon, several examples of where phase 3 data has not confirmed findings from phase 2 assessment have been reported in a range of therapy areas, including oncology.[21] These findings are a reminder that conducting well controlled trials of appropriate size and duration remains essential to confirm the efficacy and safety of a new treatment option.[21]

Standards of care for the management of malignant pleural mesothelioma remained relatively consistent during the time this study was conducted and no major differences in post-progression therapy or post-progression immune checkpoint inhibitor use existed between treatment groups in phase 3. At the time of analysis, use of post-progression therapy was lower (33%) than previously reported in the MAPS study (67%), although this possibly reflects the early discontinuation of patients from the LUME-Meso trial and poor patient follow-up. Given the infrequent subsequent therapy and absence of major differences between treatment groups reported here, it is unlikely that post-study treatment could have negated any potential first-line treatment benefits. Furthermore, exposure of patients to study medications was similar between both phases of the study. Dose reductions of pemetrexed and cisplatin were more common in the nintedanib group than the placebo group, but these were seen in both the phase 2 and phase 3 parts of the trial.

Overall survival data did not show a significant difference between treatment groups. However, overall survival data were immature and we cannot categorically exclude a negative effect of the concomitant administration of nintedanib with chemotherapy. The overall safety profile of nintedanib in combination with chemotherapy was consistent with the known safety profile in combination with backbone chemotherapy from previous studies,[22,23] and no major unexpected safety findings were reported in this study. However, a higher proportion of patients in the nintedanib group had adverse events that were grade 3 or 4 or were considered serious or led to dose reduction than in the placebo group. The addition of nintedanib to chemotherapy did not lead to an increase in fatal adverse events, which were more frequent in the placebo group. Incidences of vascular adverse events often associated with VEGF or VEGF receptor inhibitors were not commonly reported with nintedanib treatment.

Data from the phase 3 MAPS study with bevacizumab in combination with pemetrexed and cisplatin provided validation of inhibition of angiogenesis as a relevant first-line therapeutic strategy in patients with malignant pleural mesothelioma.[12] However, an earlier phase 2 study that investigated the addition of bevacizumab to gemcitabine plus cisplatin did not improve progression-free survival or overall survival in the first-line setting.[24] Studies of the multitargeted small-molecule tyrosine kinase inhibitors with VEGF receptor inhibitory activity, including cediranib, dasatinib, sorafenib, sunitinib, and vatalanib have not shown adequate clinical activity as second-line treatments when used as monotherapy.[25] However, first-line treatment with cediranib, a VEGF receptor and PDGF receptor inhibitor combined with pemetrexed and cisplatin improved progression-free survival in a randomised phase 2 trial.[26] As such, only two studies in malignant pleural mesothelioma have shown clinical benefit with the addition of an antiangiogenic drug to chemotherapy as first-line treatment, and neither drug is approved for use in this patient population. The results of LUME-Meso would not support further exploration of nintedanib in combination with pemetrexed and cisplatin as a first-line treatment in malignant pleural mesothelioma. There remains a need for effective treatments and, although immune checkpoint inhibitors have changed the treatment paradigm across various cancer types, their role in the first-line treatment of malignant pleural mesothelioma remains to be established. Results from an ongoing phase 3 trial investigating nivolumab (a programmed cell death 1 immune checkpoint inhibitor) plus ipilimumab (a cytotoxic T-lymphocyte antigen 4 inhibitor) versus pemetrexed plus cisplatin or carboplatin are awaited.[27]

Platelet count is a well established prognostic factor in malignant pleural mesothelioma,[20] as well as in other cancer types,[28,29] and exploratory analyses reported here suggest this was also the case in our study population. It has been hypothesised that increased platelet count might augment tumour growth and angiogenesis by secreting proangiogenic factors such as VEGF and PDGF within the tumour microenvironment.[30] Subgroup analyses of the data from the LUME-Meso study suggest that baseline platelet count might be predictive of overall survival with nintedanib. Because nintedanib is a known inhibitor of PDGF receptors, this inhibition might contribute to blocking the deleterious effect of increased platelets in this patient group. This might help to explain the results observed for patients receiving nintedanib in the high platelet group but not for the low platelet group. However, these analyses remain highly exploratory given

that the primary endpoint of the study was not met and the study was not prospectively designed to answer this question. In our opinion, this finding would need prospective confirmation before being used to select patients for treatment. It is important to note that interpreting the clinical relevance of exploratory findings from a trial with a negative primary outcome remains challenging, particularly because these are based on overall survival data from only 28% of the total number of treated patients. To our knowledge, the MAPS study is the only other study to have assessed treatment outcome by platelet count; no significant interaction was reported (p=0·14).[12] Although the data from this study also suggest a potential progression-free survival treatment effect based on baseline white blood cell count, the analysis was limited by a low number of patients with a high white blood cell count at baseline (38 [8%] of 458). The associated low power and wide confidence intervals prevent any meaningful treatment recommendations from being drawn.

The strengths of the phase 3 LUME-Meso study include the double-blind design, large sample size, rapid accrual, inclusion of central independent review of disease progression, and the high level of concordance between central and investigator review. To our knowledge, this is the first well controlled, large-scale mesothelioma trial to show high concordance, and as such makes an important contribution to the study of this difficult-to-measure disease. A number of limitations should also be considered. Interim overall survival data were immature at the time of this analysis, although this was a secondary endpoint and does not affect the absence of benefit observed in the primary efficacy endpoint of progression-free survival. The absence of central pathological review to confirm the histology of patients enrolling in the trial and the absence of provision in the protocol for patients to switch to carboplatin if cisplatin was not tolerated should both be noted, although these points are unlikely to have had an effect on the study findings.

In conclusion, the primary endpoint of the phase 3 part of the LUME-Meso study was not met. As such, the previous phase 2 efficacy findings were not confirmed. The safety profile of nintedanib in combination with pemetrexed or cisplatin was consistent with the known safety profiles of these drugs. New treatment options are still needed in patients with malignant pleural mesothelioma.

#### Contributors

GVS, RG, AKN, TN, JvM, SP, JB, UvW, and AST contributed to the conception and design of the study. RG, AKN, TN, JvM, SP, NJV, FG, RA, MJ, GLC, PT, FO, DAF, SN, AS, KK, SC, JBS, NP, MR, and AST were involved in the provision of study material or patients or data acquisition. All authors were involved in data analysis and interpretation and manuscript writing and approved the final version for submission.

#### Declaration of interests

GVS received fees for honoraria from AstraZeneca, Roche, Pfizer, Merck Sharp and Dohme (MSD), and Eli Lilly; consulting or advisory roles from Eli Lilly; speaker's bureau from Eli Lilly and MSD; and travel, accommodation, and expenses from Bayer. RG received research funding (to her institution) from Roche International, Boehringer Ingelheim, AbbVie and AstraZeneca. AKN received fees for consulting or advisory roles from Bayer, AstraZeneca, Sellas Life Sciences, Trizell, Boehringer Ingelheim, Epizyme, Roche and MSD; travel, accommodation, and expenses from AstraZeneca and Boehringer Ingelheim, and research funding to her institution from AstraZeneca. TN received fees for honoraria from Boehringer Ingelheim, Ono, MSD, Kyorin, and Olympus. SP received non-financial editorial support from Millennium Pharmaceuticals, Inc and an institutional grant for research infrastructure from the UK National Health Service, during the conduct of the study; outside of the submitted work, SP has received grants for institutional research funding from Boehringer Ingelheim, Epizyme, Bristol-Myers Squibb (BMS), Clovis Oncology, Roche, Lilly, Takeda, and Pfizer; fees and non-financial support for honoraria, a consulting role and travel, accommodations, and expenses from Boehringer Ingelheim; fees and non-financial support for a consulting role, travel, accommodations, and expenses from BMS and MSD; fees for honoraria and a consulting role from Roche and AstraZeneca; fees for honoraria from Takeda and Chugai Pharma; and fees for a consulting role from Novartis, Pfizer, Guardant Health, and AbbVie. NJV received fees for an honorarium from Boehringer Ingelheim for services on the steering committee of this study. FG received fees for travel, accommodation, and expenses from PharmaMar and Boehringer Ingelheim. MJ received fees for speaker's bureau, travel, accommodation, and expenses from Boehringer Ingelheim, AstraZeneca, Roche, Novartis, MSD, BMS, and Pfizer. GLC received fees for research funding from Bayer. PT received fees for travel, accommodation, and expenses from BMS, Pierre Fabre, and MSD. FO received fees (all in Lung Cancer) for advisory honoraria from Roche and Merck, speaker honoraria from AstraZeneca, and a research grant for this mesothelioma trial from Boehringer Ingelheim. DAF received fees for consulting or advisory roles from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Clovis, Eli Lilly, Lab21, Oncos, and Polaris; research funding from Boehringer Ingelheim, Bergen Bio, Bayer, BMS, Pierre Fabre, Eli Lilly, Roche-Genentech; and speaker's bureau from Boehringer Ingelheim, Roche, BMS, and MSD. SN received fees for speaker's bureau from Boehringer Ingelheim, AstraZeneca, Roche, MSD, BMS, Eli Lilly, Takeda, and Pfizer. AS received fees for consulting or advisory boards from BMS, MSD, Boehringer Ingelheim, AstraZeneca, and Roche; and received fees as primary investigator for clinical trials (to his institution) from BMS, MSD, Boehringer Ingelheim, AstraZeneca, Lilly, Epizyme, Bayer, and Roche. SC received fees for consulting or advisory boards from BMS, Eli Lilly, Roche, and Boehringer Ingelheim. JBS received fees for consulting or advisory roles from AstraZeneca, Pfizer, MSD, Roche, and Boehringer Ingelheim. NP received fees for advisory boards from BMS, Merck-KgA, Boehringer Ingelheim, AstraZeneca, Roche, Bayer, Novartis, Merck, Pfizer, and Takeda; research funding from Bayer and Pfizer; and travel funding from Boehringer Ingelheim, BMS, and Roche. MR received fees for honoraria, consulting or advisory roles and speaker's bureau from Boehringer Ingelheim, F Hoffmann-La Roche, Lilly, AstraZeneca, BMS, MSD, Merck, Novartis, Pfizer, and Celgene. AST received fees for consulting or advisory boards from BMS, Eli Lilly, Genentech, Roche, Novartis, Ariad, EMD Serono, Merck, Seattle Genetics, AstraZeneca, Boehringer Ingelheim, Sellas Life Science, and Takeda; and research funding from Eli Lilly, Millennium, Polaris, Genentech, Merck, Boehringer Ingelheim, BMS, Ariad, Epizyme, and Seattle Genetics. UvW, MK, and JB are employees of Boehringer Ingelheim. DV was an employee of Boehringer Ingelheim at the time the study was conducted. All other authors declare no competing interests.

#### Data sharing

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (eg, study report, study protocol, and statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the Boehringer

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