LUME-Meso: Design and Rationale of the Phase III Part of a Placebo-Controlled Study of Nintedanib and Pemetrexed/Cisplatin Followed by Maintenance Nintedanib in Patients with Unresectable Malignant Pleural Mesothelioma

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Abstract

Malignant pleural mesothelioma (MPM) is a rare but aggressive disease: median survival is 6–9 months if untreated. Standard first-line treatment for patients with unresectable MPM is cisplatin/pemetrexed, with a median overall survival (OS) of ~1 year. Improvements in first-line treatment options are needed. With the benefit of adding bevacizumab to standard therapy demonstrated in the MAPS study, vascular endothelial growth factor (VEGF) pathway inhibition has gained renewed interest as a treatment approach. Nintedanib is an oral angiokinase inhibitor targeting multiple signalling pathways implicated in the pathogenesis of MPM, including the VEGF receptor. The phase III part of the international, phase II/III LUME-Meso study is evaluating the efficacy and safety of nintedanib plus pemetrexed/cisplatin in patients with unresectable epithelioid MPM. Originally, this was a double-blind, randomised, phase II exploratory study and was amended to include a confirmatory phase III part following the recommendation of an internal Data Monitoring Committee and review of phase II data. The phase III part plans to enrol 450 chemotherapy-naïve patients, who will be randomised to receive pemetrexed/cisplatin on Day 1 and nintedanib or placebo on Days 2–21, for a maximum of 6 cycles. Patients without disease progression who are eligible to continue study treatment will receive maintenance treatment with nintedanib or placebo until disease progression or undue toxicity. The primary endpoint is progression-free survival; OS is the key secondary endpoint. The study will use an adaptive design, including an interim analysis to reassess the number of OS events required to ensure sufficient power for OS analysis. The study is currently enrolling.

Clinical trial identifier: NCT01907100.

Keywords: Antiangiogenesis, VEGF, Epithelioid, Adaptive design

Abbreviations

bid, twice daily; CI, confidence interval; DMC, Data Monitoring Committee; ECOG PS, Eastern Cooperative Oncology Group performance status; FGF, fibroblast growth factor; HR, hazard ratio; iv, intravenous; MPM, malignant pleural mesothelioma; OS, overall survival; PD, progressive disease; PDGF, platelet-derived growth factor; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; VEGF, vascular endothelial growth factor

Introduction

Malignant pleural mesothelioma (MPM) is rare, although its incidence is increasing globally, and is expected to peak in Europe between 2015 and 2020.[1, 2] It is principally caused by occupational exposure to asbestos, but the proportion of patients with non-occupational exposure has also increased.[2] Despite being banned in Europe, asbestos production and use is still widespread internationally, particularly in Russia, China, Kazakhstan and Brazil.[2, 3] Thus, the incidence of MPM in asbestos-using countries is expected to continue to grow.[1, 2]

MPM is often diagnosed at an advanced stage,[4] with an average patient survival time of 6–9 months when left untreated.[5] Combination doublet chemotherapy with cisplatin/pemetrexed is considered to be the front-line standard-of-care treatment for patients with unresectable MPM,[1, 4] yielding a median overall survival (OS) time of approximately 1 year.[6] This is currently the only approved regimen,[4] although carboplatin/pemetrexed is also considered to be a suitable first-line treatment option.[1, 4] With the poor prognosis and the global incidence increasing, there is a clear need for new treatment options.

Several signalling pathways involved in regulating angiogenesis have been implicated in the pathogenesis and prognosis of MPM, including vascular endothelial growth factor (VEGF).[7, 8] The VEGF pathway is a key regulator of angiogenesis and therefore tumour growth, and is an important mitogen for MPM cells.[7] Patients with MPM also often have very high serum concentrations of VEGF, which is considered to be a negative prognostic factor.[7]

Clinical evidence of efficacy for the inhibition of VEGF pathway was demonstrated in the MAPS trial investigating the combination of bevacizumab, pemetrexed and cisplatin versus pemetrexed and cisplatin. OS was significantly longer in the bevacizumab arm (median 18.8 months [95% confidence interval (CI), 15.9–22.6] vs 16.1 months [95% CI 14.0–17.9]; hazard ratio [HR], 0.77 [95% CI 0.62–0.95]; *P* = .0167) in patients with MPM.[9] An increase in survival has not been demonstrated with any treatment in MPM since the approval of pemetrexed by the US Food and Drug Administration in 2004. These results demonstrated that targeting the VEGF pathway can be a successful approach to treating unresectable MPM.

Nintedanib is an oral, angiokinase inhibitor with multiple angiogenesis targets, including VEGF receptors 1–3, platelet-derived growth factor (PDGF) receptors α/β, fibroblast growth factor (FGF) receptors 1–3, as well as FLT3, RET, Abl and Src signalling.[10] Nintedanib (VARGATEF®) in combination with docetaxel is approved in the European Union and additional countries for the treatment of patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology after first-line

chemotherapy.[11] It can be co-administered with various anticancer drugs, demonstrating potential clinical benefit and a manageable safety profile in multiple tumour types.[10] Targeting three major proangiogenic signalling pathways (VEGF, PDGF and FGF) in patients with unresectable MPM may result in greater benefit than other studied antiangiogenic strategies. Moreover, nintedanib has inhibitory activity against Src.[10] Src plays a role in multiple cancer signalling pathways, is implicated in mesothelioma pathogenesis and inhibition of Src has been proposed as a treatment approach for MPM.[8, 12] In preclinical studies, nintedanib strongly reduced the growth and migratory activity of MPM cell lines and prolonged survival in an orthotopic MPM xenograft model,[13] and it may be viewed as a logical candidate for the treatment of unresectable MPM.

LUME-Meso is a randomised, double-blind, placebo-controlled, phase II/III study. The study compares nintedanib in combination with the standard therapy of pemetrexed/cisplatin, followed by maintenance nintedanib, versus placebo in combination with pemetrexed/cisplatin followed by placebo monotherapy for the treatment of patients with unresectable MPM. Originally a double-blind, randomised, phase II exploratory study, the trial was expanded to include a confirmatory phase III part, following recommendations from an internal Data Monitoring Committee (DMC) after reviewing phase II study data. Enrolment into the phase II study has been completed and results of the primary endpoint, PFS, have been presented.[14] Following these results, nintedanib was granted orphan drug designation for the treatment of mesothelioma by the U.S. Food & Drug Administration on 12 December, 2016. Patients are currently being enrolled into the phase III part, which will be analysed independently.

Patients and Methods

Study Objectives, Design and Dosing Regimen

The overall objective of LUME-Meso is to evaluate the safety and efficacy of standard therapy plus nintedanib followed by continuing nintedanib, versus standard cisplatin/pemetrexed therapy plus placebo followed by continuing placebo, as first-line treatment for patients with unresectable MPM. LUME-Meso is a double-blind, randomised, multicentre, placebo-controlled, phase II/III study. The phase III part broadly follows the phase II design. Enrolled patients are randomised in a 1:1 ratio to receive a maximum of 6 cycles of pemetrexed (500 mg/m^2)/cisplatin (75 mg/m^2) on Day 1 plus nintedanib (200 mg twice daily [bid]) or matched placebo (bid) on Days 2–21 (**Figure 1**). Patients will continue to receive nintedanib or placebo maintenance therapy until unequivocal disease progression (PD), unmanageable toxicity, withdrawal of consent or death. Patients benefiting from

treatment beyond PD, in the opinion of the investigator, will be able to continue receiving treatment (nintedanib or placebo). Based on the phase II results, which included patients with epithelioid and biphasic histology, planned enrolment to the phase III part is for 450 patients of epithelioid histology only.

Eligibility Criteria

The study will be conducted in accordance with the Declaration of Helsinki and necessary ethics committee approval was obtained. All patients provided written informed consent. The phase III part of the study is enrolling patients with histologically confirmed unresectable MPM of the epithelioid subtype. Although patients eligible for radical resection or elective surgery (e.g. pleurectomy) are ineligible, prior surgery ≥4 weeks prior to randomisation is permitted if there has been complete healing and residual measurable disease remains. The main inclusion and exclusion criteria are detailed in **Table 1**.

Study Endpoints

The primary endpoint is progression-free survival (PFS), with OS as the key secondary endpoint. Other secondary endpoints are evaluation of objective tumour response and disease control rate, according to modified Response Evaluation Criteria in Solid Tumors.[15] An additional objective in the phase III part of the study is evaluation of health-related quality of life (measured using the EQ-5D health status self-assessment questionnaire[16] and the mesothelioma version of the Lung Cancer Symptom Scale [LCSS-Meso]).[17] An exploratory analysis will be conducted by collecting biological samples to investigate the value of potentially predictive or prognostic biomarkers, such as mesothelin, merlin (NF2) and BAP1, via immunohistochemical staining or molecular genetic assays.

Safety will be monitored throughout the study via assessment of changes in laboratory parameters, and the frequency and severity of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Statistical Design

For analysis of the phase III OS, an adaptive design will be utilised, allowing the required number of events to be reassessed at a pre-planned interim analysis.[18] This enables the uncertainty of the treatment effect to be accounted for, ensuring that the study is

sufficiently powered to statistically assess OS. The statistical power of a trial, and thus its success, is dependent on the accuracy of the original clinical estimates. One advantage of an adaptive design is that it ensures, despite uncertainties in these parameters at commencement, that the trial is powered appropriately to achieve its objectives and results in an efficient trial with potentially reduced study duration and demand on resources.[18]

For the double-blind, randomised, phase II study, sample size was selected for proof-of-clinical-concept and all planned analyses were intended to be descriptive. Following DMC analysis, it was recommended that the study be expanded to include a confirmatory phase III part. Under recommendation from regulatory authorities, the phase II data were unblinded and the primary PFS analysis was undertaken to assist precise planning of the phase III part, including estimation of sample size. Phase II patients will not be included in the confirmatory phase III analyses.

The results obtained at the time of the primary PFS analysis of the phase II part of the study were used to estimate the sample size and statistical assumptions for the phase III part of the study. At the time of the primary PFS analysis, the PFS data were considered to be mature (79% of events available) but the OS data were considered to still be immature with only 53% of events available. Based on this analysis, the phase III part of the study was planned with a sample size of 450 patients. This would provide a power of 90% to detect a statistically significant and clinically meaningful improvement in the primary endpoint, PFS. In planning the statistical analysis of the key secondary endpoint, OS, in the phase III part, a two-stage adaptive design is being implemented. This will account for the greater degree of uncertainty around the estimated OS treatment effect resulting from the still immature OS dataset available at the time of the primary phase II PFS analysis. For the analysis of OS in the phase III part, two potential scenarios will be evaluated at the time of the primary PFS analysis. If at the time of the primary PFS analysis the difference in PFS between study arms is statistically significant, an interim OS analysis will be performed by an external DMC. If the difference in OS between study arms is statistically significant, then the study will be declared positive for the primary and key secondary endpoints and enrolment will be stopped; if the difference is not yet statistically significant, the final number of OS events will be reassessed. This provision ensures that the trial will provide 80% power to detect a statistically significant and clinically meaningful OS treatment effect at the time of the final OS analysis in the phase III part of the trial.

Conclusion

The LUME-Meso phase II/III trial will determine if the addition of nintedanib to the standard treatment regimen of pemetrexed/cisplatin offers clinical benefit in terms of PFS, the primary endpoint, and OS, the key secondary endpoint. The phase III part of the trial is active, and patients with unresectable MPM that meet the eligibility criteria are currently being enrolled at participating centres across North and South America, Europe, Africa, Australia and Asia.

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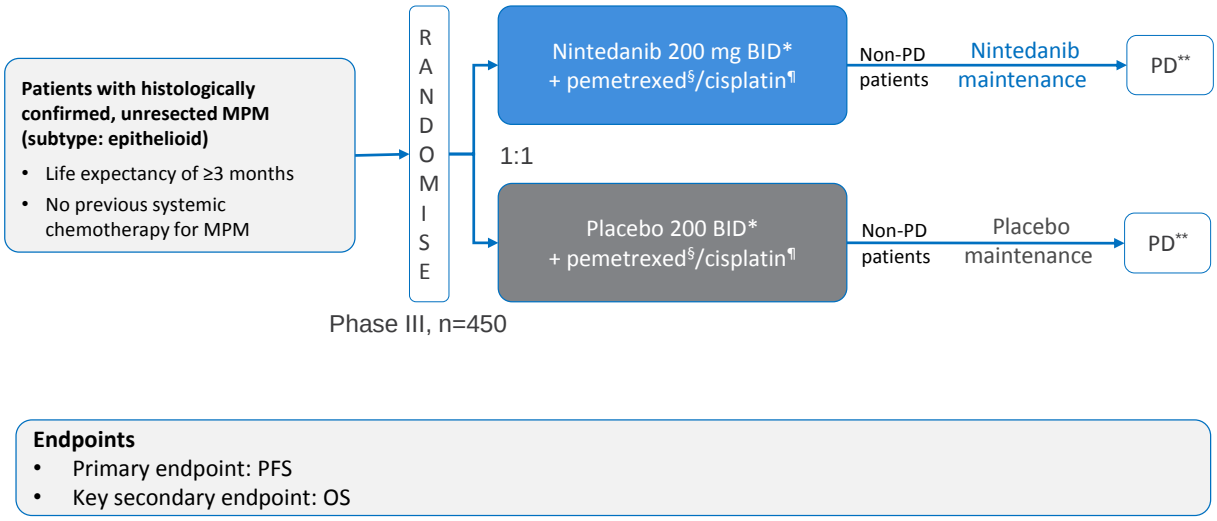
Figure 1. Study Design for the Phase III Part of the LUME-Meso Study



*Nintedanib administered on Days 2–21.

§Pemetrexed 500 mg/m^2 iv over 10 minutes on Day 1 of each 21-day cycle for a maximum of 6 cycles.

¶Cisplatin 75 mg/m^2 iv over 2 hours on Day 1 of each 21-day cycle for a maximum of 6 cycles.

**Treatment beyond progression is allowed if clinical benefit is perceived.

bid, twice daily; iv, intravenous; MPM, malignant pleural mesothelioma; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Table 1. Main Inclusion and Exclusion Criteria for Enrolment in the Phase III Part of the LUME-Meso Study

Key Inclusion Criteria
Male or female ≥18 years
Histologically confirmed MPM of epithelioid histology
Life expectancy ≥3 months
ECOG PS 0 or 1
Measureable disease according to modified RECIST criteria
Key Exclusion Criteria
Previous systemic chemotherapy for MPM
Prior treatment with nintedanib or any other prior first-line therapy
Patients with sarcomatoid and biphasic subtype MPM
Patients with symptomatic neuropathy
Radiotherapy within 3 months prior to baseline imaging
Patients that may be eligible for or being considered for radical resection or elective surgery during the course of the study
Active brain metastases
Creatinine clearance <60 mL/min (using standard Cockcroft–Gault formula or from measurement of glomerular filtration rate)

ECOG PS, Eastern Cooperative Oncology Group performance status; MPM, malignant pleural mesothelioma; RECIST, Response Evaluation Criteria In Solid Tumors.