LUME-Meso Phase II/III study: nintedanib + pemetrexed/cisplatin in chemotherapy-naïve patients with malignant pleural mesothelioma

Anne S. Tsao,1 Nicholas J. Vogelzang,2 Anna K. Nowak,3 Sanjay Popat,4 Rabab Gaafar,5 Jan van Meerbeeck,6 Takashi Nakano,7 José Barrueco,8 Nassim Morsli,9 Giorgio V. Scagliotti10

1Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA; 2US Oncology Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada, USA; 3School of Medicine and Pharmacology QEII, Medical Centre Unit, University of Western Australia, Crawley, Western Australia, Australia; 4Royal Marsden Hospital NHS Foundation Trust, London and Surrey, UK; 5National Cancer Institute, Cairo University, Fom El Khalig, Cairo, Egypt; 6Department of Thoracic Oncology, Antwerp University Hospital, Edegem, Belgium; 7Otemae Hospital, Osaka, Japan; 8Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, USA; 9Boehringer Ingelheim France S.A.S., Paris, France; 10University of Turin, Department of Oncology, S. Luigi Hospital, Torino, Italy

Presented at the IASLC 18th World Conference on Lung Cancer, Yokohama, Japan, 15–18 October 2017

Corresponding author email address: astsao@mdanderson.org
INTRODUCTION

• Malignant pleural mesothelioma (MPM) is an aggressive neoplasm, with 7–9 months survival if left untreated\(^1\)

• Combination doublet therapy with cisplatin and pemetrexed is the front-line standard-of-care treatment for patients with unresectable MPM\(^2,3\) and yields a median overall survival (OS) of approximately 1 year\(^1\)
STUDY RATIONALE

• Nintedanib is an oral inhibitor targeting vascular endothelial growth factor (VEGF) receptors 1–3, platelet-derived growth factor (PDGF) receptors α/β and fibroblast growth factor (FGF) receptors 1–3, as well as Src and Abl kinase signalling (Figure 1)⁴
  – While VEGF inhibition by bevacizumab has been demonstrated as a viable approach in the MAPS study,⁵ nintedanib is the first agent to combine VEGF receptor inhibition with targeting of the PDGF pathway, which is associated with poor prognosis in MPM, as well as the FGF receptor pathway and Src and Abl kinases. These are all implicated in the pathogenesis of MPM in preclinical studies⁶–⁸

• Preclinically, nintedanib strongly reduces the colony-forming capacity and migratory activity of MPM cell lines, and this appears to have a direct effect on the MPM cells.⁹ Nintedanib also increased survival in an orthotopic mouse model of MPM⁹

• Nintedanib was granted orphan drug designation by the US Food & Drug Administration for the treatment of patients with mesothelioma in December 2016
Nintedanib also inhibits other targets that have been proposed to be implicated in MPM:
- Src
- Abl

FGFR 1–3 and VEGFR 1–3

FGFR 1–3 and VEGFR 1–3

PDGFR α/β and FGFR 1–3

PDGFR α/β

- nintedanib + nintedanib

Smooth muscle cell

Endothelial cell

Pericyte

Tumour-associated angiogenic blood vessel

Nintedanib also inhibits other targets that have been proposed to be implicated in MPM:
- Src
- Abl

FGF(R), fibroblast growth factor (receptor); MPM, malignant pleural mesothelioma; PDGF(R), platelet-derived growth factor (receptor); VEGF(R), vascular endothelial growth factor (receptor).
PHASE II RESULTS

- LUME-Meso is a two-arm, randomised, double-blind, placebo-controlled, parallel-group, Phase II/III trial comparing nintedanib + chemotherapy versus placebo + chemotherapy in adults aged ≥18 years.

- The Phase II part recruited 87 chemotherapy-naïve patients with unresectable epithelioid or biphasic MPM from 18 centres across eight countries (Australia, Canada, Denmark, France, Germany, Italy, UK, US). Patients were randomised 1:1 to receive nintedanib + pemetrexed/cisplatin or placebo + pemetrexed/cisplatin.
  - The majority of patients (89%) had epithelioid histology (39 patients in the nintedanib group and 38 patients in the placebo group).
  - Updated progression-free survival (PFS) at the time of primary OS analysis was improved with nintedanib treatment (hazard ratio [HR]=0.54, 95% confidence interval [CI]: 0.33–0.87; p=0.010; median PFS: nintedanib 9.4 months vs placebo 5.7 months).\(^\text{10}\)
    - The greatest benefit was observed in patients with epithelioid histology (HR=0.49, 95% CI: 0.30–0.82; p=0.006; median PFS: 9.7 vs 5.7 months).
    - The number of patients with biphasic MPM was too low for meaningful conclusions.
  - A trend towards improvement in OS favouring nintedanib treatment was observed in all patients (HR=0.77, 95% CI: 0.46–1.29; p=0.319; median OS: 18.3 vs 14.2 months).
    - The benefit of nintedanib treatment was greatest in patients with epithelioid histology (HR=0.70, 95% CI: 0.40–1.21; p=0.197; median OS: 20.6 vs 15.2 months).
PHASE III STUDY OBJECTIVE

- The overall objective of the trial is to evaluate the safety and efficacy of nintedanib + pemetrexed/cisplatin, followed by continuing nintedanib monotherapy, as first-line treatment for patients with unresectable epithelioid MPM (clinical trial identifier: NCT01907100)
  - The primary endpoint is PFS; OS is the key secondary endpoint
The LUME-Meso trial was extended to include a confirmatory Phase III part (Figure 2)
- The Phase II data were used to inform the sample size calculations for the Phase III part
- The Phase II results also led to the decision to limit recruitment into the Phase III part to MPM patients with epithelioid histology

The Phase III part is currently enrolling at approximately 140 participating centres in 27 countries across North and South America, Europe, Africa, Asia and Australia (Figure 3)

Statistics
- For Phase III data, a hierarchical testing procedure will be implemented to analyse PFS and OS
  - A benefit of PFS will be tested first, and if the test is significantly in favour of nintedanib, a benefit of OS will be tested
- A two-stage adaptive design will be used to analyse the Phase III OS
  - A preplanned interim analysis of OS will be conducted at the time of the primary PFS analysis of the Phase III part, when the number of OS events may be reassessed to ensure that the study is sufficiently powered to statistically assess OS as well as PFS
FIGURE 2. STUDY DESIGN

Patients with histologically confirmed, unresected epithelioid MPM

Endpoints
• Primary endpoint: PFS
• Secondary endpoints:
  – OS (key)
  – Objective tumour response evaluated according to mRECIST
  – Disease control according to mRECIST

• Selected additional endpoints:
  – Time to and duration of objective tumour response
  – Health-related quality of life

*On Days 2–21; §Pemetrexed 500 mg/m² iv over 10 minutes on Day 1 of each 21-day cycle; ¶Cisplatin 75 mg/m² iv over 2 hours on Day 1 of each 21-day cycle; **Treatment beyond progression is allowed if clinical benefit is perceived.

bid, twice daily; iv, intravenous; MPM, malignant pleural mesothelioma; mRECIST, modified Response Evaluation Criteria in Solid Tumours; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
FIGURE 3. LOCATIONS OF PARTICIPATING STUDY SITES

North America
- Canada
- Mexico
- USA

South America
- Argentina
- Chile

Europe
- Austria
- Belgium
- Croatia
- Czech Republic
- Denmark
- France
- Germany
- Italy
- The Netherlands
- Norway
- Poland
- Portugal
- Spain
- Sweden
- UK

Asia
- Israel
- Japan
- Russia
- Turkey

Australia

Africa
- Egypt
- South Africa
PHASE III STUDY DESIGN (CONT’D)

Key eligibility criteria
• The study includes chemotherapy-naïve patients with histologically confirmed, unresectable epithelioid MPM
• Additional major inclusion and exclusion criteria are summarised in Table 1
### TABLE 1. KEY PATIENT INCLUSION/EXCLUSION CRITERIA

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male or female ≥18 years</td>
</tr>
<tr>
<td>Histologically confirmed MPM of epithelioid histology</td>
</tr>
<tr>
<td>ECOG PS 0 or 1</td>
</tr>
<tr>
<td>Measurable disease according to mRECIST criteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous systemic chemotherapy for MPM</td>
</tr>
<tr>
<td>Prior treatment with nintedanib or any other systemic therapy</td>
</tr>
<tr>
<td>Patients with sarcomatoid and biphasic subtype MPM</td>
</tr>
<tr>
<td>Patients with symptomatic neuropathy</td>
</tr>
<tr>
<td>Radiotherapy within 3 months prior to baseline imaging</td>
</tr>
<tr>
<td>Patients who may be eligible to undergo surgical resection</td>
</tr>
<tr>
<td>Active brain metastases</td>
</tr>
<tr>
<td>Patients with mild-to-moderate renal insufficiency taking NSAIDs and unable/unwilling to interrupt treatment</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status; MPM, malignant pleural mesothelioma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NSAID, non-steroidal anti-inflammatory drug.
Outcome measures

• Primary and secondary endpoints are listed in Figure 2
• The study includes exploratory biomarker analyses that will focus on exploring predictive/prognostic biomarkers in tumour and blood specimens

Safety

• Safety will be evaluated by the incidence and severity of adverse events and changes in laboratory parameters according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
REFERENCES


ACKNOWLEDGEMENTS

Disclosures: The authors were fully responsible for all content, were involved at all stages of poster development and have approved the final version.

Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by inVentiv Medical Communications, UK, during the preparation of this poster.

Disclaimer: Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without written permission from the authors.

Corresponding author: Anne S. Tsao (astsao@mdanderson.org).