Phase II LUME-Meso study of first-line nintedanib plus chemotherapy in malignant pleural mesothelioma: additional efficacy analyses

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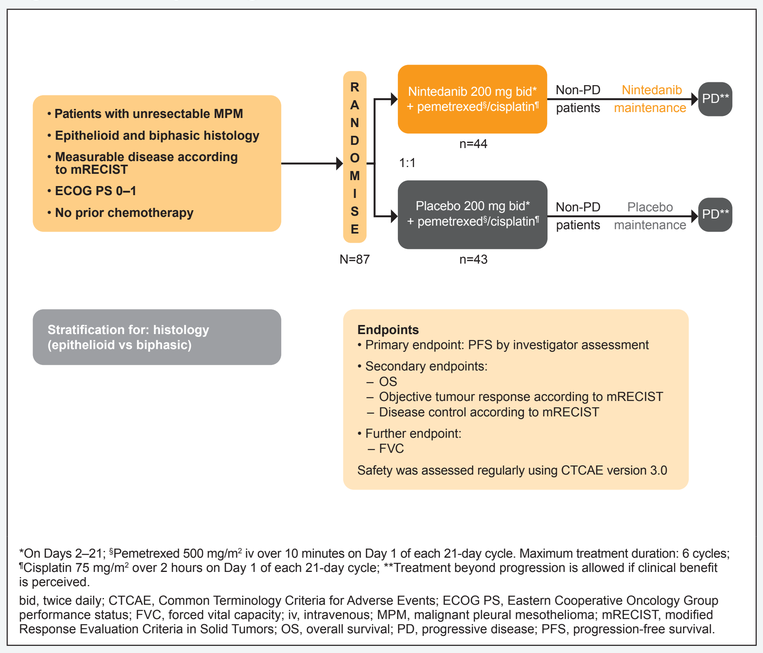
INTRODUCTION

- Malignant pleural mesothelioma (MPM) is a rare neoplasm that is usually diagnosed at an advanced stage[1]
- Prognosis for patients with MPM is poor, with median survival reported to be as little as 7 months[1]
- Pemetrexed/cisplatin is the only globally approved first-line treatment for patients with unresectable MPM[2,3]
- The clinical trial that led to approval of the pemetrexed/cisplatin regimen in MPM reported an improvement in median overall survival (OS) with pemetrexed/cisplatin versus cisplatin alone in patients with unresectable MPM (12.1 vs 9.3 months; hazard ratio [HR]=0.77)[4]
- Follow-up analyses of data from this trial investigated whether tumour response may be predictive of OS, independent of treatment[5]
- These analyses showed that patients with epithelioid histology who achieve a response to treatment have longer OS than those who do not (median OS: 20.6 vs 9.4 months; HR=0.34 [95% confidence interval (CI): 0.24–0.49]; p<0.001)[5]
- The authors concluded that a reduction in tumour burden was strongly associated with OS in epithelioid MPM treated with cisplatin or pemetrexed/cisplatin[5]
- We report the results of a similar analysis that evaluated OS by response status using data from the Phase II part of the LUME-Meso study
- LUME-Meso is a randomised, double-blind, Phase II/III trial, comparing nintedanib plus pemetrexed/cisplatin to placebo plus pemetrexed/cisplatin as first-line treatment in patients with unresectable MPM (NCT01907100)[6]
- Nintedanib is an oral angiokinase inhibitor targeting vascular endothelial growth factor receptor 1–3, platelet-derived growth factor receptors α/β and fibroblast growth factor receptors 1–3, as well as Src and Abl[7,8]

METHODS

- The Phase II study design is shown in **Figure 1**[6]

Figure 1. Study design[6,9]



*On Days 2–21; §Pemetrexed 500 mg/m² iv over 10 minutes on Day 1 of each 21-day cycle. Maximum treatment duration: 6 cycles; ¶Cisplatin 75 mg/m² over 2 hours on Day 1 of each 21-day cycle; **Treatment beyond progression is allowed if clinical benefit is perceived.

bid, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; FVC, forced vital capacity; iv, intravenous; MPM, malignant pleural mesothelioma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Statistical methods

- In the Phase II part of the LUME-Meso study, sample size was calculated to evaluate the treatment effect of adding nintedanib to pemetrexed/cisplatin and assumed a HR of 0.75 for progression-free survival (PFS), corresponding to a median PFS of 8 months (nintedanib plus pemetrexed/cisplatin) versus 6 months (placebo plus pemetrexed/cisplatin)[6]
- The primary PFS analysis took place after 69 events (79%; 4 March 2016)[6]
- The primary OS analysis took place after 62 deaths (71%; 19 January 2017)[6]
- For the descriptive analysis reported here, patients from the Phase II part of the LUME-Meso study were categorised by best overall response (complete response [CR] plus partial response [PR] vs stable disease [SD] plus progressive disease [PD])
- Response to treatment was assessed at the beginning of each cycle according to modified Response Evaluation Criteria in Solid Tumors.[10] Best overall response was determined from the start of treatment until PD or end of follow-up
- OS was compared between the two groups (CR plus PR vs SD plus PD), regardless of treatment assignment, in the overall patient population and in patients with epithelioid histology
- Patients with missing response data or who were not evaluable for response were excluded from the analysis
- All statistics provided are intended to be descriptive

RESULTS

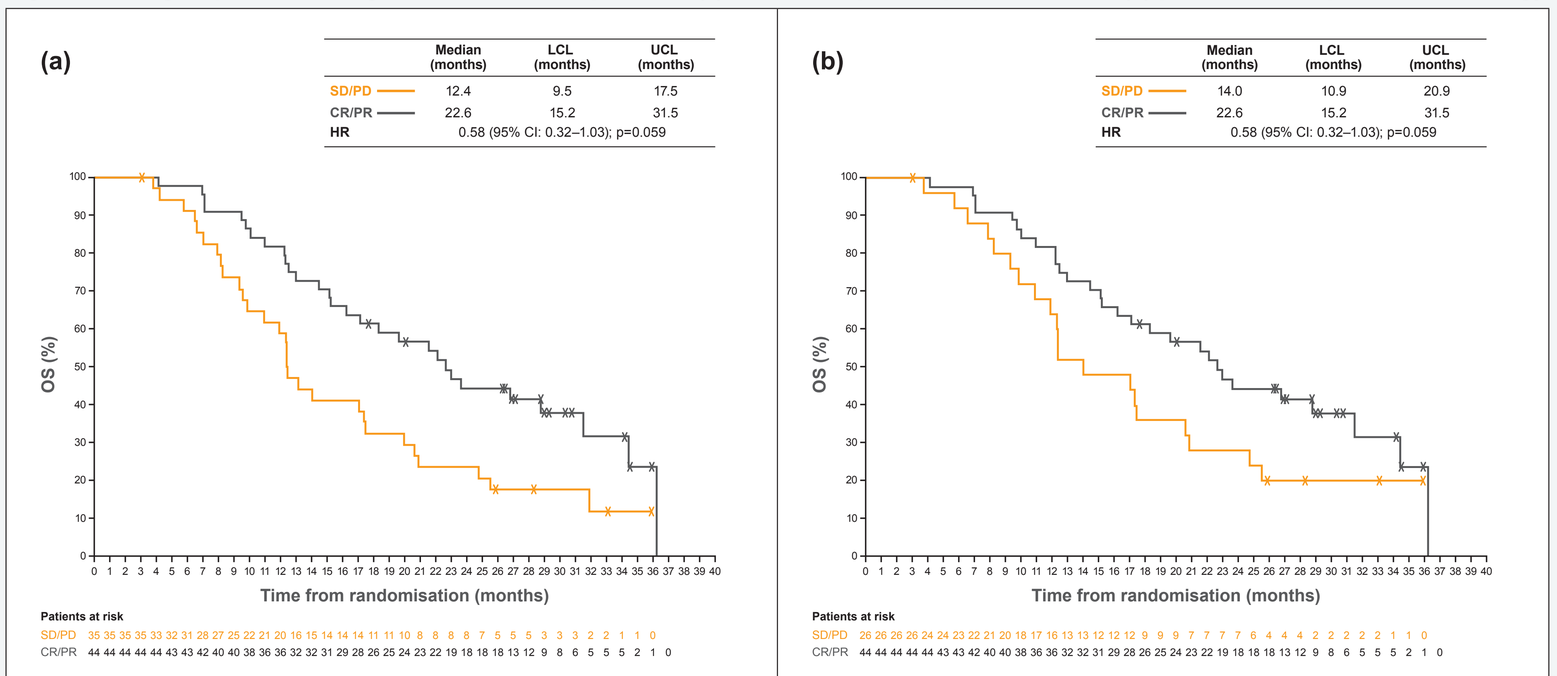
Patient population

- 87 patients were randomised (44 and 43 to nintedanib and placebo, respectively)[6]
- Clinical characteristics and demographics for baseline parameters were generally comparable between the study arms[6]

Treatment exposure

- In both treatment groups, the median number of pemetrexed/cisplatin courses was six[6]
- Median duration of nintedanib/placebo treatment was 7.8 months (range 0.1–33.2) in the nintedanib arm and 5.3 months (range 0.4–28.9) in the placebo arm[6]

Figure 2. OS, grouped according to best overall response in (a) the overall patient population and (b) patients with epithelioid histology



CI, confidence interval; CR, complete response; HR, hazard ratio; LCL, lower confidence limit; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; UCL, upper confidence limit.

OS and PFS

- Nintedanib demonstrated an improvement in the primary endpoint of PFS (HR at the time of the primary PFS analysis=0.56; 95% CI: 0.34–0.91; p=0.017), with a trend for longer OS (HR=0.77; 95% CI: 0.46–1.29; p=0.319), compared with placebo[6]
- The benefit of nintedanib was greatest in patients with epithelioid histology (n=77) for:[6]
  - PFS: primary analysis, HR=0.51; 95% CI: 0.30–0.86; p=0.010; updated analysis at time of OS analysis, HR=0.49; 95% CI: 0.30–0.82; p=0.006
  - OS: HR=0.70; 95% CI: 0.40–1.21; p=0.197

Analysis of OS by response status

Overall study population

- In the overall study population, a total of 79 patients were evaluable for the analysis of OS by response status. Of these, no CRs were reported, 44 patients achieved a PR, and 35 patients had SD or PD as best overall response
- Best overall response status of PR was associated with prolonged OS versus SD/PD (HR=0.58; 95% CI: 0.32–1.03; p=0.059)
- Median OS was 22.6 months (95% CI: 15.2–31.5) in patients who achieved a PR, and 12.4 months (95% CI: 9.5–17.5) in patients who had SD or PD as best overall response (**Figure 2a**)

Subgroup of patients with epithelioid histology

- In the population of patients with epithelioid histology, a total of 70 patients were evaluable for the analysis of OS by response status. Of these, 44 patients achieved a PR, and 26 patients had SD or PD as best overall response
- As in the overall study population, best overall response status of PR was associated with prolonged OS versus SD/PD (HR=0.58; 95% CI: 0.32–1.03 p=0.059)
- Median OS was 22.6 months (95% CI: 15.2–31.5) in patients who achieved a PR, and 14.0 months (95% CI: 10.9–20.9) in patients who had SD or PD as best overall response (**Figure 2b**)

Safety

- Most frequently reported adverse events (AEs) in the Phase II part of the LUME-Meso trial are summarised in **Table 1**[6]
- In this study, AEs that are commonly associated with anti-angiogenic agents were either balanced between treatment arms or reported in fewer patients in the nintedanib arm[6]
- Neutropenia was the most frequent Grade ≥3 AE (nintedanib, 43.2%; placebo, 12.2%); the rate of febrile neutropenia was low (nintedanib, 4.5%; placebo, 0%)[6]
- A lower proportion of patients in the nintedanib arm than in the placebo arm experienced AEs leading to discontinuation (6.8% vs 17.1%, respectively)[6]

Table 1. Most common AEs (any grade AEs with an incidence ≥10% higher in the nintedanib vs placebo arm)

	Nintedanib plus pemetrexed/cisplatin (n=44)		Placebo plus pemetrexed/cisplatin (n=41)	
AE,* n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhoea	31 (70.5)	3 (6.8)	15 (36.6)	0
Neutropenia	29 (65.9)	19 (43.2)	12 (29.3)	5 (12.2)
Electrolyte imbalance	25 (56.8)	7 (15.9)	16 (39.0)	4 (9.8)
Anaemia	20 (45.5)	4 (9.1)	13 (31.7)	2 (4.9)
Liver-related investigation	20 (45.5)	10 (22.7)	3 (7.3)	1 (2.4)
Abdominal pain	18 (40.9)	0	6 (14.6)	0
Specific liver-related investigation (tailored)	17 (38.6)	6 (13.6)	1 (2.4)	1 (2.4)
Increased ALT	17 (38.6)	6 (13.6)	1 (2.4)	1 (2.4)
Thrombocytopenia	14 (31.8)	5 (11.4)	5 (12.2)	0
Increased AST	13 (29.5)	0	1 (2.4)	0
Increased GGT	11 (25.0)	6 (13.6)	1 (2.4)	0
Increased ALKP	9 (20.5)	0	1 (2.4)	0

*AEs by worst CTCAE grade and user-defined group terms.

AE, adverse event; ALKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma–glutamyltransferase.

CONCLUSIONS

- The results of the Phase II part of the LUME-Meso study show that achieving a response was associated with prolonged OS, regardless of treatment assignment, in patients with unresectable MPM
- The observed association was similar in the overall patient population and in patients with epithelioid histology
- These results are consistent with those reported in other studies in MPM, showing that reduction in tumour burden was strongly associated with OS in patients with epithelioid histology[5]
- The Phase III part of this study, in patients with epithelioid MPM, is ongoing (NCT01907100)[9]

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