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

PP04.05

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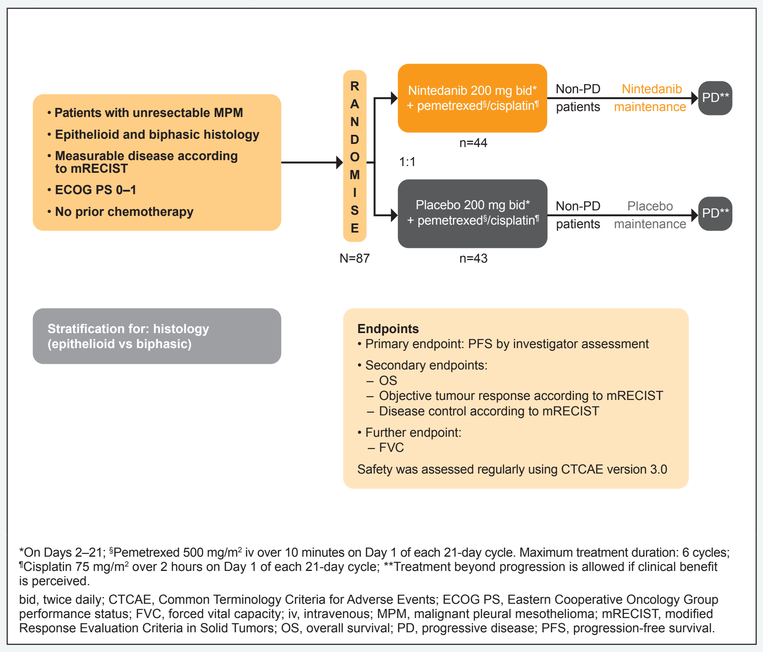
INTRODUCTION

- 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

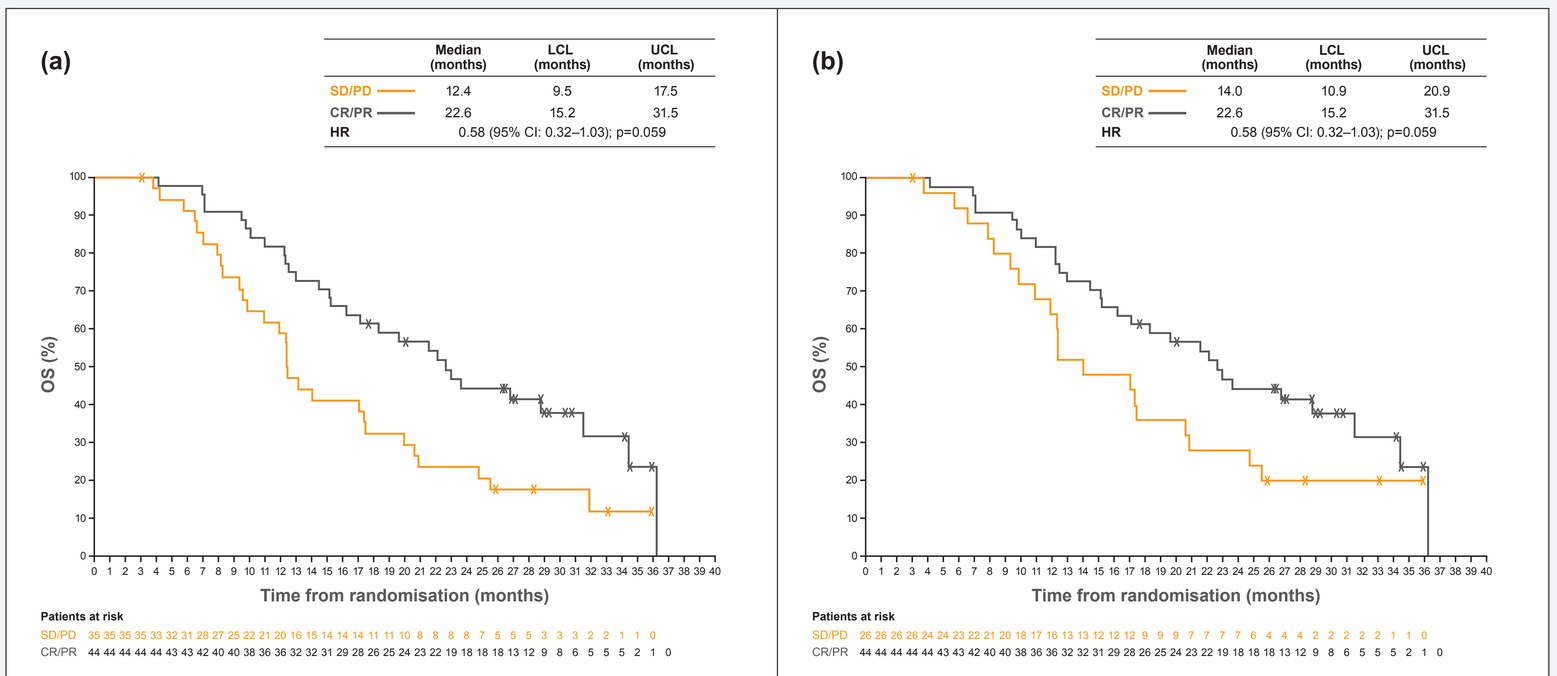
Patient population

- 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]

REFERENCES

1. Taioli E, et al. PLoS One 2015;10:e0145039
2. NCCN Clinical Practice Guidelines in Oncology: Malignant Pleural Mesothelioma. Version 2-2017, 2017. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx (Accessed 27 February 2018)
3. Baas P, et al. Ann Oncol 2015 31:v31–9
4. Vogelzang et al. J Clin Oncol 2003 21:2636–44
5. Mansfield A, et al. J Thorac Oncol 2017;12:S2156–7
6. Grosso F, et al. J Clin Oncol 2017;35:3591–600
7. Hilberg F, et al. Cancer Res 2008;68:4774–82
8. Boehringer Ingelheim. Data on file
9. Boehringer Ingelheim. Available at: https://clinicaltrials.gov/ct2/show/NCT01907100 (Accessed 2 March 2018)
10. Byrne MJ, Nowak AK. Ann Oncol 2004;15:257–60

ACKNOWLEDGEMENTS

Disclosures: The authors were fully responsible for all content and editorial decisions, were involved in all stages of poster development, and have approved the final version. During the preparation of this poster, medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Syneos Health, UK.

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Presented at the IMIG Congress, Ottawa, Canada, 2–5 May 2018.