Nintedanib + pemetrexed/cisplatin in malignant pleural mesothelioma: Phase II biomarker data from the LUME-Meso study

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INTRODUCTION
- Nintedanib is an oral, twice daily, triple angiokinase inhibitor of vascular endothelial growth factor receptor (VEGFR) 1–3, platelet-derived growth factor receptor α/β and fibroblast growth factor receptor 1–3, as well as Src and Akt kinase signalling.
- The randomised Phase II LUME-Meso study is evaluating the efficacy and safety of nintedanib versus placebo, each in combination with pemetrexed in patients with malignant pleural mesothelioma, in patients with previously untreated, unresectable malignant pleural mesothelioma.
- In Phase II, nintedanib demonstrated an improvement in the primary endpoint of progression-free survival (PFS) (hazard ratio [HR] 0.54; p<0.03), with a trend for longer overall survival (OS) (HR=0.77; p=0.319), compared with placebo.
- Benefit was most pronounced in patients with epithelioid tumours.
- Exploratory analyses were conducted to investigate potential associations of biomarker microarray density (MVD), plasma-derived angiogenic factors and genomic markers with treatment outcomes in the Phase II LUME-Meso patient population.
- In line with the population under evaluation in the Phase III part of the study, this poster focuses on results for patients with epithelioid tumours.

METHODS
Study design
- The design of the Phase II part of the LUME-Meso trial is shown in Figure 1

Figure 1. LUME-Meso Phase II study design

Biomarker analyses
- Biomarker assessments were mandatory in the Phase II part of the study.
- MVD was evaluated in archival tumour specimens by manual or Chalkley count of platelet aggregation (Platelet aggregation; PECAM-1; also known as CD31) immunohistochemical staining at three MVD ‘hotspots’ per sample.
- For each sample, separate analyses were conducted for highest and average scores.
- Blood samples were collected at baseline and, for patients receiving monotherapy, at month 3 (Cycle 3) and at end of treatment (EoT).
- Plasma concentrations of 58 angiogenic factors were analysed by multiple immunoassays AngiogenesisMAP® panel (Myriad RBM, Austin, Texas, USA).
- Selected single-nucleotide polymorphisms (SNPs) were evaluated in the germline panel using iPLEX GOLD (n=966518 and n=9662818), VEGFEx (P2.7, n=307626 and n=3070621) and mesothelin (MSLN; n=376447 and n=4002650).

Statistical methods
- All analyses were exploratory and considered hypothesis generating.
- For predictive and prognostic analyses, the population was dichotomised for each biomarker.
- For MVD and baseline angiogenic factor levels, the median value was used as a cut-point (i.e. >median vs ≤median).
- For SNPs, patients with the major genotype were compared with those with other genotypes.
- Predictive relevance was evaluated by determining PFS/OS treatment effects in the biomarker-positive versus negative subgroups, and testing for treatment-by-biomarker interaction.
- Predictive relevance was assessed by comparing PFS/OS between biomarker-positive and negative subgroups within the placebo arm.
- Analyses were corrected for multiplicity using false-discovery rate (FDR) adjustment (Simes method, p≤0.05).
- To investigate pharmacodynamic changes, changes in angiogenic factor levels were compared between arms by analysis of variance (ANOVA).

RESULTS
Patient population
- Of 77 patients with epithelioid tumours, 48, 71 and 67 had available data for MVD, angiogenic factor and genomic analyses, respectively.

MVD
- No significant predictive effects of MVD were observed (Figure 2). The PFS and OS benefits of nintedanib appeared slightly greater in patients with higher average Chalkley score, but were similar across subgroups with high or low median scores.

Figure 2. Predictive analysis of MVD for (a) OS and (b) PFS in patients with epithelioid histology

• Of 28 patients with intermediate- to high-frequency genotypes for the two FL2 SNPs, the major genotype was compared with other genotypes.
- For the major SNP rs307626, OS HR (95% CI) was 0.49 (0.24–1.00) for the major homozygous genotypes versus 1.63 (0.35–8.51) for other genotypes (test for interaction: unadjusted p=0.030, FDR-adjusted p=0.190). For FL2 rs307626, OS HR (95% CI) was 0.48 (0.20–1.16) for the major Aa genotype versus 1.82 (0.64–5.26) for other genotypes (test for interaction: unadjusted p=0.049, FDR-adjusted p=0.257).

Table 1. Pharmacodynamic analysis of adjusted mean % change in angiogenic factor levels in patients with epithelioid histology who received monotherapy

CONCLUSIONS
- These exploratory analyses represent the first biomarker results for nintedanib-treated MPM.
- No biomarkers showed clear significant association with treatment benefit; however, treatment associations were limited by small subgroup size, especially for low-frequency genotypes.
- There were potential signals for greater PFS and/or OS improvements in patients with low plasma endothelin, major homogenous FL2/FL2Pf genotypes and a higher average Chalkley MVD score.
- These findings warrant further evaluation in the ongoing Phase III part of the LUME-Meso study.

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