Identification of a Clinical Biomarker for Second-line Combination Treatment with Nintedanib in Adenocarcinoma Non-small Cell Lung Cancer (NSCLC) Patients in Two Phase III Trials

#P388

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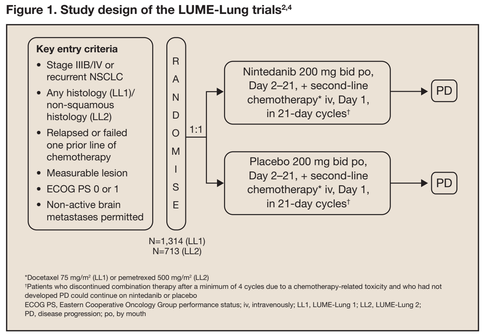
INTRODUCTION

- To date, no biomarkers of clinical effect have been identified for inhibitors of vascular endothelial growth factor (VEGF) or VEGF receptor (VEGFR)
- Nintedanib is an oral, triple angiokinase inhibitor of VEGFR-1–3, PDGFR-α/β and FGFR-1–3,[1] in late clinical development for the second-line treatment of advanced or recurrent NSCLC
- In the Phase III study, LUME-Lung 1, treatment with nintedanib 200 mg twice daily (bid) plus docetaxel improved centrally assessed progression-free survival (PFS; primary endpoint) versus placebo plus docetaxel (HR=0.79; 95% CI: 0.68–0.92; p=0.002) for second-line NSCLC patients
  - examination of OS, the key secondary endpoint, showed that nintedanib significantly prolonged survival in patients with adenocarcinoma histology (HR=0.83; 95% CI: 0.70–0.99; p=0.036)[2,3]
- In the independent Phase III LUME-Lung 2 trial, second-line patients with non-squamous NSCLC received nintedanib 200 mg bid plus pemetrexed or placebo plus pemetrexed[4]
  - based on a preplanned futility analysis of investigator-assessed PFS by an external Data Monitoring Committee (DMC), the study was stopped after randomising 713/1,300 planned patients
  - analysis of the primary endpoint (centrally assessed PFS, ITT population) revealed a statistically significant improvement with nintedanib plus pemetrexed versus placebo plus pemetrexed (HR=0.83; 95% CI: 0.70–0.99; p=0.0435)[4]
- To better understand the futility outcome of LUME-Lung 2 and to identify a patient population that benefited from treatment with nintedanib, further detailed analyses have been performed, as recommended by the DMC

METHODS

- LUME-Lung 1 and 2 were independent, multicentre, randomised, double-blind, Phase III trials involving patients with stage IIIB/IV or recurrent NSCLC after failure of first-line chemotherapy (Figure 1)[2,4]
  - patients with non-squamous histology were enrolled into LUME-Lung 2, while patients with all histologies were enrolled into LUME-Lung 1

Figure 1. Study design of the LUME-Lung trials[2,4]



*Docetaxel 75 mg/m² (LL1) or pemetrexed 500 mg/m² (LL2)
†Patients who discontinued combination therapy after a minimum of 4 cycles due to a chemotherapy-related toxicity and who had not developed PD could continue on nintedanib or placebo
ECOG PS, Eastern Cooperative Oncology Group performance status; iv, intravenously; LL1, LUME-Lung 1; LL2, LUME-Lung 2; PD, disease progression; po, by mouth

- Primary endpoint in both trials: PFS by central independent review (ITT analysis), modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.0; key secondary endpoint: OS
- Both trials underwent a futility analysis after approximately 356 events, i.e. 50% of the PFS events required for the primary analysis
- LUME-Lung 1 passed the futility analysis, whereas LUME-Lung 2 did not.

Identification of a clinical biomarker

- The approach followed the principles of a prognostic and predictive enrichment concept.[5] In the absence of molecular markers, histology was used to differentiate the tumour populations
- Any identified clinical biomarker was required to be both prognostic and predictive, with a consistently observed treatment effect for both investigator- and centrally-assessed PFS and OS
- Step 1, prognostic baseline variables were identified in the placebo arm of LUME-Lung 2.
- Step 2, their interaction with treatment was investigated to confirm whether they were also predictive of benefit with nintedanib
- Hypotheses developed through analysis of LUME-Lung 2 were to be validated in the independent LUME-Lung 1 trial in patients of the same histology

Identification of prognostic variables

- In step 1, a recursive partitioning tree method was used,[6–8] supplemented by a stepwise selection approach, with Cox proportional hazards modelling[9]
  - both methods were applied to the investigator-assessed PFS dataset
  - the covariates tested are listed in Table 1

Table 1. Investigated prognostic variables

Baseline characteristic	Randomisation stratification factor	Prespecified in both protocols
Tumour histology (LL1: squamous vs non-squamous) (LL2: adenocarcinoma vs nonadenocarcinoma)	✓	✓
Baseline ECOG PS (0 vs 1)	✓	✓
Prior bevacizumab therapy (yes vs no)	✓	✓
Brain metastases at baseline (yes vs no)	✓	✓
Liver metastases (yes vs no)	✗	✓
Gender (male vs female)	✗	✓
Age (<65 vs ≥65 years)	✗	✓
Best response to first-line chemotherapy (CR/PR/SD vs PD/unknown/NA/missing)	✗	✓
Concomitant bisphosphonates at baseline (yes vs no)	✗	✓
Disease stage at diagnosis (<IIB/IV vs IIB vs IV)	✗	✓
Region (LL1: Asia vs rest of world) (LL2: Asia vs non-Asia)	✗	✓
Time since start of first-line therapy*	✗	✓
Adrenal metastases (yes vs no)†	✗	✗
Number of metastatic organs at baseline†	✗	✗
Lactate dehydrogenase level at baseline†	✗	✗

*Time between start of first-line therapy and randomisation into the trial. †Additionally identified from the literature.
✓, yes; ✗, no; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; LL1, LUME-Lung 1; LL2, LUME-Lung 2; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease

Identification of predictive variables

- The interaction between identified prognostic covariates and nintedanib-related treatment effect was analysed using treatment-by-covariate interaction tests for categorical covariates and HR-by-treatment interaction plots for continuous covariates[10]
  - in the interaction tests, an adjusted Cox proportional hazards model was applied to determine HRs and 95% CIs
  - for continuous prognostic covariates, HR-by-treatment interaction plots were produced with HRs estimated at different values of the covariate

Confirmation and validation

- First, internal confirmation and validation of the clinical biomarker was performed using centrally assessed PFS data and interim OS data obtained at the time of the primary analysis of the LUME-Lung 2 trial
- Second, independent, external validation of the biomarker was performed using centrally assessed PFS data and interim OS data obtained at the time of the primary analysis of the LUME-Lung 1 trial
- The last independent validation step was performed with final OS data from LUME-Lung 1
- To ensure comparability across studies, the clinical biomarker was confirmed and validated using data from non-squamous patients only

RESULTS

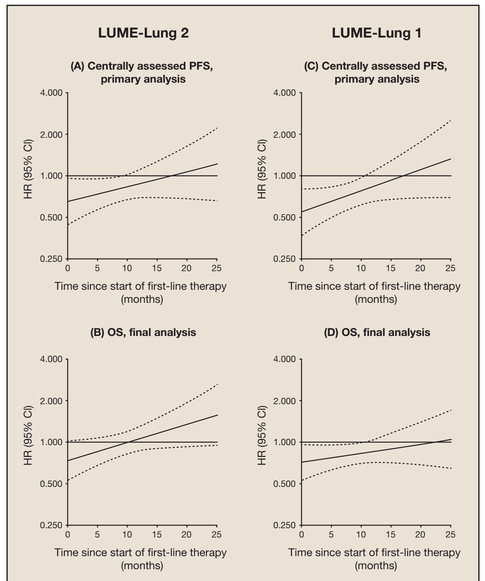
Identification of prognostic variables

- Using investigator-assessed PFS data from the placebo arm of LUME-Lung 2, recursive partitioning identified time since start of first-line therapy as a potentially prognostic variable
  - the stepwise selection approach identified time since start of first-line therapy, gender, lactate dehydrogenase (LDH) levels and smoking status as potentially prognostic variables
- In the confirmatory analyses using centrally assessed PFS data from the placebo arm of LUME-Lung 2 (primary analysis), recursive partitioning identified time since start of first-line therapy as a potentially prognostic variable
  - the stepwise selection analysis of these data identified time since start of first-line therapy, region, LDH levels and presence/absence of liver metastases as potentially prognostic variables

Identification of a predictive variable

- Time since start of first-line therapy was the only prognostic and predictive clinical biomarker for the treatment effect of nintedanib plus pemetrexed (LUME-Lung 2) or docetaxel (LUME-Lung 1)
  - the results of the LUME-Lung 1 analysis showed that the effect observed in non-squamous patients was primarily driven by patients with adenocarcinoma histology[6]
- An inverse relationship between the length of time since start of first-line therapy and the treatment effect of nintedanib plus second-line chemotherapy was shown for PFS and OS (Figure 2); the shorter the time from start of first-line therapy to randomisation, the better the treatment effect
- To categorise the continuous variable 'time since start of first-line therapy', a cut-off of 9 months was chosen based on the width of the 95% CI and the time when the upper boundary of the 95% CI approached a HR of 1 (T<9mo)

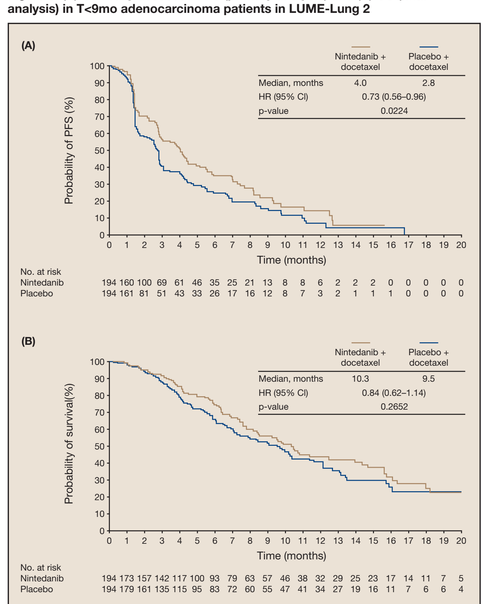
Figure 2. HR as a function of time since start of first-line therapy in advanced NSCLC patients with adenocarcinoma tumour histology: (A) centrally assessed PFS (primary analysis) and (B) OS (final analysis) in LUME-Lung 2; and (C) centrally assessed PFS (primary analysis) and (D) OS (final analysis) in LUME-Lung 1



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival

- As shown in Figure 3, statistically significant prolongation of (A) centrally assessed PFS and (B) a trend for improved OS with nintedanib plus pemetrexed versus placebo plus pemetrexed was seen in T<9mo adenocarcinoma patients in LUME-Lung 2

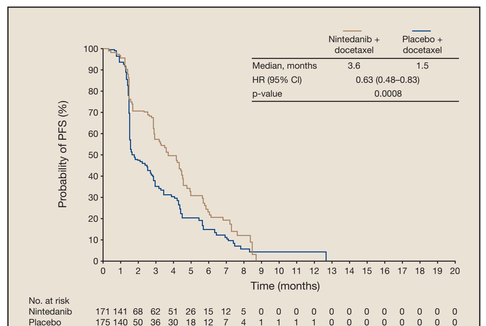
Figure 3. (A) Centrally assessed PFS (primary analysis) and (B) OS (final analysis) in T<9mo adenocarcinoma patients in LUME-Lung 2



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

- The external validation analysis of LUME-Lung 1 data in T<9mo adenocarcinoma patients showed a statistically significant improvement in centrally assessed PFS with nintedanib plus docetaxel, with an increase in median PFS more than double that observed in placebo plus docetaxel patients (Figure 4)

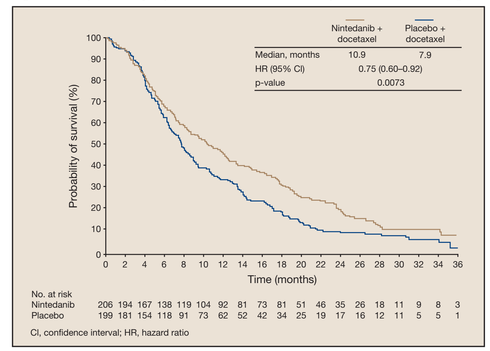
Figure 4. Centrally assessed PFS (primary analysis) in T<9mo adenocarcinoma patients in LUME-Lung 1



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

- The final validation step, using OS data from LUME-Lung 1 demonstrated that:
  - the adenocarcinoma patient population derived a significant treatment benefit, regardless of time since the start of first-line therapy[3] (Figure 2D)
  - time since the start of first line therapy is a predictive marker for clinical effect with nintedanib treatment
  - in the population of adenocarcinoma patients with a particularly poor treatment prognosis (patients who progressed during or shortly after first-line therapy defined here as a time since first-line therapy <9 months) treatment with nintedanib in combination with docetaxel resulted in a statistically significant improvement in OS, with a 25% reduction in the risk of death (HR=0.75, p=0.0073, Figure 5). These patients experienced a 3-month improvement in median OS (nintedanib 10.9 months, placebo 7.9 months)

Figure 5. OS (final analysis) in T<9mo adenocarcinoma patients in LUME-Lung 1



CI, confidence interval; HR, hazard ratio

CONCLUSIONS

- Significant clinical benefit was observed for the overall patient population with adenocarcinoma tumour histology
- Using data from two large, independent studies, time since the start of first-line therapy was the only prognostic and predictive clinical biomarker for the treatment effect of nintedanib, in combination with either docetaxel or pemetrexed, for advanced NSCLC patients of adenocarcinoma tumour histology, progressing following prior treatment with platinum-based chemotherapy
- A treatment benefit was evident in those adenocarcinoma patients with a particularly poor prognosis who progressed during or shortly after first-line treatment. These patients experienced a 3-month improvement in OS and more than double the median PFS compared with placebo plus docetaxel in LUME-Lung 1

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Abbreviations: CI, confidence interval; HR, hazard ratio; FGFR, fibroblast growth factor receptor; NSCLC, Non-Small Cell Lung Cancer; OS, overall survival; PFS, progression-free survival; PDGFR, platelet-derived growth factor receptor

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