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Nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with relapsed or refractory, advanced non-small cell lung cancer (LUME-Lung 2): A randomized, double-blind, phase III trial

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ABSTRACT

Objectives: LUME-Lung 2 investigated the efficacy/safety of nintedanib plus pemetrexed in patients with pretreated non-squamous non-small cell lung cancer (NSCLC).
Materials and methods: Patients with stage IIIB/IV or recurrent non-squamous NSCLC who had received one prior chemotherapy regimen were randomized (1:1 stratified by histology [adenocarcinoma/non-adenocarcinoma], prior bevacizumab, Eastern Cooperative Oncology Group performance status and presence of brain metastases) to receive intravenous pemetrexed 500 mg/m^2 on Day 1 plus nintedanib 200 mg orally twice daily or matching placebo on Days 2–21, every 3 weeks until progression/unacceptable toxicity. Progression-free survival (PFS) by independent central review was the primary endpoint. Overall survival (OS) was the key secondary endpoint.
Results: Based on the pre-planned futility analysis of investigator-assessed PFS, conducted by an independent data monitoring committee, recruitment was halted on 18 June 2011 after 713 (n = 353 nintedanib/pemetrexed; n = 360 placebo/pemetrexed)/1300 planned patients had enrolled. There were no safety concerns. Subsequent analysis demonstrated a significant improvement in PFS favoring nintedanib/pemetrexed over placebo/pemetrexed (median 4.4 months vs 3.6 months; hazard ratio [HR] = 0.83, 95% confidence interval [CI] 0.70–0.99, p = 0.0435). There was no significant difference in OS (median 12.0 months vs 12.7 months; HR = 1.01, 95% CI 0.85–1.21, p = 0.8940) after 514 deaths. Nintedanib/pemetrexed resulted in a higher incidence of grade ≥3 elevated

Abbreviations: NSCLC, non small cell lung cancer; VEGF(R), vascular endothelial growth factor (receptor); PDGF(R), platelet-derived growth factor (receptor); FGR(R), fibroblast growth factor (receptor); PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; RECIST, response evaluation criteria in solid tumors; ECOG PS, Eastern Cooperative Oncology Group performance status; CT, computed tomography; MRI, magnetic resonance imaging; AE, adverse event; CTCAE, common toxicity criteria for adverse events; QoL, quality of life; DMC, data monitoring committee; ITT, intention-to-treat; IQR, interquartile range; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

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alanine aminotransferase (23.3% vs 7.3%), elevated aspartate aminotransferase (12.1% vs 1.7%) and diarrhea (3.5% vs 1.1%) compared with placebo/pemetrexed, but no difference in hypertension, bleeding or thrombosis.
Conclusion: Although recruitment stopped prematurely, combining nintedanib with pemetrexed significantly prolonged PFS in patients with advanced non-squamous NSCLC after first-line chemotherapy, with a manageable safety profile.

1. Introduction

For patients with advanced non-small cell lung cancer (NSCLC), without known targetable mutations, platinum-based combination therapy is the recommended first-line therapy [1,2]. However, nearly all patients experience disease progression and eligible patients will require second-line treatment, mainly with pemetrexed, docetaxel or erlotinib monotherapy [1,2].

Signaling pathways regulated by vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), and their associated receptors (VEGFR, PDGFR and FGFR, respectively), play an important role in tumor angiogenesis [3]. Inhibition of these angiogenic targets has shown substantial antitumor activity in preclinical models of human cancer, including NSCLC [4]. Nintedanib is an oral, potent triple angiokinase inhibitor with proven preclinical antiangiogenic and antitumor activity, targeting all subtypes of VEGFR, PDGFR and FGFR [4].

The combination of nintedanib plus docetaxel in previously treated patients with advanced or recurrent NSCLC was assessed in the phase III LUME-Lung 1 trial (NCT00805194; 1199.13) [5]. In LUME-Lung 1, patients who met similar eligibility criteria as in the current study (except that patients with squamous cell carcinoma were enrolled in LUME-Lung 1) were randomized to receive nintedanib plus docetaxel or placebo plus docetaxel. Nintedanib plus docetaxel significantly improved centrally reviewed progression-free survival (PFS; median 3.4 months vs 2.7 months; hazard ratio [HR] = 0.79, 95% confidence interval [CI]: 0.68–0.92, $p = 0.0019$) in all patients and significantly prolonged overall survival (OS) in the prespecified population of patients with adenocarcinoma tumor histology (median 12.6 months vs 10.3 months; HR = 0.83, 95% CI: 0.70–0.99, $p = 0.0359$) compared with docetaxel alone. Nintedanib combined with docetaxel is approved in the European Union and other countries for the treatment of patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumor histology after first-line chemotherapy, and has also been approved as monotherapy for the treatment of patients with idiopathic pulmonary fibrosis.

Combination therapy with nintedanib and pemetrexed has been shown to enhance antitumor activity compared with either agent alone in *in vivo* experiments in xenograph models, and has also shown a marked impact on the proliferation and survival of tumor and endothelial cells *in vitro* [6]. Nintedanib in combination with pemetrexed has previously been shown to have a manageable tolerability in platinum-pretreated patients with advanced NSCLC in a phase I study, with a median PFS of 5.4 months [7]. Although pemetrexed is frequently used in the first-line setting as part of platinum doublet therapy in patients with non-squamous NSCLC [8], it is not used universally and pemetrexed continues to be used in the second-line setting in some patients. Based on the expected lack of drug–drug interactions, a global, randomized, placebo-controlled, phase III trial (LUME-Lung 2, NCT00806819; 1199.14) was conducted in parallel to LUME-Lung 1 to assess whether using nintedanib plus pemetrexed (nintedanib–pemetrexed) for previously treated patients with advanced or recurrent, non-squamous NSCLC led to greater efficacy than using pemetrexed alone.

2. Materials and methods

2.1. Patients

We carried out this study in 202 centers in 32 countries (North and South America, Europe, Asia and Australia/Oceania). Patients were 18 years or older with histologically or cytologically confirmed stage IIIB/IV or recurrent, non-squamous NSCLC, and either had relapsed or had failed one prior line of chemotherapy (excluding neoadjuvant and/or adjuvant chemotherapy for recurrent disease). All patients had at least one measurable target tumor lesion, according to modified Response Evaluation Criteria In Solid Tumors version 1.0 (RECIST v1.0) [9], that had not been irradiated within the past 3 months; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and a life expectancy of at least 3 months. Exclusion criteria included patients with active brain metastases (defined as stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic or requiring treatment with anticonvulsants). Patients with radiographic evidence of cavitary or necrotic tumors, centrally located tumors with radiographic evidence (computed tomography [CT] or magnetic resonance imaging [MRI]) of local invasion of major blood vessels, or a recent history (<3 months) of clinically significant hemoptysis or a major thrombotic or clinically relevant major bleeding event in the past 6 months, were also excluded from the study, as were those who had received prior therapy with VEGF/VEGFR inhibitors (other than bevacizumab) or pemetrexed. Detailed eligibility criteria are described in Appendix Table S1.

The trial was approved by local independent ethics committees, including an independent review board, and complied with the Declaration of Helsinki and Good Clinical Practice principles. All patients provided written informed consent and were free to withdraw from the study at any time.

2.2. Procedures

Patients were randomized in a 1:1 ratio to receive nintedanib–pemetrexed or placebo–pemetrexed (see Appendix for details). Patients were stratified by ECOG PS (0 vs 1), previous bevacizumab treatment (yes vs no), histology (adenocarcinoma vs non-adenocarcinoma) and presence of stable brain metastases (yes vs no). Pemetrexed 500 mg/m^2 was administered intravenously on Day 1, combined with either oral nintedanib 200 mg twice daily or matching placebo, given on Days 2–21, every 3 weeks. Two capsules of nintedanib 100 mg or placebo were to be taken in the morning and again in the evening, after food. Patients received treatment until unacceptable toxicity or disease progression, or until they met another of the predefined withdrawal criteria (see Appendix for details of adverse event (AE) management).

Target lesions were evaluated by central independent review according to modified RECIST [9] at baseline (within 4 weeks of the start of study treatment) and every 6 weeks after the first admin-