

Anti-angiogenic therapy in advanced non-small cell lung carcinoma (NSCLC): is there a role in subsequent lines of therapy?

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Early in 2014, Reck and colleagues published the results of the LUME Lung-1 trial in *Lancet Oncology* (1). This trial evaluated the addition of nintedanib, an oral triple angiokinase inhibitor or placebo, to standard second-line chemotherapy with docetaxel. The trial, conducted largely in European countries, randomized 1,314 patients to docetaxel plus nintedanib 200 mg twice daily, or docetaxel plus placebo. Treatment continued until disease progression, or unacceptable toxicity. Eligible patients had stage IIIB/IV or recurrent non-small cell lung carcinoma (NSCLC) that had progressed after first-line chemotherapy. Patients with contraindications to the use of VEGF-R directed therapy (untreated brain metastases, underlying major bleeding or thrombotic disorders, cavitary lesions, lesions invading major blood vessels and a history of hemoptysis) were excluded. Prior therapy with bevacizumab was allowed, although fewer than 5% of patients in both arms had previously received bevacizumab. Stratification was based on Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), prior bevacizumab therapy (yes vs. no), squamous versus non squamous histology, and the presence of brain metastases (yes vs. no). The primary outcome was progression free survival (PFS).

The trial demonstrated that the addition of nintedanib to docetaxel significantly improved PFS compared with docetaxel plus placebo [3.4 vs. 2.7 months (m); HR 0.79; 95% CI: 0.68-0.92, $P=0.002$]. A hierarchical analysis was undertaken for overall survival (OS). If the primary outcome was met, a stepwise analysis of OS was conducted starting with patients with adenocarcinoma who progressed in less than nine months from starting first-line therapy, followed by all patients with adenocarcinoma, and lastly the entire study population. Among patients with adenocarcinoma who progressed within 9 months from initiating first line treatment,

OS was significantly improved (10.9 vs. 7.9 m; HR 0.75; 95% CI: 0.60-0.92; $P=0.036$). Similarly, improved OS was observed in all patients with adenocarcinoma (12.6 vs. 10.3 m; HR 0.83; 95% CI: 0.70-0.99; $P=0.036$). However, there was no OS benefit observed in the entire study population (10.1 vs. 9.1 m; HR 0.94; 95% CI: 0.83-1.05; $P=0.272$).

The improvement in PFS is not readily explained by an increase in response to therapy. The response rate for docetaxel plus nintedanib was similar to that of docetaxel alone (4.4% vs. 3.3%, $P=0.31$). However, there was a higher rate of disease stabilization in the combination arm, resulting in a significant improvement in the disease control rate (DCR) for docetaxel plus nintedanib (54% vs. 41.3%, $P<0.0001$).

The improvement in efficacy though, was associated with greater toxicity. Adverse events (all grades) occurring more frequently in patients receiving docetaxel plus nintedanib included: diarrhea (42.3% vs. 21.8%), reversible alanine transaminase elevations (28.5% vs. 8.4%), nausea (24.2% vs. 18%), elevated aspartate aminotransferase (22.5% vs. 6.6%), decreased appetite (22.2% vs. 15.6%) and vomiting (16.9% vs. 9.3%). The overall incidence of grade 3 or higher adverse events was 71.3% in the nintedanib arm compared with 64.3% in the docetaxel alone arm. Withdrawals related to adverse events were similar (22.7% vs. 21.7%). Grade 3 or higher hypertension, bleeding, or thromboses were comparable.

There are some limitations to consider in interpreting the results from the LUME Lung-1 trial. The improvement in PFS is modest, representing approximately a 3-week gain in median PFS and less than the 30% minimum reduction in PFS that has been suggested to represent a clinically important difference (2). The decision to undertake a hierarchical analysis for OS was made late in the conduct of the trial, after the primary analysis for PFS was conducted and not from the outset of the study design. The hypothesis

concerning patients with adenocarcinoma progressing less than nine months from initial treatment arose from exploratory analyses of the LUME Lung-2 trial evaluating the combination of nintedanib plus pemetrexed (3). While these were interesting findings, this subgroup analysis of LUME Lung-1 represents a non-randomized comparison and does not allow firm conclusions regarding any OS benefit, particularly given the absence of a survival benefit in the overall study population (4). These findings therefore, remain exploratory. Under these circumstances of marginal benefit it is important to examine the toxicity data. The addition of nintedanib to docetaxel results in increased toxicity. There is a small but meaningful increase in the number of deaths that appear unrelated to disease progression (5.4% *vs.* 3.8%) that needs to be weighed against a modest improvement in PFS.

Angiogenesis is considered a hallmark of malignancies such as lung cancer, as it is an integral part of tumor growth, progression and metastasis (5). Proangiogenic pathways have been attractive therapeutic targets, as they are commonly expressed in NSCLC. Vascular endothelial growth factor (VEGF) pathway is the most recognized proangiogenic pathway. Bevacizumab, a monoclonal antibody directed against serum VEGF-A, is an established treatment for patients with NSCLC (6). Additional proangiogenic pathways include platelet derived growth factor (PDGF) and fibroblast derived growth factor (FGF) (7,8). Expressions of these pathways provide mechanisms of resistance to antiangiogenic therapies and support the evaluation of agents with a broader spectrum of antiangiogenic activity.

Therefore, the question remains whether the addition of nintedanib to docetaxel might improve OS in a subgroup of NSCLC patients. Nintedanib has activity against platelet derived growth factor receptor (PDGF-R) and fibroblast growth factor receptor (FGF-R) in addition to VEGF-R (9). This offers a theoretical improvement in efficacy over other compounds with a narrower spectrum of anti-angiogenic activity. Therefore it is important to examine the findings of LUME Lung-1 in the context of what is already known about anti-angiogenic therapy in the second-line treatment of NSCLC.

A similarly designed randomized trial, LUME Lung-2, evaluated the addition of nintedanib to pemetrexed (10). This trial was discontinued early following an interim analysis demonstrating futility, although the final analysis also showed a modest improvement in PFS (4.4 *vs.* 3.6 m; HR 0.83; 95% CI: 0.70-0.99; *P*=0.04). This trial only included patients with adenocarcinoma, and yet no

improvement in OS was noted for the addition of nintedanib in this population. As noted by the authors, many other trials have evaluated anti-angiogenic agents in the second-line setting. Studies evaluating vandetanib alone (11), or in combination with chemotherapy (12), the addition of, bevacizumab to chemotherapy or erlotinib (13,14), and the addition of agents such as sunitinib (15) or sorafenib (16) to erlotinib have all shown some improvement in PFS. However, none of these trials demonstrated any gain in OS. To date no agent has demonstrated sufficient benefit to be incorporated into treatment algorithms for second-line therapy of NSCLC (17).

A number of questions remain concerning nintedanib in second-line therapy for NSCLC. LUME Lung-1 allowed the entry of patients who received bevacizumab therapy in the first-line setting. However, fewer than 5% of patients had actually received prior bevacizumab. Therefore it is unclear whether any improvement in disease control from nintedanib would be observed in patients who received prior anti-angiogenic therapy. There is not a lot of information known concerning mechanisms of resistance to bevacizumab in lung cancer and whether the broader anti-angiogenic activity of nintedanib would overcome such resistance. This has particular implications for jurisdictions such as the USA, where bevacizumab is more widely utilized in the treatment of NSCLC.

Additional questions remain concerning the identification of predictive biomarkers for anti-angiogenic therapy in NSCLC. Markers such as baseline serum VEGF, intracellular adhesion molecule (ICAM) and β FGF may have prognostic value, but are not predictive for OS (18). To date there are no established predictive biomarkers for anti-angiogenic therapies (19). There are no data from translational studies from LUME Lung-1 to further this field of research. However, it is now recognized that lung adenocarcinomas demonstrate significant molecular heterogeneity (20). Future research needs to examine the prognostic and predictive value of molecular phenotypes and benefit from anti-angiogenic therapies in NSCLC.

In conclusion, the LUME Lung-1 trial provides some evidence of increased efficacy for the addition of nintedanib to docetaxel. The results of subgroup analyses suggest that patients with more aggressive disease might have improved OS from the combination therapy. However, these results are not ready for implementation into clinical practice at this time. An ongoing trial (LUME-Columbus, NCT02231164) evaluating nintedanib plus docetaxel and limited to NSCLC patients with adenocarcinoma will ultimately answer this question and define the role of nintedanib in NSCLC.

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