Lung Cancer: Targets and Therapy

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REVIEW

Clinical potential of nintedanib for the second-line treatment of advanced non-small-cell lung cancer: current evidence

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Abstract: The therapeutic landscape in non-small-cell lung cancer (NSCLC) is changing. The description of molecular alterations leading to NSCLC carcinogenesis and progression (so-called oncogenic driver mutations) and the development of targeted agents interfering with the tumor-promoting intracellular signaling pathways have improved the outcome for many patients with advanced/metastatic NSCLC. However, many patients with stage IV NSCLC do not have one of the targetable predictive biomarkers, and are therefore in need of classical chemotherapy. This especially applies to squamous cell cancer. A platinum-based doublet chemotherapy is the standard of care for patients with stage IV NSCLC. As second-line therapies, docetaxel, pemetrexed, and the EGFR tyrosine-kinase inhibitor erlotinib have demonstrated benefit in Phase III randomized trials. Recently, the addition of the angiokinase inhibitor nintedanib to docetaxel has proven efficacious, and is a new treatment option in the second-line setting. Preclinical and clinical data of nintedanib for the treatment of lung cancer patients are reviewed here.

Keywords: nintedanib, lung cancer, angiokinase inhibitor, VEGFR, PDGF, FGFR

Introduction

Lung cancer is associated with a high mortality rate.[1] Non-small-cell lung cancer (NSCLC) is the most common subtype of lung cancer, accounting for approximately 85% of all cases. Traditional chemotherapy for advanced NSCLC has shown limited activity while producing substantial toxicity. Recent efforts in improving the therapy of NSCLC have therefore focused on the development of new treatments targeting specific signaling pathways shown to be important for tumor progression and metastasis. Angiogenesis is such an essential pathway,[2,3] and has shown independent prognostic value in various malignancies.[4–6] Angiogenesis inhibition has therefore been intensively investigated, and has shown significant antitumor activity in various tumors.[7,8]

VEGF promotes endothelial cell migration and proliferation, and is therefore a key factor of angiogenesis in normal and cancer tissue. There are three different receptors for VEGF: VEGFR-1, VEGFR-2, and VEGFR-3. However, the biological effects of VEGF are mediated by VEGFR-1 and VEGFR-3, whereas VEGFR-2 has been shown to have a primary role in endothelial cell activation. VEGF is expressed in most cancers, including lung cancer.[9] Elevated VEGF levels are associated with higher grade and poorer differentiation of tumors, and result in a worse outcome.[10–12]

PDGFR also has a role in promoting angiogenesis, tumor growth, and metastasis.[13] Several PDGFR tyrosine kinases are expressed on endothelial cells and pericytes. They control the survival of endothelial cells and pericyte–endothelial cell contact.[14,15] PDGFR activation leads to cell migration and proliferation, as well as angiogenesis.[16,17]

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FGF signaling is mediated by FGFRs. FGF signaling contributes to tissue homeostasis, tissue repair, angiogenesis, and inflammation.[18] The FGFR tyrosine kinase is involved in angiogenesis, cell proliferation, and survival.[17,19]

A combined inhibition of several pathways involved in angiogenesis might be rational, due to the fact that tumor cells have the ability to escape the sustained inhibition of VEGF by regulating proangiogenic factors, such as PDGF and FGF.[14,20–22]

Antiangiogenic treatment in lung cancer

Bevacizumab was the first approved drug targeting angiogenesis.[23] Bevacizumab blocks VEGF-A, and is currently approved combined with chemotherapy in various solid tumors, including nonsquamous lung cancer. Among 215 patients receiving bevacizumab monotherapy, the most common grade 3 (G3) or G4 toxicities were hypertension (in 12 patients [5.6%]), proteinuria (in nine patients [4.2%]), fatigue (in eleven patients [5.1%]), and dyspnea (in 12 patients [5.6%]).[24] In patients with squamous NSCLC, severe bleedings have been described with bevacizumab, but also with other antiangiogenic drugs.[25,26] Bevacizumab was approved in 2004 in combination with a platinum-based chemotherapy in the first-line setting in patients with nonsquamous NSCLC based on two randomized Phase III trials. In an Eastern Cooperative Oncology Group (ECOG) trial, 4,599 trial patients were randomized between carboplatin/paclitaxel alone and the same chemotherapy combination with bevacizumab.[24] The addition of bevacizumab significantly improved overall survival (OS) (median 12.3 versus 10.3 months, hazard ratio [HR] 0.79; P=0.03). The Avastin in Lung Cancer (AVAiL) trial randomized patients to either cisplatin/gemcitabine alone or the same chemotherapy in combination with bevacizumab in two different dosages.[27] Both dosages significantly improved progression-free survival (PFS), but failed to improve OS.[28]

Ramucirumab is a human IgG_1 monoclonal antibody specifically binding to the extracellular domain of VEGFR-2. The REVEL trial randomized 1,253 patients progressing after one prior platinum-based doublet chemotherapy to docetaxel plus ramucirumab or docetaxel plus placebo.[29,30] This study showed a significant prolongation of the primary end point – OS (median OS 10.5 versus 9.1 months, HR 0.857; P=0.0235). OS was improved in nonsquamous cell carcinoma (median OS 11.1 versus 9.7 months, HR 0.83), as well as in squamous cell carcinoma (median OS 9.5 versus 8.2 months, HR 0.88). The overall response rate for the whole study population was 22.9% versus 13.6% (P<0.001) and median PFS was 4.5 versus 3.0 months (HR 0.762, P<0.0001).

Ramucirumab also showed clinical benefit in patients pretreated with bevacizumab; 14% and 14.7% of patients had had prior bevacizumab. Patients in the ramucirumab group had more bleeding or hemorrhage events of any grade (29% versus 15%), although rates of G3 or worse events were much the same.

In contrary to monoclonal antibodies, small molecules inhibit tyrosine kinases within specific signaling pathways. Sorafenib is a multikinase inhibitor targeting VEGFR-2, VEGFR-3, PDGFR, RAF, and c-Kit.[31] Sorafenib was investigated in two randomized Phase III trials (ESCAPE, Evaluation of Sorafenib, CArboplatin and Paclitaxel Efficacy in NSCLC;[26] NExUS, NSCLC research Experience Utilizing Sorafenib[32]) in combination with chemotherapy. Neither trial showed a benefit in outcome for patients treated with sorafenib. In both trials, a similar rate of severe bleeding events in patients with squamous cell carcinoma, as with bevacizumab, was described. The NExUS trial was amended, and patients with squamous cell carcinoma were excluded from the trial after the toxicity results of the ESCAPE trial were published.[32] In the BATTLE trial, sorafenib demonstrated clinical activity in NSCLC, especially with wild-type EGFR and with a specific gene signature.[33] However, the MISSION trial showed that treatment with sorafenib as third- or fourth-line therapy does not result in improved OS in patients with NSCLC. A post hoc biomarker analysis suggested that patients with *EGFR*-mutant cancers may benefit.[34,35]

Sunitinib inhibits VEGFR, PDGFR, c-Kit, RET, and Flt-3. Sunitinib was tested in Phase II trials in pretreated metastatic NSCLC, and showed clinical activity.[36,37] Vandetanib is an inhibitor of EGFR, VEGFR, and RET. It was investigated in four randomized trials ZEST (ZACTIMA Efficacy when Studied versus Tarceva),[38] ZEAL (ZACTIMA Efficacy with Alimta in Lung cancer),[39] ZODIAC (ZACTIMA in combination with Docetaxel In non-smAll cell lung Cancer),[40] ZEPHYR (ZACTIMA Efficacy trial for NSCLC Patients with History of EGFR-TKI and chemo-resistance).[41] either as a single agent or in combination with chemotherapy. Vandetanib was not associated with an OS benefit in any of these trials. A meta-analysis of four trials evaluating vandetanib confirmed these results.[42]

Development of nintedanib

Nintedanib is an orally available inhibitor of VEGFR-1, -2, and -3, FGFR-1, -2, and -3, and PDGFRα and -β tyrosine

kinases ("triple kinase inhibitors").[43] Nintedanib also has inhibitory activity against members of the Src family of kinases and against Flt-3.[43] Structurally, nintedanib is an indolinone derivative. It binds to the adenosine-5′-triphosphate (ATP)-binding site in the kinase domain of the aforementioned receptors, and therefore inhibits angiogenic signaling by preventing receptor dimerization.[43,44]

Nintedanib has inhibited tumor growth in various preclinical models.[43] Furthermore, it was shown that nintedanib could significantly enhance the cytotoxicity of doxorubicin and paclitaxel by inhibiting the function of ATP-binding cassette transporters, which are one of the main causes of multidrug resistance.[45] In vivo, nintedanib demonstrates antitumor activity in different human xenograft models, including NSCLC (Calu-6), colorectal cancer (HT-29), ovarian carcinoma (SKOV-3), renal cell carcinoma (Caki-1), and prostate cancer (PAC-120).[43] In tumor xenografts, nintedanib reduces tumor-microvessel density and the number of PDGFRβ-expressing perivascular cells, as measured by immunohistochemistry.[43]

Early clinical trials with nintedanib

In the first Phase I trial, 61 patients with advanced tumors were enrolled and treated at different dose levels.[46] Patients were treated for 4 weeks, followed by an interruption of 1 week. The most frequent drug-related adverse events (AEs) were mild to moderate. G3 or higher AEs with once-daily nintedanib versus twice-daily nintedanib occurring in >5% of patients were reversible hepatic enzyme elevation (G3 12% versus 0; G4 4% versus 2.8%), aspartate aminotransferase elevation (G3 8% versus 2.8%), alanine aminotransferase elevation (G3 0 versus 5.6%), γ-glutamyl transpeptidase elevation (G3 4% versus 5.6%), CD4 lymphocyte decrease (G3 16% versus 5.6%), hypertension (G3 4% versus 0), diarrhea (G3 0 versus 2.8%), nausea (G3 0 versus 5.6%), and vomiting (G3 0 versus 2.8%). The maximum tolerated dose (MTD) of nintedanib was determined to be 250 mg for both once- and twice-daily dosing. In this heavily pretreated patient population, one complete response (CR) and two partial responses (PRs) were observed in patients with metastatic renal cell carcinoma and colorectal cancer. The twice-daily dosing allows for higher drug exposure without adding additional toxicity. Based on this trial showing an acceptable safety profile and first signals of clinical activity, the twice-daily dosing was recommended for further Phase II clinical trials. In an Asian population, another Phase I trial included 21 patients with advanced cancer and determined the MTD at 200 mg twice daily. Reversible liver-enzyme elevations were the only dose-limiting toxicities (DLTs).[47] In this trial, no CR or PR was described.

Early trials of nintedanib in NSCLC

In a Phase I open-label study, nintedanib was tested in combination with the folate antagonist pemetrexed in patients with recurrent metastatic NSCLC of all histological subtypes who had previously received at least one platinum-based chemotherapy.[48] Patients were treated with the standard dose of pemetrexed of 500 mg/m^2 given intravenously on day 1 and with nintedanib on days 2–21 of a 21-day cycle. The dose of nintedanib was escalated from 100 mg given twice daily to the MTD. In this trial, the MTD of nintedanib in combination with pemetrexed was found to be 200 mg twice daily. The most frequent DLTs were gastrointestinal disorders (86.4%), general disorders, and administration-site conditions (76.9%), mainly rash. One patient showed a CR, and 50% of patients showed stable disease as best overall response. No clinically relevant pharmacokinetic interactions between nintedanib and pemetrexed were observed.

Based on Phase I trials in advanced gynecological malignancies showing the feasibility of the combined treatment of nintedanib with standard doses of carboplatin and paclitaxel,[49] an open-label dose-escalation study investigated the safety and tolerability of carboplatin area under the curve 6 mg/mL/min and paclitaxel 200 mg/m^2 in combination with nintedanib (starting dose 50 mg twice-daily). This trial defined the MTD as 200 mg twice daily. During the first treatment, cycle six DLTs occurred. These included liver-enzyme elevations, thrombocytopenia, abdominal pain, and rash. The combination treatment showed relevant activity, with seven confirmed PRs (26.9%). Disease stabilization was described in a further ten patients. This led to a clinical benefit ratio of 84.6%. No significant pharmacological interactions between chemotherapy and nintedanib were found.[50]

A Phase II trial evaluated two different twice daily dosages of nintedanib (150 mg [n=36] or 250 mg [n=37] as a single agent in 73 pretreated NSCLC patients with an ECOG performance status (PS) of 0–2.[51] The trial reported median PFS of 6.9 weeks and OS of 21.9 weeks. The rate of disease stabilization was 46%. Patients with an ECOG PS of 0–1 had median PFS of 11.6 weeks and median OS of 37.7 weeks.[51] The most commonly reported AEs were nausea (57.5%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%), and reversible alanine aminotransferase (13.7%) and aspartate aminotransferase elevations (9.6%). Patients in the higher-dose group

showed a higher rate of liver-enzyme elevations. All other toxicities were well balanced between the two groups.

Phase III trials of nintedanib in NSCLC

The LUME-Lung 1 trial included NSCLC patients independently of histological subtype, and investigated the combination of docetaxel and nintedanib. A total of 655 patients from 211 centers in 27 countries with stage IIIB/IV recurrent NSCLC progressing after first-line chemotherapy were randomized either to docetaxel 75 mg/m^2 combined with nintedanib 200 mg orally twice daily or docetaxel 75 mg/m^2 combined with placebo on days 2–21 of a 3-week cycle.[52] Patients were stratified by ECOG PS, histology, presence of brain metastases, and previous treatment with bevacizumab. The combination of docetaxel and nintedanib significantly improved the primary end point of PFS, with an absolute gain of 0.7 months (median 3.4 versus 2.7 months, HR 0.79; *P*=0.0019). Median OS was 10.1 versus 9.1 months (HR 0.94, *P*=0.2720). In patients with adenocarcinoma histology, nintedanib significantly improved median OS from 10.3 to 12.6 months (HR 0.83, *P*=0.0359). A more pronounced effect on median OS was found in patients with adenocarcinoma progressing within 9 months after initiation of first-line therapy (10.9 versus 7.9 months, HR 0.75; *P*=0.0073). However, the time interval between first-line chemotherapy and progression was not a prespecified clinical end point or stratification parameter of the trial. G3 or worse adverse events that were more common in the docetaxel plus nintedanib arm than in the control arm were diarrhea, reversible increases in alanine aminotransferase, and reversible increases in aspartate aminotransferase. Toxicities of both treatment arms are summarized in Table 1. The authors concluded that the combination of docetaxel and nintedanib is an active second-line therapy in patients with advanced NSCLC previously treated with one line of platinum-based therapy, especially for patients with adenocarcinoma. Besides the previously published BR.21 trial[53] and TAX 317 trial,[54] the LUME-Lung 1 trial is the only prospective randomized Phase III trial showing a significant improvement in OS in the second-line metastatic setting. Furthermore, it is the first trial in the second-line setting combining a targeted agent with chemotherapy to show a survival benefit, with median OS longer than 1 year in patients with adenocarcinoma NSCLC versus an active comparator. However, it has to be mentioned that the absolute

Table 1 Overview of adverse events with a frequency >5% classified by Common Terminology Criteria for Adverse Events (version 3.0) in all patients who received at least one dose of study drug in the LUME-Lung 1 study

	Docetaxel plus nintedanib (n=652)				Docetaxel plus placebo (n=655)			
	All grades	G3	G4	G5	All grades	G3	G4	G5
Any SAE	34.4%	7.4%	7.5%	16.4%	31.5%	8.9%	6.0%	11.8%
Any AE	93.6%	21.2%	33.7%	16.4%	93.0%	21.2%	31.3%	11.8%
Diarrhea	42.3%	6.0%	0.5%	0.2%	21.8%	2.4%	0.2%	0
Decreased neutrophils	37.1%	9.0%	23.0%	0	35.9%	8.7%	21.2%	0
Fatigue	30.4%	4.9%	0.6%	0.2%	26.9%	3.2%	0.5%	0
Increased ALT	28.5%	7.8%	0	0	8.4%	0.9%	0	0
Decreased WBC count	24.5%	11.5%	4.9%	0	24.4%	11.1%	4.1%	0
Nausea	24.2%	0.8%	0	0	18.0%	0.9%	0	0
Increased AST	22.5%	3.4%	0	0	6.6%	0.5%	0	0
Decreased appetite	22.2%	1.1%	0.3%	0	15.6%	1.1%	0	0.2%
Dyspnea	19.0%	2.1%	0.5%	2.3%	16.8%	11.5%	3.2%	1.8%
Vomiting	16.9%	0.6%	0.2%	0	9.3%	0.5%	0	0
Alopecia	16.4%	0.2%	0	0	18.2%	0	0	0
Cough	15.2%	0.8%	0	0.2%	16.8%	0.6%	0	0
Neutropenia	13.8%	3.2%	8.9%	0	14.4%	2.9%	9.2%	0
Pyrexia	12.7%	0.5%	0.3%	0	15.0%	0.3%	0	0
Decreased hemoglobin	11.2%	1.1%	0.3%	0	12.1%	1.8%	0.3%	0
Constipation	5.4%	0	0	0	11.6%	0.5%	0	0
Asthenia	8.9%	2.0%	0	0.3%	9.8%	1.2%	0.2%	0.2%
Chest pain	8.6%	0.6%	0.5%	0.3%	9.5%	1.5%	0.6%	0
Febrile neutropenia	7.4%	2.6%	4.4%	0	4.9%	2.1%	2.6%	0
Anemia	5.4%	0.8%	0.3%	0	7.5%	1.2%	0.2%	0.2%
Pneumonia	5.1%	2.1%	0.5%	0.5%	5.5%	2.1%	0	1.2%

Note: Data from Reck et al.[52]

Abbreviations: SAE, severe adverse event; ALT, alanine aminotransferase; WBC, white blood cell; AST, aspartate aminotransferase; AD, adverse event.

Table 2 Overview of major ongoing clinical trials with nintedanib including patients with lung cancer; from http://www.clinicaltrials.gov. Accessed May 23, 2014

Trial	NCT number	Description	Primary end point
Phase I			
BARIS	01349296	Nintedanib and everolimus in solid tumors	MTD, tolerability
VENUS-1	01684111	Dose-escalation trial of nintedanib in combination with intravenous vinorelbine in elderly patients with advanced NSCLC	MTD
VENUS-2	01683682	Dose escalation trial of nintedanib in combination with intravenous carboplatin and vinorelbine in elderly patients with advanced NSCLC	MTD
Phase II	01948141	Nintedanib in treating patients with advanced non-small-cell lung cancer who have failed up to two previous chemotherapy regimens: laboratory biomarker analysis	PFS rate within the entire FGFRI-amplified group
	01441297	Nintedanib as second-line treatment for patients with small-cell lung cancer	ORR

Abbreviations: NCT, National Clinical Trial; NSCLC, non-small-cell lung cancer; MTD, maximum tolerated dose; PFS, progression-free survival; ORR, overall response rate; FGFR1, fibroblast growth factor receptor 1.

survival benefit in the adenocarcinoma subpopulation was only 6 weeks, and the additional toxicity is meaningful. LUME-Lung 2 (NCT00806819) investigated the efficacy and safety of nintedanib 200 mg twice daily combined with pemetrexed compared with pemetrexed and placebo in patients with stage IIIB/IV or recurrent nonsquamous NSCLC after relapse or failure of first-line chemotherapy. Based on the results of a preplanned futility analysis of investigator-assessed PFS, conducted by an independent data-monitoring committee, recruitment was halted early after 713 of 1,300 planned patients had enrolled and ongoing patients were unblinded, as the analysis suggested that the study was futile and that the primary end point of centrally assessed PFS would likely not be met. However, it was shown that the primary end point of PFS was significantly improved in the experimental arm (median PFS 4.4 versus 3.6 months, HR 0.83; P=0.0435).[55] The overall response rate was comparable (9.1% versus 8.3%), and OS was not significantly different (median OS 12.2 versus 12.7 months, HR 1.03; P=0.7921). Overall, there was a higher incidence of G3/4 adverse events in the nintedanib plus pemetrexed arm than the placebo plus pemetrexed arm (58.5% versus 42.3%). However, nintedanib plus pemetrexed was not associated with an increase in serious AEs (30.0% versus 32.8%). Table 2 provides an overview on current clinical trials evaluating nintedanib in patients with lung cancer.

Conclusion

Tumor angiogenesis is a complex and crucial mechanism in tumorigenesis and tumor progression. Inhibition of angiogenesis by targeting the VEGF pathway has resulted in improved patient survival in different solid tumors. However, VEGF is not the only player in the angiogenesis signaling, and various resistance mechanisms to VEGF-targeting agents have been described.[56] Therefore, novel treatment approaches are urgently needed. This might be possible by combining anti-angiogenic drugs with substances targeting other important signaling pathways or by the discovery of novel compounds targeting angiogenesis by multiple pathways.

Compared to other angiogenesis inhibitors, nintedanib has a different profile of targeting VEGFR, PDGFR, and FGFR. It also has a distinct pharmacokinetic profile.[43] Nintedanib seems to be very well tolerated with no severe bleeding, which makes it an interesting angiogenesis inhibitor, especially in patients with squamous cell histology. However, results from the first randomized Phase III trial (LUME-Lung 1) showed higher efficacy in adenocarcinoma patients.[52]

In future studies, it will be important to do correlative biomarker analyses to establish predictive markers for response and elucidate mechanisms of resistance. The discovery of specific patient populations that will derive benefit from nintedanib or other antiangiogenic drugs is an unmet need in NSCLC treatment.

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