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Nintedanib in non-small cell lung cancer: from preclinical to approval

Christian Caglevic, Massimiliano Grassi, Luis Raez, Angela Listi, Marco Giallombardo, Eva Bustamante, Ignacio Gil-Bazo and Christian Rolfo

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***Abstract*:** Angiogenesis is a driving force of a tumor's development. Targeting this process is an attractive option, as this is a feature shared by most of the solid tumors. A lot of antiangiogenic drugs have been developed following this path, including bevacizumab, sorafenib, sunitinib, vandetanib, ramucirumab, motesanib and many others. The latest drug of this class to be approved for patients with non-small cell lung cancer (NSCLC) was nintedanib, a triple angiokinase inhibitor. This molecule targets vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and fibroblast growth factor (FGF) pathways, avoiding the tumor's switch to normal escape mechanisms. The pharmacokinetic, pharmacodynamic and toxicity profiles of nintedanib have been tested in several studies. These trials revealed it to be very interesting, as this agent did not lead to the classical adverse events of other tyrosine kinase inhibitors. A phase III clinical trial that recently concluded provided us with relevant information in patients with NSCLC of adenocarcinoma histology. Here we present a short overview of the tumor angiogenesis pathways and antiangiogenic drugs. In particular, we will focus on nintedanib, from the preclinical studies to the latest phase III clinical trial that allowed this new agent to be approved by the European Medicines Agency as a second-line treatment option in association with docetaxel for NSCLC patients with adenocarcinoma histology.

Keywords: antiangiogenic drugs, BIBF1120, nintedanib, non-small cell lung cancer, NSCLC, tyrosine kinase inhibitor

Correspondence to:
Christian Rolfo, MD, PhD, MBHA
Head of Phase I - Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital and Antwerp University, Wilrijkstraat 10, 2650 Edegem, Belgium
christian.rolfo@uza.be

Christian Caglevic, MD
Oncology Department, Arturo Lopez Perez Cancer Foundation, Santiago, Chile

Massimiliano Grassi, Erasmus project MD student
Phase I - Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital, Edegem, Belgium

Luis Raez, MD, FACP, FCCP, MACSG
Thoracic Oncology Program, Memorial Cancer Institute, Memorial Health Care System, Pembroke Pines, FL, USA

Angela Listi, BsC, MsC
Department of Surgical, Oncological and Stomatological Sciences, Section of Medical Oncology, University of Palermo, Italy

Marco Giallombardo, BsC, MsC
Phase I - Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital, Edegem, Belgium
Department of Biopathology and Medical Biotechnology and Forensic Section of Biology and Genetics, University of Palermo, Italy
Tumor Immunotherapy Laboratory, Oncology Department, Antwerp University Hospital, Edegem, Belgium

Eva Bustamante, BsC, PhD
Molecular Biology Unit, Arturo Lopez Perez Cancer Foundation, Santiago, Chile

Ignacio Gil-Bazo, MD, PhD
Department of Oncology, Clínica Universidad de Navarra, Pamplona, Spain

Introduction

The recent advent of targeted therapies has radically changed the treatment strategies of many solid tumors, including non-small cell lung cancer (NSCLC). The new tailored agents, such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and EML4-ALK inhibitors, are able to inactivate specific molecular alterations that occur in specific oncogenes, rendering cancer cell survival strictly dependent on such aberrant genes, as has been well explained by the 'oncogene addiction theory' [Torti and Trusolino, 2011]. However, only a minority of tumors are oncogene addicted, and chemotherapy remains the only treatment option available for the majority of cancer patients. In such a setting, targeting the angiogenesis pathways represents an alternative and a very attractive strategy. Indeed, tumor development, progression and metastasis are strongly linked to angiogenesis. Angiogenesis is a very complex process, highly regulated by many molecules with both pro-angiogenic and antiangiogenic activity.

The tumor microenvironment is composed of hyperproliferating cells that need large amounts of oxygen and nutrients. Such cells are able to deregulate the angiogenic process inducing an abnormal secretion of pro-angiogenic factors and the consequent development of disorganized, tortuous, enlarged, high permeable blood vessels, which are needed for both tumor growth and its metastatic potential [Nishida *et al.* 2006].

There are a lot of endogenous regulators that activate different pathways leading to neo-angiogenesis, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet derived growth factor (PDGF) and many others [Onimaru and Yonemitsu, 2011]. Some targeted agents with

antiangiogenic properties have been approved for the treatment of NSCLC. Bevacizumab and ramucirumab are two monoclonal antibodies which target VEGF and VEGFR-2, respectively. Nintedanib is a triple angiokinase inhibitor that blocks VEGFR-1-2-3, FGFR-1-2-3 and PDGFR-α-β, targeting the pro-angiogenic pathway downstream of VEGF [Rolfo *et al.* 2013].

In this review we briefly discuss the pharmacokinetics and pharmacodynamics of this new molecule, providing all clinical data emerging from phase I–III studies that led to the recent approval by the European Medicines Agency (EMA) as a second-line treatment in association with docetaxel in patients with NSCLC. There are several clinical trials ongoing or planned that are studying the potential benefits of nintedanib in different solid tumors, hematological tumors and in non-neoplastic diseases as well (NSCLC, SCLC, mesothelioma, melanoma, ovarian cancer, cervix cancer, endometrial cancer, breast cancer, thyroid cancer, glioblastoma, gastroesophageal cancer, colorectal cancer, hepatocarcinoma, urothelial cancer, prostatic cancer, renal cancer, acute myeloid leukemia, multiple myeloma, pulmonary fibrosis and other diseases). Some trials for NSCLC that are ongoing or that are planned to start soon with nintedanib include: induction chemotherapy for stages IB-IIIA NSCLC in combination with cisplatin plus docetaxel; treatment for advanced or metastatic disease combining nintedanib with docetaxel, with pemetrexed (second line), with cisplatin–gemcitabine doublet (first line), and nintedanib as monodrug treatment after a second line of treatment.

State of the art in the deep world of angiogenesis inhibitors in NSCLC

Since the discovery of these angiogenic pathways, several drugs have been developed for the treatment of NSCLC (Table 1). The first antiangiogenic drug to be approved was bevacizumab, a VEGF-A inhibitor, that is still used as a first-line treatment for nonsquamous NSCLC in combination with different chemotherapies. The latest clinical trials in which bevacizumab has been tested in patients with advanced NSCLC as a first-line treatment are a phase II study in 175 patients treated with paclitaxel plus carboplatin with and without bevacizumab (progression-free survival [PFS] 6.9 *versus* 5.9 months; overall survival [OS] 22.8 *versus* 23.4 months), and two phase III clinical trials investigating docetaxel plus carboplatin with and without bevacizumab in 117 patients (OS 19.1 *versus* 15.3 months), and gemcitabine plus cisplatin with and without bevacizumab in 698 patients (PFS 6.5 *versus* 6.1 months; OS 13.4 *versus* 13.1 months) [Niho *et al.* 2012; Boutsikou *et al.* 2013; Reck *et al.* 2009].

Another molecule with antiangiogenic activity is sorafenib, a VEGFR-2, VEGFR-3, PDGFR-v, RAF and c-kit inhibitor. Sorafenib is used in renal cell carcinoma patients and in hepatocellular carcinoma patients. It was also tested in a phase II clinical trial *versus* placebo in 81 patients with NSCLC 'after a second-line treatment' (PFS 3.3 *versus* 2 months; OS 13.7 *versus* 9 months) and in a phase III study in 772 patients in combination with chemotherapy (gemcitabine plus cisplatin) which showed no positive results (PFS 6 *versus* 5.5 months; OS 12.4 *versus* 12.5 months) [Wakelee *et al.* 2012; Paz-Ares *et al.* 2012].

Sunitinib is another target agent for VEGFR, PDGFR, c-kit and Flt-3 and has approval for patients with metastatic renal cell carcinoma, for previously treated patients with gastrointestinal stromal tumor that failed standard treatment, and for some neuroendocrine tumors of the pancreas. Sunitinib has also been tested in previously treated patients with NSCLC in two phase II studies: one in combination with erlotinib that showed just a minimal effect in the setting of second- and third-line treatment in PFS (2.8 *versus* 2 months) and in OS (8.2 *versus* 7.6 months), and the other in combination with pemetrexed, with poor results (PFS 3.7 *versus* 4.9 months; OS 6.7 *versus* 10.5 months) [Groen *et al.* 2013; Heist *et al.* 2014].

The mechanism of action for vandetanib is directed against VEGFR, EGFR and RET, and it has obtained approval for medullary thyroid cancer. In several trials in NSCLC this drug did not show any significant improvement in PFS, nor in OS [Aisner *et al.* 2013; Ahn *et al.* 2013].

Ramucirumab is one of the latest developed drugs and is a VEGFR-2 inhibitor. A phase III study (REVEL) comparing ramucirumab plus docetaxel *versus* docetaxel alone in 1253 stage IV patients with NSCLC as second-line treatment after platinum-based therapy reported significant improvement in overall response rate (ORR; 22.9% versus 13.6%, $p < 0.001$), median PFS

Table 1. Results of angiogenesis inhibitors' clinical trials in non-small cell lung cancer.

Anti-angiogenic agent	Study	Phase	Arms	Number of patients	PFS months (+vs-agent)	OS months (+vs-agent)
Bevacizumab	Niho *et al.* [2012]	II	Pac+Carbo±Beva	175	6.9 *versus* 5.9	22.8 *versus* 23.4
	Boutsikou *et al.* [2013]	III	Doc+Carbo±Beva	117	Not given	19.1 *versus* 15.3
	Reck *et al.* [2009]	III	Gem+Cisp±Beva	698	6.5 *versus* 6.1	13.4 *versus* 13.1
Sorafenib	Wakelee *et al.* [2012]	II	Sora *versus* Placebo	81	3.3 *versus* 2	13.7 *versus* 9
	Paz-Ares *et al.* [2012]	III	Gem+Cisp±Sora	772	6 *versus* 5.5	12.4 *versus* 12.5
Sunitinib	Groen *et al.* [2013]	II	Erlotinib±Suni	132	2.8 *versus* 2	8.2 *versus* 7.6
	Heist *et al.* [2014]	II	Pemetrexed±Suni	83	3.7 *versus* 4.9	6.7 *versus* 10.5
Vandetanib	Aisner *et al.* [2013]	II	Vandet *versus* placebo	162	4.5 *versus* 4.2	9.8 *versus* 9.4
	Ahn *et al.* [2013]	II	Vandet *versus* placebo	117	2.7 *versus* 1.7	15.6 *versus* 20.8
Ramucirumab	Garon *et al.* [2014]	III	Docetaxel ± Ram	1253	4.5 *versus* 3	10.5 *versus* 9.1
Motesanib	Scagliotti *et al.* [2012]	III	Pac+Carbo±Mot	1905	5.6 *versus* 5.4	13 *versus* 11
	Kubota *et al.* [2014]	III	Pac+Carbo±Mot	227	7 *versus* 5.3	20.6 *versus* 14.5

OS, overall survival; PFS, progression-free survival.

(4.5 *versus* 3.0 months; hazard ratio [HR] 0.762; $p < 0.0001$), and median OS (10.5 *versus* 9.1 months; HR 0.857; 95% confidence interval [CI] 0.751–0.98; $p = 0.0235$). The benefits were similar in nonsquamous and squamous histology. The most common and severe side effects were neutropenia (34.9% *versus* 28.0%), febrile neutropenia (15.9% *versus* 10.0%), fatigue (11.3% *versus* 8.1%), leukopenia (8.5% *versus* 7.6%), hypertension (5.4% *versus* 1.9%) and pneumonia (5.1% *versus* 5.8%). Grade 5 toxicities such as pulmonary hemorrhage were comparable in both arms (5.4% *versus* 5.8%) [Garon *et al.* 2014]. Ramucirumab was approved by the US Food and Drug Administration for the treatment of metastatic NSCLC in combination with docetaxel in December 2014, and is also approved for advanced gastric cancer that has presented disease progression after standard chemotherapy.

Motesanib (AMG70) is an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR and Kit. A phase III study (MONET1) was performed comparing motesanib plus carboplatin and paclitaxel *versus* carboplatin and paclitaxel but it failed to show any benefit in OS. However, a recent second analysis in a subgroup of 227 Asian people showed relevant data in OS (20.6 *versus* 14.5 months) and PFS (7 *versus* 5.3 months) [Scagliotti *et al.* 2012; Kubota *et al.* 2014].

Nintedanib

The molecule

Nintedanib, formerly BIBF 1120, is an indolinone, a substituted oxindole derivative that was synthesized to block adenosine triphosphate (ATP)-binding sites in the kinase domain of pro-angiogenic receptors inhibiting the downstream signaling pathways related to neoangiogenesis.

A phase 0 *in vitro* and *in vivo* study showed a marked inhibition of tumor growth in xenograft models of human NSCLC as well as in renal cell carcinoma, colorectal cancer, ovarian cancer

and prostate carcinoma [Hilberg *et al.* 2008]. Pharmacokinetic studies in mice showed a maximal plasma concentration of about 1000 nmol/l at 1 hour after oral administration of nintedanib as well as plasma levels below 8 nmol/l at 24 h postadministration. The terminal half-life of nintedanib is in the range of 7–19 h [Stopfer *et al.* 2011].

This characteristic pharmacokinetic profile can be explained by the rapid metabolism of nintedanib by methyl ester cleavage, resulting in the generation of the main metabolite BIBF1202, which contains a free acid residue. This is a very important feature and could be one of the reasons why nintedanib produces less classical antiangiogenic adverse effects and has a great accessibility to the tumor vessels.

Pharmacodynamics

Pharmacodynamic studies were very promising, as nintedanib was found to be an inhibitor of vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), fibroblast growth factor receptors (FGFR-1, FGFR-2, FGFR-3), platelet derived growth factor receptors (PDGFR-α, PDGFR-β) as well as the receptor of kinases of RET, the tyrosine kinase FLT3 and sarcoma viral oncogene (Src) (see Figure 1).

The three VEGF receptors have different functions. VEGFR-1 is required for the recruitment of hematopoietic stem cells and for the migration of monocytes and macrophages. VEGFR-2 stimulates proliferation, migration and survival of endothelial cells and increases vascular permeability. VEGFR-3 regulates the lymphatic endothelial cell function. VEGF takes also part in tumorigenesis, directly stimulating cancer stem cell proliferation [Holmes *et al.* 2007]. For these reasons, high levels of VEGF are correlated with more aggressive and poorer prognosis tumors.

Platelet-derived growth factor (PDGF) leads to stromal recruitment, affecting tumor growth, angiogenesis, invasion and metastasis [Andrae *et al.* 2008].

Another important pathway targeted by nintedanib is related to FGF, a molecule that promotes angiogenesis and cell proliferation [Cao *et al.* 2012].

VEGF, PDGF and FGF are just three of the multitude of molecules involved in the regulation of angiogenesis and tumor cell survival. As a multitarget inhibitor, nintedanib leads to an important decrease of microvessel density and pericyte coverage and this leads to a diminished perfusion and thereby to the death of tumor cells.

It has been also described in a preclinical study with models of lung and pancreatic cancer that nintedanib does not increase the markers of epithelial to mesenchymal transition (EMT) that usually allow tumor cells to switch from one pathway to another. This evidence is very important, and could explain why this drug does not promote the change to a more aggressive tumor subtype and does not induce chemotherapy resistance, different to many other promising angiokinase inhibitors [Cenik *et al.* 2013].

Toxicity and safety profile, phase I studies

Clinical trials have been conducted to set the maximum tolerated dose (MTD), toxicity, safety, pharmacokinetics and pharmacodynamics of nintedanib. In one of these, among 61 patients with advanced solid tumors who received nintedanib, 25 received 50–450 mg once daily and 36 received 150–300 mg twice daily in a 4 weeks with 1 week off regimen. Pharmacokinetic analyses revealed that the dose of 200 mg twice daily allowed increased drug exposure without additional toxicity.

Concerning the safety and toxicity profile, no treatment-related deaths were observed. The most common adverse events were grade 1–2 nausea (68.9%), vomiting (45.9%), diarrhea (44.3%) and grade 3–4 reversible liver enzyme elevation. More relevant data regarded the diminishment of CD4 lymphocytes. Unlike other angiokinase inhibitors, nintedanib was not associated with significant hypertension, nor with hand–foot syndrome. All of these findings and some clinically important signs of efficacy have resulted in novel clinical trials of this molecule [Mross *et al.* 2010].

With respect to NSCLC, a phase I study with a combination of nintedanib and pemetrexed in patients with advanced-stage NSCLC that had recurrence after a first-line platinum based chemotherapy has been conducted. These patients received a starting dose of 100 mg of nintedanib twice daily with pemetrexed 500 mg/m^2 once every 21 days, with increasing doses of nintedanib until the MTD was reached. The most frequent

Therapeutic Advances in Respiratory Disease
2015, 9 : 4 164-172

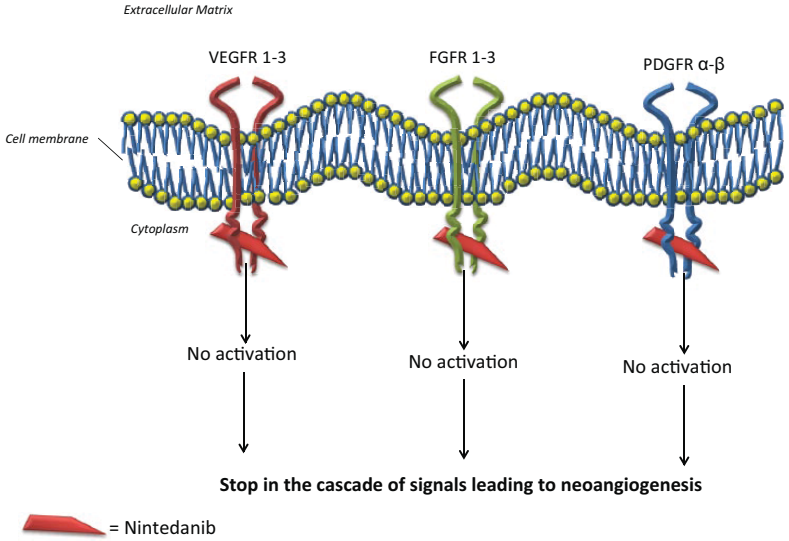

Figure 1. Nintedanib binds the intracellular domains of angiogenic agents blocking the signals.
FGFR, fibroblast growth factor receptor; PDGFR, platelet derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

adverse events were fatigue (65.4%), nausea (61.5%), anorexia (53.8%), rash (38.5%), diarrhea (34.6%) and vomiting (34.6%) but the most frequent serious adverse event was pneumonia (7.7%). During the treatment that looked for the MTD, 26.9% of the patients experienced grade 3 events that included elevated alanine aminotransferase (ALT; 7.6%) and aspartate aminotransferase (AST; 3.8%), vomiting (3.8%), esophageal pain (3.8%), nausea (3.8%), fatigue (19.2%), confusion (3.8%) and anorexia (3.8%), setting the DLT (dose limiting toxicity). Not significant interactions were found with this combination of drugs, and in 50% of the patients stable disease was reached with a median PFS of 5.4 months [Ellis *et al.* 2010].

Doebele and colleagues investigated nintedanib combined with paclitaxel (Taxol) plus carboplatin in stage IIIB–IV NSCLC first-line patients [Doebele *et al.* 2012]. They gave to the patients a starting dose of 50 mg of nintedanib twice daily on days 2–21 plus paclitaxel (200 mg/m^2) and carboplatin [area under curve (AUC) = 6 mg/ml/min] on day 1 of each 21-day cycle in order to establish safety and the nintedanib MTD for this combination. The MTD was settled at 200 mg of nintedanib twice a day; at 250 mg treatment was declared not tolerable because three of the three treated patients developed DLT during the first treatment cycle: grade 3 gamma-glutamyltransferase increase, grade 3 ALT increase and grade 3 abdominal pain.

At the end of the study, the most frequently reported adverse events related to nintedanib were diarrhea (53.8%), fatigue (50%) and nausea (46.2%). A total of 30.8% of the patients developed grade 1–2 hypertension, but only half of the cases were related to nintedanib, and only six DLT events occurred during the first cycle (grade 4 thrombocytopenia, grade 3 ALT increase, AST increase, abdominal pain and rash).

Very promising data about clinical efficacy were obtained; they showed that of a total of 13 patients treated with the MTD, nine achieved a partial response and two disease stability.

Examination of plasma was performed to find out whether there was an interaction between nintedanib and paclitaxel plus carboplatin: these results suggested that there was not a significant difference compared with the normal pharmacokinetics [Doebele *et al.* 2012].

Efficacy in phase II trials

Reck and colleagues conducted a phase II study to investigate the efficacy, safety, tolerability and pharmacokinetics of nintedanib in patients with stage IIIB/IV NSCLC who failed a first- or a second-line platinum-based chemotherapy [Reck *et al.* 2011]. A

total of 73 patients were enrolled (36 received nintedanib 250 mg twice daily and 37 received 150 mg twice daily). Dose reduction was allowed to 150 mg b.i.d. or 100 mg b.i.d. The data collected showed no significant difference between the two arms concerning median PFS (6.9 months) and OS (21.9 months). In a subanalysis PFS was longer in patients with ECOG 0–1 than in those with ECOG 2 (11.6 *versus* 6 weeks; HR 3.194, $p = 0.0002$).

Concerning the pharmacokinetics, in the group treated with the nintedanib 150 mg b.i.d. dose, nintedanib plasma concentration, after 3 hours from the first drug administration, was 18.2 ng/ml (0.662–77.0 ng/ml) and in the group treated with 250 mg b.i.d. the plasma concentration was 27.8 ng/ml (2.66–179 ng/ml). There was only slight accumulation of nintedanib plasma concentrations from day 1 to day 43 in both dose groups.

The most common adverse effects were similar in patients with squamous and non-squamous cell cancer histologies: they were mostly grade 1–2 nausea (57.5%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible ALT (13.7%) and AST elevations (9.6%). Neither hand–foot syndrome nor cases of severe hypertension and only rare grade 2 thromboembolic events were reported, representing the classical side effects of antiangiogenic drugs.

A similar clinical efficacy was shown in both arms as 46% of all patients and 59% of patients with ECOG 0–1 showed a tumor stabilization (defined as such if a patient's first overall disease assessment at 6 weeks was stable disease [SD], complete response or partial response [PR]) with a medium reduction of the tumor mass of 25%. Grade 3 adverse events were more frequently associated with the highest dosage (5.3% *versus* 33.3% requiring interruption to treatment due to adverse events). Even if all patients recovered after nintedanib discontinuation, these data led the authors to indicate a lower dosage as the best option [Reck *et al.* 2011].

Nintedanib phase III studies

The efficacy of nintedanib in NSCLC has been evaluated in two phase III randomized clinical trials: Lume-Lung1 and Lume-Lung2.

LUME-Lung1

This phase III, double blinded, randomized, placebo-controlled clinical trial compared

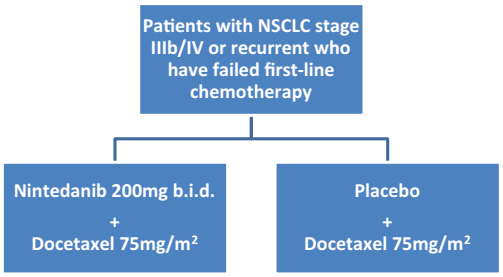

Figure 2. Lume-Lung 1: study design.
NSCLC, non-small cell lung cancer.

chemotherapy (docetaxel plus placebo) against docetaxel plus nintedanib. A total of 1314 patients with stage IIIb/IV or recurrent NSCLC who failed previous chemotherapy were included (Figure 2).

The primary endpoint was PFS and the key secondary endpoint was OS analyzed in different prespecified groups (patients with adenocarcinoma who progressed within 9 months after start of first-line therapy, patients with adenocarcinoma, and all patients). A total of 655 patients received docetaxel plus nintedanib and 659 docetaxel plus placebo. The regimen was docetaxel 75 mg/m² by intravenous infusion on day 1 and nintedanib 200 mg or placebo twice daily orally on days 2–21 until unacceptable toxicity or disease progression. Nintedanib dose reductions were allowed only twice (to 150 mg and then to 100 mg twice daily) and it could be continued as single agent in case of chemotoxicity after the fourth cycle of docetaxel.

After 7.1 months the first preplanned analysis showed a higher PFS in the nintedanib arm (3.4 *versus* 2.7 months; HR 0.79; $p = 0.0019$). A subsequent analysis was performed at 31.7 months in order to evaluate the OS. These results were very impressive in patients with adenocarcinoma who progressed within 9 months after the first line (10.9 *versus* 7.9 months; HR 0.75; $p = 0.0073$). A similar activity was observed in all of the patients with adenocarcinoma (12.6 *versus* 10.3 months; HR 0.83; $p = 0.0359$). An even more significant result was detected in an extended analysis of a subgroup of patients who were refractory from the beginning to the first-line treatment, achieving an improvement in OS of 3.5 months (9.8 *versus* 6.3 months; HR 0.62; $p = 0.0246$).

In the analysis of the entire population (all histologies), the addition of nintedanib to

chemotherapy led to a positive trend, although not significant, in improvement in OS (10.1 *versus* 9.1 months; HR 0.94; $p = 0.2720$).

Another important effect that was demonstrated with the combination of docetaxel and nintedanib was the reduction of tumor size and of target lesions.

The more common grade 3 or greater side effects reported for the nintedanib plus docetaxel arm included diarrhea (6.6% *versus* 2.6%), increased ALT (7.8% *versus* 0.9%), nausea (0.8% *versus* 0.9%), increased AST (3.4% *versus* 0.5%), decreased appetite (1.4% *versus* 1.2%) and vomiting (0.8% *versus* 0.5%). For the most part hematological side effects were solved by reducing the dose of docetaxel. Gastrointestinal side effects were mostly attributed to nintedanib.

During the study 60 patients died due to major adverse events possibly related with the study treatments, including sepsis (0.8% docetaxel + nintedanib *versus* 0.2% docetaxel + placebo), pneumonia (0.3% docetaxel + nintedanib *versus* 1.1% docetaxel + placebo), respiratory failure (0.6% docetaxel + nintedanib *versus* 0% docetaxel + placebo) and pulmonary embolism (0% docetaxel + nintedanib *versus* 0.5% docetaxel + placebo [Reck *et al.* 2014].

LUME-Lung2

This phase III trial compared chemotherapy (pemetrexed) plus placebo against pemetrexed plus nintedanib in patients with stage IIIb/IV or recurrent NSCLC in the setting of second-line treatment. The primary endpoint was PFS and the key secondary endpoint was OS. A total of 713 patients were included but the trial was stopped due to the results of the preplanned Data Monitoring Committee futility analysis, which suggested that the primary endpoint would not be met [Hanna *et al.* 2013].

Conclusions

New treatments for NSCLC are being tested every day in order to increase the patients' survival and improve their quality of life, but until now only a few drugs have proved to be effective for this purpose. Nintedanib has been shown to be a valid option as a single agent or in combination with different chemotherapies schemas.

Nintedanib, as with other tyrosine kinase inhibitors, can be administered orally. However, it has a more interesting safety profile, as it does not lead to the typical side effects of antiangiogenic drugs such as hypertension or hand–foot syndrome, probably because of its innovative triple-blocking mechanism of action.

Until a few months before the time of writing only phase I and II studies results were available, but now the first phase III clinical trial has given us new and interesting data concerning the efficacy of nintedanib in association with docetaxel as second-line treatment in patients with advanced NSCLC. As this combination was demonstrated to improve patients' survival, on 21 November 2014, the combination of nintedanib and docetaxel obtained EMA approval as a second-line option for NSCLC patients with adenocarcinoma histology. This is a great success and surely a step in the right direction in the deep world of angiogenesis inhibition, although we must realize that we are still far away from the conclusion of studies into this molecule. More knowledge about this class of new drugs and about the pathways involved in tumor growth is needed.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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