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Boehringer Ingelheim is developing nintedanib as a triple angiogenesis inhibitor for advanced lung cancer

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For the past 15 years, Boehringer Ingelheim's research centre in Vienna, Austria, has been identifying novel angiogenesis inhibitors for the treatment of cancer. The drug candidate nintedanib is being developed as a therapeutic agent to treat advanced non-small cell lung cancer (NSCLC) and other solid tumours. In November 2014, the European Medicines Agency approved nintedanib for use in combination with docetaxel for the treatment of adults with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy.

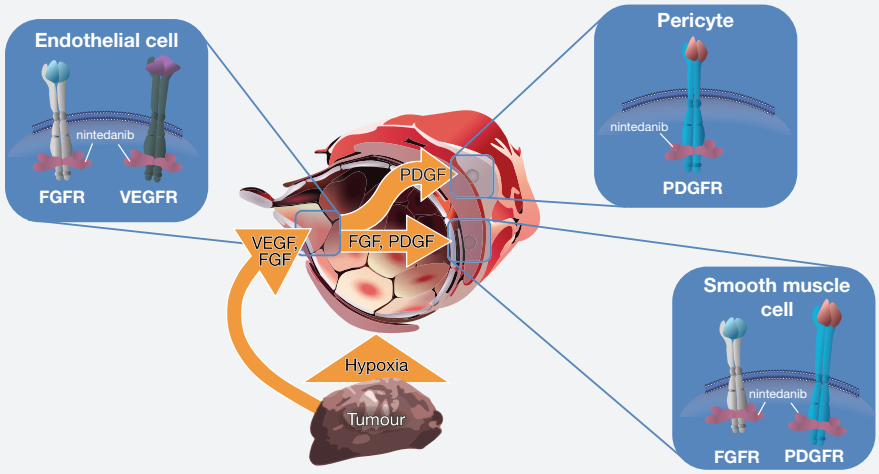
Boehringer Ingelheim has a long history of scientific excellence in the fields of pulmonary and cardiovascular medicine, metabolic disease, neurology, virology and immunology. In 1998, it launched a major research programme to use scientific advances to develop a range of targeted cancer drugs to treat various solid tumours and blood cancers. This work included an optimization programme to develop a range of angiogenesis inhibitors to cut off the blood supply to tumours. Selective inhibition of vascular endothelial growth factor receptor (VEGFR)-2 and potent inhibition of endothelial cell proliferation were identified as key characteristics for initial drug candidates. Nintedanib (BIBF 1120) ethanesulphonate, a 6-methoxycarbonyl-substituted indolinone derivative, was found to inhibit VEGFR-2 (Fig. 1a). It was then found to have a specific and balanced triple angiokinase inhibitor profile by inhibiting VEGFR-1, VEGFR-2, VEGFR-3, fibroblast growth factor receptors (FGFRs) 1–3, and platelet-derived growth factor receptor (PDGFR)-α and PDGFR-β at concentrations in the low nanomolar range[1]. Biochemical characterization of nintedanib showed that it inhibits a distinctive and narrow range of kinases at pharmacologically relevant concentrations (Fig. 1b).

The inhibition of angiogenic pathways is an important approach for preventing tumour growth, and several anti-angiogenic agents have become widely used in oncology clinical practice. Despite proven clinical benefits in some tumour types, a substantial number of patients develop resistance to currently available anti-angiogenic therapies, perhaps because the drugs have an incomplete inhibition profile. Several pro-angiogenic factors contribute to angiogenesis, so agents that target only a single angiogenic factor may have suboptimal efficacy. Also, tumours may acquire resistance to VEGFR inhibitors by using alternative signalling pathways to recruit vasculature. Therefore, although VEGFR remains one of the key drivers of angiogenesis, the simultaneous inhibition of other key receptors, including FGFR and PDGFR, which are crucially involved in the regulation of angiogenesis, could be an advantageous strategy for preventing tumour progression and may even be essential for stopping angiogenesis[1]. Nintedanib, as a potent inhibitor of three proangiogenic pathway receptor families (VEGFR, FGFR and PDGFR), is therefore considered to be a promising anti-angiogenic anticancer therapy that can not only block tumour growth and metastases, but could potentially circumvent drug resistance by inhibiting potential escape mechanisms.

Early studies

After preclinical development to characterize the molecule, early-phase clinical studies with nintedanib showed a manageable safety profile and antitumour activity in patients with solid tumours, including non-small cell lung cancer (NSCLC). It was found that nintedanib could be combined with commonly used chemotherapies owing to its limited drug–drug interaction based on its pharmacokinetic profile, the absence of interaction with CYP450 enzymes, and the manageable safety profile. The initial evidence of nintedanib's tolerability and encouraging efficacy in patients with advanced NSCLC was reported in two phase I

A



B

Kinase	IC_{50} (nmol l^{-1})
VEGFR-1	34 ± 15
VEGFR-2	21 ± 13
VEGFR-3	13 ± 10
FGFR-1	69 ± 70
FGFR-2	37 ± 2
FGFR-3	108 ± 41
FGFR-4	610 ± 117
PDGFR-α	59 ± 71
PDGFR-β	65 ± 7
InsR	>4,000
IGF1R	>1,000
EGFR	>50,000
HER2	>50,000
CDK1	>10,000
CDK2	>10,000
CDK4	>10,000
Flt-3	26
Lck	16 ± 16
Lyn	195 ± 12
Src	156 ± 40
Other kinases (n=26)	>10,000

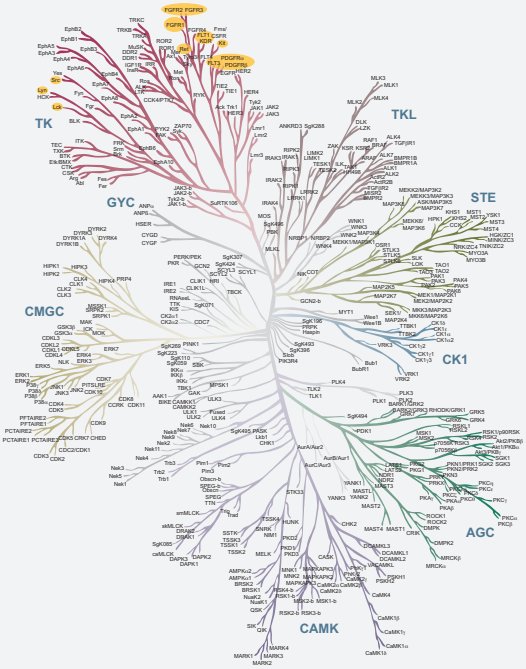


Figure 1 | The mechanism and preclinical effectiveness of nintedanib. **a**, Mechanism of action of nintedanib. Nintedanib is an oral, triple angiokinase inhibitor that targets three classes of angiogenic receptor (VEGFR, FGFR and PDGFR) that are involved in the formation and maintenance of blood vessels to tumours. **b**, Nintedanib's IC_{50} values for kinase activity (adapted with permission from ref. 15; illustration reproduced courtesy of Cell Signaling Technology, Inc., www.cellsignal.com).

combination regimens with paclitaxel and carboplatin as a first-line therapy[2] or with pemetrexed as a second-line treatment[3]. Development of nintedanib continued in NSCLC with a phase II study that reported a manageable safety profile and promising efficacy when nintedanib alone was evaluated for second- or third-line NSCLC patients[4].

Further evaluation of patients with NSCLC in the second-line stage continued with a phase III clinical development programme of nintedanib in combination with two cytotoxic chemotherapies used in this setting (pemetrexed or docetaxel). In addition, nintedanib is currently being investigated in several oncology indications, as well as for the treatment of patients with interstitial pulmonary fibrosis (IPF), a rare, progressive and fatal lung disease. Both pivotal studies in IPF met their primary endpoints[5].

Patients with advanced and/or metastatic NSCLC, who are not candidates for molecularly targeted agents such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitors, are usually treated with platinum-based chemotherapy doublets in the first-line setting. However, although most patients initially achieve some clinical benefit with first-line platinum-containing therapy, about 30% of these patients achieve a short-lasting response, and all patients eventually relapse, with the disease progressing either during or after first-line treatment. Approximately 25–30% of patients show only disease progression as the best response during the first-line treatment and therefore have a very poor prognosis[6,7]. These fast-progressing tumours are difficult to treat and have a short survival of approximately 5 months in second-line treatment[7]. Approximately one-third to half of patients who receive first-line therapy are candidates for subsequent second-line treatment[6]. Although second-line treatments are available, there is still a high unmet medical need to improve the treatment strategy for patients with NSCLC after first-line treatment has failed[6].

Over the past decade of clinical research, more than 10,000 patients with advanced NSCLC have been included worldwide in second-line phase III studies, and so far only modest clinical benefits, such as delaying disease progression, have been observed in about half of these studies. However, an improvement in overall survival (OS) was lacking for any patient population until 2013 (Table 1). Furthermore, until then there had not been any significant therapeutic improvements for those patients with the worst prognosis because they are refractory to first-line therapy. The first study to show an improvement in OS for these advanced second-line NSCLC patients against an active comparator was the LUME-Lung 1 study[8].

Further evaluation

The medical and scientific understanding of NSCLC has evolved tremendously in recent years. Today, NSCLC patients are no longer viewed as a single patient population but as a cluster of different NSCLC populations that can be identified by histological subtyping or genetic characterization of tumours harbouring specific molecular signatures. These distinct NSCLC populations respond differently to different therapies. Examples include pemetrexed, which exclusively benefits patients with non-squamous histology; EGFR inhibitors, such as afatinib, erlotinib or gefitinib, which provide the greatest benefit to patients with activating EGFR mutations; and inhibitors of EML4–ALK rearrangements, such as crizotinib, ceritinib or alectinib, which show dramatic improvements in patients with this molecular rearrangement. It is widely recognised and accepted that the development of new treatments for cancer patients needs to be tailored to the population that would benefit the most. These principles

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were applied to the phase III clinical studies evaluating nintedanib in the second-line treatment of patients with NSCLC.

Larger-scale evaluation of the efficacy and safety of second-line nintedanib in combination with standard chemotherapy was carried out in two multinational, randomized, double-blind, placebo-controlled phase III studies, which had a similar design but were independently conducted at different sites and in different regions of the world. The primary endpoint of both studies was progression-free survival (PFS) by independent central review, and the key secondary endpoint was OS. Approximately 1,300 patients with histologically or cytologically confirmed stage IIIB/IV or recurrent NSCLC who relapsed or failed one previous platinum-based chemotherapy regimen were to be enrolled in each of these two studies.

Promising results

The LUME-Lung 1 study compared a regimen of nintedanib (200 mg twice a day) or placebo on days 2–21, plus standard docetaxel (75 mg m^{-2} on day 1) for patients with advanced NSCLC (study 1199.13; ClinicalTrials.gov, number NCT00805194)[8]. The study met its primary endpoint, as the addition of nintedanib to docetaxel led to a reduction in the risk of disease progression or death in the overall patient population (median PFS, 3.4 months for nintedanib arm versus 2.7 months for placebo, hazard ratio [HR]=0.79, P=0.002), regardless of whether the patients' histology was adenocarcinoma or squamous-cell carcinoma[8]. The key secondary endpoint OS was tested in a prespecified stepwise order: first in patients with adenocarcinoma histology who progressed during or shortly after the end of first-line therapy; then in all patients with adenocarcinoma; and then in the total study population. The key secondary endpoint of OS was met for the adenocarcinoma population. Treatment with nintedanib and docetaxel significantly increased OS in the population of patients with adenocarcinoma (HR=0.83, P=0.036) compared with placebo and docetaxel (Fig. 2a). Median OS improved in a clinically meaningful way from 10.3 months with placebo to 12.6 months with nintedanib, surpassing 1 year of median OS. Indeed, the nintedanib arm of the LUME-Lung 1 study is notable because no other study achieved survival duration of more than 1 year for second-line therapy in unselected adenocarcinoma NSCLC over the preceding 10 years of clinical development. Furthermore, there were statistically significant prolonged 1-year and 2-year survival rates in the adenocarcinoma patients who received nintedanib and docetaxel (nintedanib versus placebo: 1 year, 52.7% versus 44.7%; 2 years, 25.7% versus 19.1%). In September 2014, the Committee for Medicinal Products for Human Use of the European Medicines Agency issued a positive opinion for the approval of nintedanib in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy. This was followed by approval in Europe for this indication in November 2014.

Consistent with the findings in the overall adenocarcinoma population, patients with adenocarcinoma histology who progressed during or shortly after the end of first-line therapy (defined as having progressed within 9 months of starting first-line therapy) showed a 3.0-month increase in median OS and a 25% reduction in the risk of death compared with placebo plus docetaxel (median, 10.9 months with nintedanib versus 7.9 months with placebo, HR=0.75, P=0.007) (Fig. 2b). Moreover, there were statistically significantly prolonged 1-year

Table 1 | Efficacy outcomes for patients with NSCLC in the second-line setting; selected published phase III trials (adapted from ref. 8).

STUDY	TREATMENT	COMPARATOR	IMPROVEMENT IN DISEASE PROGRESSION	IMPROVEMENT IN OVERALL SURVIVAL
Registration studies (year of registration for second-line NSCLC)				
Tax 320/Tax 317 (1999)	Docetaxel	IFO or VNL/BSC	Yes	Yes
JMEI*(2004)	Pemetrexed	DOC	No*	No*
BR-21 (2004)	Erlotinib	PLA	Yes	Yes
Other studies				
Monotherapy regimens				
ISEL	Gefitinib	PLA	Yes	No
ICOGEN*	Icotinib	GEF	No*	No*
CTONG0806[15]	Pemetrexed	GEF	Yes	No
TAILOR	Docetaxel	ERL	Yes	Yes
ZEST	Vandetanib	ERL	No	No
ARCHER 1009†[16]	Dacomitinib	ERL	No†	No†
WJOG 5108L*[17]	Gefitinib	ERL	No*	No*
LUX-Lung 8[18]	Afatinib	ERL	Yes	NR
HORG	Erlotinib	PEM	No	No
KCSG-LU08-01	Gefitinib	PEM	Yes	No
TITAN†	Erlotinib	PEM or DOC	No†	No†
DELTA	Erlotinib	DOC	No	No
INTEREST*	Gefitinib	DOC	No*	No*
V-15-32	Gefitinib	DOC	No	No
ISTANA	Gefitinib	DOC	Yes	No
Vinflunine	Vinflunine	DOC	No	No
Topotecan	Oral topotecan	DOC	No	No
Combination regimens				
BETA	Bevacizumab plus ERL	ERL	Yes	No
SUN1087	Sunitinib plus ERL	ERL	Yes	No
METLung†[19]	Onartuzumab plus ERL	ERL	No†	No†
ATTENTION†[20]	Tivantinib plus ERL	ERL	No†	No†
ZEAL	Vandetanib plus PEM	PEM	No	No
LUME-Lung 2†[10]	Nintedanib plus PEM	PEM	Yes†	No†
SELECT	Cetuximab plus PEM or DOC	PEM or DOC	No	No
ZODIAC	Vandetanib plus DOC	DOC	Yes	No
VITAL	Aflibercept plus DOC	DOC	Yes	No
REVEL[12]	Ramucirumab plus DOC	DOC	Yes	Yes
LUME-Lung 1[8]	Nintedanib plus DOC	DOC	Yes	Adenocarcinoma‡ Yes

This table includes studies with different NSCLC patient populations (all patients, non-squamous patients, squamous patients, patients with EGFR mutations, patients with wild-type EGFR, or patients who progressed quickly on first-line therapy); please refer to each study for specific details on the patient population.

*Non-inferiority study. †Study terminated early because of slow recruitment (TITAN), toxicity concerns (ATTENTION), or for futility at interim analysis (METLung, LUME-Lung 2). ‡Population in pre-defined fixed-sequence hierarchical analysis of OS.

BSC, best supportive care; DOC, docetaxel; ERL, erlotinib; GEF, gefitinib: IFO, ifosfamide; NR, not reported; PLA, placebo; PEM, pemetrexed; VNL, vinorelbine.

and 2-year survival rates in patients who received nintedanib and docetaxel (1 year, 46.8% versus 34.3%; 2 years, 20.7% versus 10.4%). The results for OS were also consistent across most subgroups of patients with adenocarcinoma, with a particularly remarkable improvement in the population with the worst prognosis. In an exploratory analysis, the patients most refractory to first-line treatment showed a reduction in the risk of death of 38% with nintedanib and docetaxel and a median OS improvement of 3.5 months (9.8 months with nintedanib versus 6.3 months with placebo). For patients with squamous-cell cancer, there was no OS benefit but no detrimental effect was observed. In the total study population, an increase in median OS of 1 month was observed (from 9.1 months with placebo to 10.1 months with nintedanib) that did not reach statistical significance (HR=0.94, P=0.272).

The LUME-Lung 1 study demonstrated that treatment with nintedanib plus docetaxel improved independently assessed PFS for all patients, with a clinically meaningful improvement in OS for adenocarcinoma patients, including those adenocarcinoma patients refractory to first-line therapy. The safety profile of nintedanib in combination with docetaxel was, as expected, based on the experience from phase I and II studies, with higher incidences of gastrointestinal adverse events (AEs), particularly diarrhoea, vomiting, nausea, decreased appetite, and reversible liver-enzyme elevations that were manageable with supportive treatment or dose reduction. The incidence of AEs associated with VEGF inhibition (such as bleeding and hypertension) was similar in both treatment arms[8]. Furthermore, AEs commonly associated with docetaxel chemotherapy (such as neutropenia, peripheral neuropathy, and mucositis) were also similarly reported among patients receiving nintedanib plus docetaxel or placebo plus docetaxel. Nintedanib did not significantly change the time to deterioration of cough, dyspnoea and pain, but the treatment benefit was observed while the patients' health-related quality of life was maintained[9].

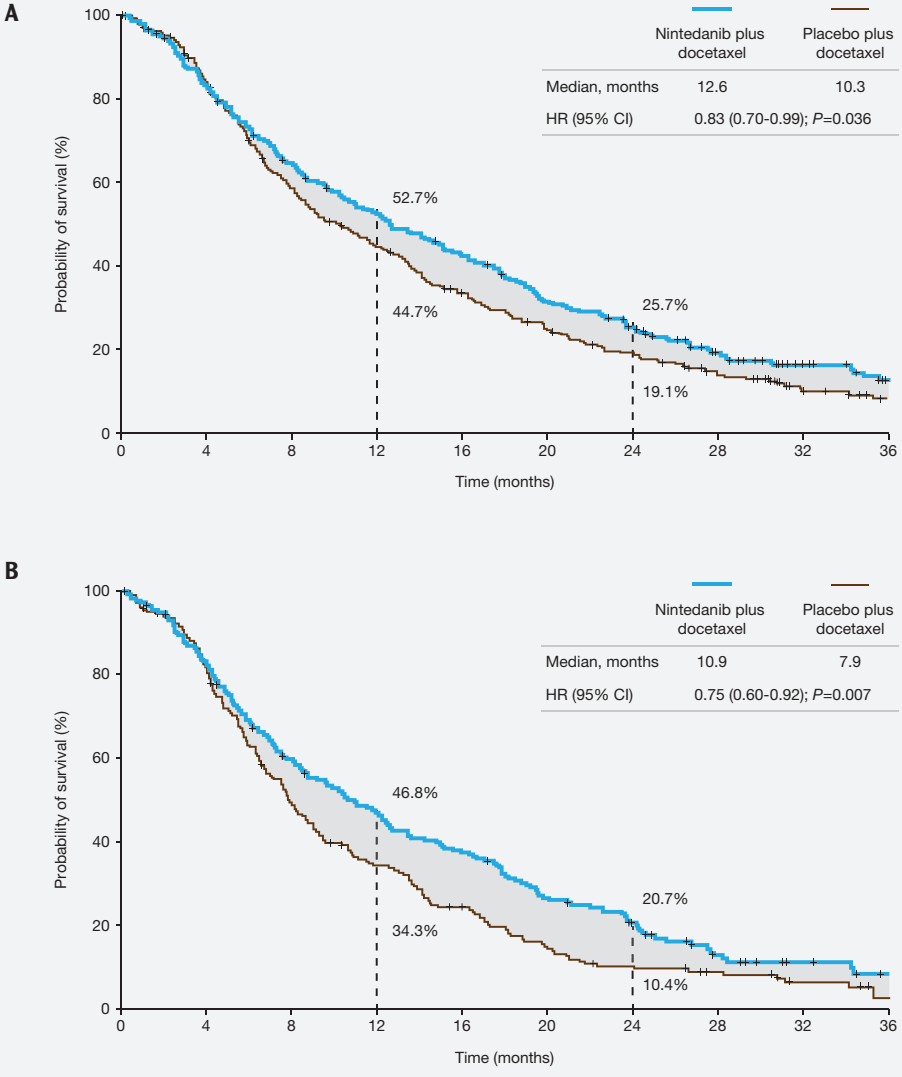

Figure 2 | Overall survival in the LUME-Lung 1 study[8]. **a**, Patients with adenocarcinoma histology. **b**, Patients with adenocarcinoma histology and a time since the start of first-line therapy of less than 9 months. CI, confidence interval; HR, hazard ratio. Adapted and reprinted from ref. 8, with permission from Elsevier.

The LUME-Lung 2 study evaluated nintedanib (200 mg twice a day) or placebo on days 2–21 plus standard pemetrexed (500 mg m^{-2} on day 1) for patients with advanced non-squamous NSCLC (study 1199.14; NCT00806819)[10]. As in the LUME-Lung 1 study, the primary endpoint was PFS by independent central review. A preplanned futility analysis based on conditional power for investigator-assessed PFS was performed after 50% of events had been observed when 713 patients of a planned 1300 had been enrolled. This analysis indicated that the study was futile and that the primary endpoint was unlikely to be met. Consequently, enrolment of additional patients was stopped, treatment randomization was unblinded, and follow-up of randomized patients was continued per protocol. There were no safety concerns regarding this decision. Despite being stopped prematurely, the evaluation of PFS by independent central review showed that the LUME-Lung 2 study did meet its primary endpoint of improving PFS with nintedanib plus pemetrexed versus placebo plus pemetrexed (HR=0.83, P=0.044)[10].

In both independent trials, there was an interaction between the time since the start of first-line therapy and the treatment effect of nintedanib in combination with chemotherapy for PFS and OS in patients with adenocarcinoma[11]. In 2014, an improvement in OS was reported in the second-line NSCLC REVEL trial with the combination of ramucirumab and docetaxel compared with docetaxel alone[12]. Similar to nintedanib, patients who progressed within 9 months of starting first-line therapy derived a better benefit from anti-angiogenic treatment with ramucirumab, suggesting that anti-angiogenic therapy might be more active in patients with faster-progressing tumours. Tumour characteristics, including tumour burden and the dynamics of disease progression, may also have predictive potential for nintedanib therapy. The expression of genes relevant to cell proliferation has been shown to be markedly

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higher for patients with rapid versus more modest disease progression, suggesting that aggressive tumours have a large fraction of proliferating cells[13]. A high rate of cell proliferation is likely to require high levels of vascularization to deliver the nutrients needed to sustain growth. This may explain the benefit of anti-angiogenic therapy with nintedanib in patients with early progressive disease. Further investigations are required to validate these potential molecular and clinical biomarkers of nintedanib benefit.

Future studies

Boehringer Ingelheim is strongly committed to the research and treatment of cancer, with the goal of improving and extending patients' lives. Nintedanib has achieved clinically meaningful efficacy, including survival benefits, when combined with docetaxel in patients with advanced NSCLC of adenocarcinoma histology progressing after first-line therapy, with increased efficacy in patients with worse prognosis resulting from early progressive disease during first-line therapy. The observed OS benefit in these patients with NSCLC in the second-line setting is similar to that observed for bevacizumab in combination with paclitaxel and carboplatin, but as a first-line treatment[14]. Overall, the clinical efficacy and tolerability data for nintedanib in cancer patients, as well as patients with IPF, is highly encouraging.

Boehringer Ingelheim endeavours to make nintedanib available to patients with advanced NSCLC and has begun compassionate-use programmes worldwide. However, there is more work to be done to understand the biological mechanisms underlying nintedanib's efficacy, including the clinical significance of VEGFR, PDGFR and FGFR inhibition that was first identified in selectivity testing and molecular characterization of tumours from patients who progress shortly after the start of first-line therapy. Identifying molecular biomarkers that can predict a response to nintedanib remains an important goal to help maximize the clinical benefit of this agent.

References

1. Hilberg, F. *et al.* BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res.* **68,** 4774–4782 (2008).
2. Doebele, R. C. *et al.* A phase I, open-label dose-escalation study of continuous treatment with BIBF 1120 in combination with paclitaxel and carboplatin as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann. Oncol.* **23,** 2094–2102 (2012).
3. Ellis, P. M. *et al.* Phase I open-label study of continuous treatment with BIBF 1120, a triple angiokinase inhibitor, and pemetrexed in pretreated non-small cell lung cancer patients. *Clin. Cancer Res.* **16,** 2881–2889 (2010).
4. Reck, M. *et al.* A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer. *Ann. Oncol.* **22,** 1374–1381 (2011).
5. Richeldi, L. *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N. Engl. J. Med.* **370,** 2071–2082 (2014).
6. Ettinger, D. S. *et al.* Non-small cell lung cancer. *J. Natl. Compr. Cancer Netw.* **10,** 1236–1271 (2012).
7. Ciuleanu, T. *et al.* Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol.* **13,** 300–308 (2012).
8. Reck, M. *et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol.* **15,** 143–155 (2014).
9. Novello, S. *et al.* Analysis of patient-reported outcomes from the LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled phase 3 study in second-line advanced non-small cell lung cancer (NSCLC) patients. *J. Thorac. Oncol.* **8,** S1207 abstr. P1203.1211-1040 (2013).
10. Hanna, N. H. *et al.* Lume-Lung 2: A multicenter, randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after failure of first-line chemotherapy. *J. Clin. Oncol.* **31,** 8034 (2013).
11. Kaiser, R. *et al.* Identification of a clinical biomarker for 2nd line combination with nintedanib in adenocarcinoma non-small cell lung cancer (NSCLC) patients in two phase III trials. *Eur. J. Cancer* **49,** S822 (2013).
12. Garon, E. B. *et al.* Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* **384,** 665–673 (2014).
13. Hilberg, F., Haslinger, C., Garin-Chesa, P. & Adolf, G. R. Molecular correlates of clinical benefit from anti-angiogenic therapy of lung adenocarcinoma: a hypothesis. *J. Clin. Oncol.* **32**, abstr. e22080 (2014).
14. Sandler, A. *et al.* Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* **355,** 2542–2550 (2006).
15. Zhou, Q. *et al.* Pemetrexed versus gefitinib as a second-line treatment in advanced non-squamous non-small-cell lung cancer patients harbouring wild-type EGFR (CTONG0806): a multicenter randomized trial. *Ann. Oncol.* doi:10.1093/annonc/mdu463 (2014).
16. Ramalingam, S. S. *et al.* Randomized, double-blinded study of dacomitinib, an irreversible pan-human epidermal growth factor receptor (HER) inhibitor, versus erlotinib for second-line/third-line therapy of locally advanced/metastatic non-small cell lung cancer (ARCHER 1009). *J. Clin. Oncol.* **32,** 8018 (2014).
17. Katakami, N. *et al.* Randomized phase III study comparing gefitinib (G) with erlotinib (E) in patients (pts) with previously treated advanced lung adenocarcinoma (LA): WJOG 5108L. *J. Clin. Oncol.* **32,** 8041 (2014).
18. Goss, G. *et al.* A randomized, open-label, phase III trial of afatinib (A) vs erlotinib (E) as second-line treatment of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following first-line platinum-based chemotherapy: LUX-Lung 8 (LL8). *Ann. Oncol.* **25,** iv426 abstr. 1222O (2014).
19. Spigel, D. R. *et al.* Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial. *J. Clin. Oncol.* **32,** 8000 (2014).
20. Azuma, K. *et al.* Tivantinib plus erlotinib versus placebo plus erlotinib in Asian patients with previously treated nonsquamous NSCLC with wild-type EGFR: First report of a phase III ATTENTION trial. *J. Clin. Oncol.* **32,** 8044 (2014).