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Nintedanib in combination with docetaxel for second-line treatment of advanced non-small-cell lung cancer

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EXPERT REVIEWS

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Non-small lung cancer (NSCLC) is a lethal malignancy when diagnosed in advanced stage. The evolution of chemotherapy and the development of agents targeting certain molecular pathways involved in tumor progression improved the prognosis. Nintedanib is a new tyrosine kinase inhibitor, which exerts its activity by blocking VEGF, FGF and PDGF receptors and inhibits the angiogenic signaling by preventing receptor dimerization. Several Phase I and II studies proved its safety and efficacy in diverse solid tumors. In patients with advanced NSCLC, the administration of nintedanib may offer an additional chemotherapy benefit in terms of response rate, progression-free survival and overall survival particularly in patients with adenocarcinoma histology, with manageable toxicity. Here, we present an analytical review of literature regarding nintedanib and we focus on its particular importance in NSCLC treatment.

KEYWORDS: adenocarcinoma • angiogenesis • nintedanib • non-small-cell lung cancer • tyrosine kinase inhibitor

Non-small-cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for 85–90% of all cases [1], and the leading cause of cancer deaths worldwide [2]. Effective treatment remains a challenge considering the disease's poor prognosis, with a 5-year survival remaining at <15% across all disease stages [3]. Most patients are diagnosed with advanced or metastatic disease and nearly all who do receive therapy eventually relapse [4].

Four to six cycles of first-line platinum-based chemotherapy in patients with performance status (PS) 0–1, or tyrosine kinase inhibitors for those whose tumors harbor EGFR mutation have been found to prolong survival, improve quality of life and control symptoms; PS 2 patients are frequently treated with monotherapy – with gemcitabine, vinorelbine and taxanes – or combination therapy with carboplatin, whereas poor PS (3–4) patients, in the absence of tumors with activating driver mutations, are offered BSC [5,6].

Currently approved second-line treatments for NSCLC patients with no driver oncogenes, such as EGFR and ALK, consist of monotherapy with docetaxel, gemcitabine, pemetrexed or erlotinib [7,8]. Although these treatments are efficacious, they have failed to show significant improvement in overall survival (OS), which ranges from 7 to 9 months. Thus, an urgent need remains for new effective second-line treatments for NSCLC patients [9].

BIBF 1120 – nintedanib in the treatment of NSCLC

Targeting angiogenesis in NSCLC – unmet needs of new therapies

Angiogenesis is one of the hallmarks of cancer [10], with VEGF being the major regulator in the malignant tissue [11,12]. Bevacizumab was the first anti-angiogenic drug to be approved in non-squamous NSCLC treatment in 2003. The addition of bevacizumab to a standard platinum-based chemotherapy regimen has shown to improve OS in patients with advanced non-squamous NSCLC, to prolong progression-free survival (PFS) and to improve response rates, through the prevention of new blood vessels development and an improved drug delivery to the tumor [13].

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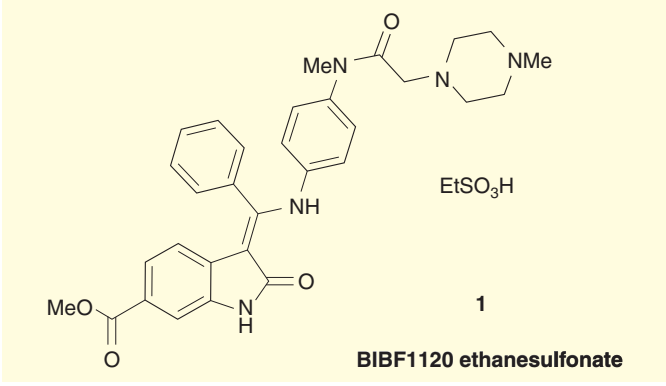

Figure 1. Molecular structure of nintedanib [24].

Additionally, small molecules with multikinase inhibiting properties, such as sunitinib, sorafenib and vandetanib have been developed. Sunitinib has been proposed as a potential therapeutic agent for advanced, refractory NSCLC patients [14]. Clinical trials of sorafenib have mostly failed to suggest an improvement in OS [15–17] as was the case of vandetanib trials [18]. Of note, ramucirumab is an example of a human IgG1 monoclonal antibody specifically binding to the extracellular domain of VEGFR-2 administrated together with docetaxel to patients with squamous and non-squamous cell carcinoma after one prior platinum-based chemotherapy. The REVEL trial [19,20] has shown a significant OS prolongation in the docetaxel plus ramucirumab versus docetaxel plus placebo group, of 4.5 and 3.0 months, respectively.

Despite their success, the limitations of the different antiangiogenic agents are increasingly recognized, with insufficient efficacy, development of resistance and toxicities undermining the long-term success of VEGF-targeted therapies. Because clinical benefit seems to be transient in the majority of cancer patients who initially respond to therapy, several escape mechanisms have been considered [21]. Casanovas *et al.* [22] have shown that cancer tissues are able to develop resistance against the VEGF signaling blockade by switching from VEGF secretion to alternative ligands, notably bFGF. FGF-2 in particular, a potent angiogenesis stimulator that is frequently overexpressed in tumors, has been correlated with poor outcomes in NSCLC [23]. The PDGF pathway has also been regarded as an alternate pro-angiogenic mechanism that drives disease progression. Moreover, toxicities, such as hypertension, bleeding, risk of gastrointestinal perforation, dermatological symptoms and mucositis, remain a serious challenge in cancer therapy as they may limit treatment with VEGF and VEGFR inhibitors.

Despite angiogenesis being of equal importance in all solid cancers, there is wide variability regarding how much individual patients benefit from each drug. This depends on both the organ type and cancer stage, but most of this variability in tumor responsiveness is still unaccounted for [21].

BIBF 1120 – chemistry

Nintedanib (chemical name: (3*Z*)-3-{[4-{methyl[(4-methylpiperazin-1-yl)acetyl]amino}phenyl)amino](phenyl)methylidene}-2-oxo-2,3-dihydro-1H-indole-6-carboxylate) (Figure 1), known by its development code BIBF 1120, was synthesized in 1998 under a chemical lead optimization program, designed to identify ATP-competitive inhibitors of VEGFR-2 and other pro-angiogenic receptor tyrosine kinases in the context of cancer therapy [21]. The convergent synthesis of nintedanib and its ethanesulfonate salt comprise a sequence of five linear steps (including the formation of the final salt form) and a two-step sequence for the preparation of the aniline side chain [24]. Structurally, nintedanib ethanesulfonate is a 6-methoxycarbonyl-substituted indolinone derivative. Indolinone is a derivative compound of indoline, a bicyclic secondary amine consisting of a benzene ring fused to a pyrrolidine ring. Nintedanib binds to the ATP-binding site in the kinase domain of the VEGF, FGF and PDGF receptors and inhibits angiogenic signaling by preventing receptor dimerization [21].

Pharmacodynamics

BIBF 1120 pharmacodynamic properties comprises wider targeting profiles, longer duration of action, enhancement of cytotoxicity by other compounds and less adverse effects compile a promising profile.

BIBF 1120 is a triple angiokinase inhibitor with a wide action profile, targeting three receptor classes involved in the formation of blood vessels: VEGFR-1, -2, -3 (with an IC_{50} in preclinical studies of 13–34 nmol/l), FGFR-1, -2, -3 (IC_{50} of 69, 37 and 108 nmol/l, respectively) and PDGFR-α, -β tyrosine kinases (IC_{50} of 59 and 65 nmol/l, respectively) [21]. Inhibition of these three receptors found on endothelial cells, tumor cells and pericytes allows BIBF 1120 to potentially prevent both tumor growth and dissemination and provides a possible solution to intrinsic and acquired resistance observed with other single or dual angiogenesis inhibitors. Nintedanib has been also found to inhibit Fms-like tyrosine kinase 3 and members of the Src-family (Src, Lyn, Lck), which may give a therapeutic potential for conditions such as hematological diseases and ovarian cancer [24].

Nintedanib has inhibited tumor growth in various preclinical models [21]. Furthermore, it has been shown to significantly enhance the cytotoxicity of other drugs, including doxorubicin and paclitaxel by inhibiting the function of ATP-binding cassette transporters, which constitute one of the main causes of multidrug resistance [25].

Nintedanib also demonstrated significant antitumor activity in xenograft models of different tumor types, including NSCLC, ovarian and prostate carcinoma [21]. In H460 cell NSCLC xenografts, it also demonstrated synergistic effects in combination with the cytotoxic drugs docetaxel or pemetrexed [26]. For instance, the combination of nintedanib with docetaxel resulted in 27% tumor shrinkage whereas monotherapy with nintedanib or docetaxel at the same dose has much less efficacy. Similar observations were made for the combination of nintedanib and pemetrexed in Calu-6 cell NSCLC xenografts [26].

BIBF 1120 differs from other angiogenesis inhibitors on multiple levels. First, it has a distinctive targeting profile, as it acts through the inhibition of VEGFR, PDGFR and FGFR. Sunitinib is active against Raf and VEGFR kinases, vandetanib against VEGFR and EGFR, ramucirumab against VEGFR-2 and sunitinib against VEGFR-1, -2, -3, PDGFRs, KIT, Fms-like tyrosine kinase 3 and RET kinases. Second, BIBF 1120 presents a cellular duration of action, as a sustained inhibition of receptor activation with as yet unknown mechanistic basis has been found and, third, with regards to its pharmacological kinetics, BIBF 1120 blocks VEGFR activation after a 1-h exposure for >32 h, the latest time possible under the required cell culture conditions [21].

Pharmacokinetics

Nintedanib capsules are administered orally after food intake, as food increases drug exposure by approximately 20% compared with administration under fasted conditions (90% CI: 95.3–152.5%) and delays its absorption (median tmax fasted: 2.00 h; fed: 3.98 h) [27]. In healthy volunteers, BIBF 1120 absorption when administered orally was fast, with drug concentrations being already detectable 15 min after dosing. Maximum plasma concentrations were reached 3 h after dosing [28], whereas in Phase I studies in cancer patients maximum concentration was reached within 2–4 h [29–32] after oral intake. In preclinical studies, nintedanib, once absorbed, was extensively distributed in tissues as indicated by high volumes of distribution at steady state in all investigated species [24]. This was confirmed in Phase I studies where the apparent volume of distribution ranged from 10,100 to 25,400 l at steady state [32] or measured at 8580 l during the terminal phase, which translates into a high tissue distribution [31].

In preclinical studies, the drug showed concentration-independent plasma protein binding in the concentration range of 50–2000 mg/ml, with albumin being the major binding protein and the fraction of nintedanib bound to albumin at 97.8% in human plasma [24]. BIBF 1120 terminal half-life was detected between 7 and 19 h in healthy individuals [28], a half-life suitable for once- or twice-daily dosing, and in Phase I studies it was fairly similar, ranging from 7.5 to 19 h [30–33]. Following multiple twice-daily administration of nintedanib, only slight accumulation of nintedanib exposure has been observed in Phase II studies, with a mean accumulation ratio of 1.33 based on Cmax and 1.66 based on area under the curve $(AUC)_{0\text{-}12\ h}$ [34].

In healthy males, BIBF 1120 metabolism was predominantly characterized by the ester cleavage of the methyl ester moiety yielding the carboxylate BIBF 1120. Subsequent to ester cleavage, BIBF 1120 was conjugated to glucuronic acid yielding the 1-*O*-acylglucuronide. Thus, the majority of BIBF 1120 metabolism was CYP450 enzyme-independent [28], allowing for an eventual combination with cytotoxic chemotherapies. Regarding BIBF 1120 metabolism, its metabolites are excreted via the biliary system into the feces, whereas urinary excretion is minor [28]. Mass balance results have shown an overall recovery of 94.7% 168 h after dosing and recovery was assumed to be complete 96 h after dosing [28].

In a Phase I study of advanced NSCLC patients treated with a combination of nintedanib and docetaxel, the pharmacokinetic (PK) analysis revealed no apparent interactions between the two compounds. The PK profile of nintedanib following docetaxel administration was similar to that seen in Phase I nintedanib monotherapy studies, suggesting that docetaxel has no clinically relevant effect on the PK of nintedanib [35].

Clinical efficacy

Phase I studies

The first Phase I study evaluating nintedanib was carried out by Lee *et al.* [33]. This trial enrolled 39 patients with advanced malignancies, including NSCLC in whom BIBF 1120 was orally administered once daily. Maximum tolerated dose (MTD) was identified at 400 mg and the most common toxicities were gastrointestinal events (nausea, vomiting, diarrhea, abdominal pain) and fatigue, whereas a reversible elevation of liver enzymes was seen at ≥200 mg/day. Out of 29 patients who received treatment for at least 8 weeks, 10 patients showed stable disease (SD), 1 prostate cancer patient had significant prolongation of his prostate-specific antigen doubling time from 2 to 10 months and a renal cancer patient experienced SD for 11 months. PK analysis showed increasing mean Cmax and AUC values with nintedanib dose, displaying high inter-patient variability. Cmax values were reached after ~3 h after dosing and the mean $t_{1/2}$ ranged from 7.5 to 14.0 h.

A dose-escalation Phase I study evaluated BIBF 1120 administration once or twice daily to 61 chemotherapy-pretreated patients with advanced solid tumors, including two patients with lung cancer [32]. MTD was determined at 250 mg and it was suggested for the first time that two daily administrations allowed an increase in total daily exposure without additional toxicity. Adverse effects were mild or moderate with gastrointestinal events being more frequent in the first treatment cycle. The main dose-limiting toxicity (DLT) was liver enzymes elevation (alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ-glutamyl transpeptidase), which was fully reversible within 2 weeks of treatment discontinuation or dose reduction. PK analysis revealed moderately fast absorption with a terminal half-life suitable for once- or twice-daily dosing, with no indication of deviation from 'dose-linear pharmacokinetic' behavior of BIBF 1120. Clinical efficacy-wise, important signs were observed with single-agent BIBF 1120, including one complete response in a renal cell carcinoma patient and two partial response in a renal cell and a colorectal cancer patient.

Additionally, a Phase I dose-escalation study [30] of 21 Japanese patients with advanced solid tumors identified MTD at 200 mg twice daily, one dose lower than in Caucasian patients, with such difference being attributed to differences in genotypic variants between the two populations. Gastrointestinal side effects occurred predominantly at the MTD of BIBF 1120 or

at higher doses, but were easily manageable. The PK analysis confirmed a dose-linear increase for Cmax and AUC. Cmax values were reached within 3 h after administration, and steady state was reached at least on day 8. All DLTs were liver enzyme elevations, fully reversible within 2 weeks to treatment discontinuation or dose reduction, with no bilirubin increase being noted. Three of four patients with body surface area (BSA) <1.5 in the 200 mg twice-daily cohort developed DLTs, whereas no DLTs were reported in eight patients with BSA ≥1.5 treated at the same dose. This finding suggested that body size, such as body weight or BSA, might confer liver enzyme elevations on BIBF 1120.

Based on the knowledge that the combination of conventional cytotoxic chemotherapy with an angiogenesis inhibitor (bevacizumab) has been shown to improve first- and second-line treatment options in NSCLC, a Phase I study [31] investigated the safety, tolerability and MTD of BIBF 1120 with pemetrexed in patients with recurrent advanced stage NSCLC. Twenty-six patients received a standard dose of pemetrexed on day 1 followed by oral BIBF 1120 (200 mg twice daily) on day 2 through day 21. Half of the patients experienced SD with a median PFS of 5.4 months. With regard to DLTs, fatigue was the most frequently observed adverse event (AE) and the trial revealed that the overall AE profile was consistent with the safety profiles observed with BIBF 1120 and pemetrexed monotherapy. No clinically relevant influence of BIBF 1120 on PK parameters of pemetrexed was observed, showing that such combination is feasible.

A Phase I study [29] in 26 advanced NSCLC patients evaluated the addition of BIBF 1120 to paclitaxel-carboplatin backbone as first-line treatment. The rationale for this combination therapy was based on the existing molecular evidence for an active FGF signaling pathway in a subset of NSCLC cell lines, proposing FGF inhibition as a potential target. Importantly, the non-overlapping AE profile of BIBF 1120 with paclitaxel and carboplatin, suggested that this combination therapy could be tolerated and feasible. The MTD was 200 twice daily, since the combination was generally well tolerated with only 2 out of 13 patients experiencing a DLT (thrombocytopenia, ALT and AST increase, rash). The most frequently reported AEs were gastrointestinal disorders and elevated AST and ALT values. With regards to clinical efficacy, 12 patients achieved a partial response.

Another Phase I study [35] of 43 pretreated with platinum-based chemotherapy, Japanese NSCLC patients, identified nintedanib MTD at 150 and 200 mg in patients with BSA <1.5 and ≥1.5 in combination with docetaxel, respectively. An unexpectedly high number of DLTs was observed in patients with a lower BSA. All DLTs were grade 3 liver enzyme elevations, completely reversible with dose reduction or discontinuation, suggesting again that dosing according to BSA might be meaningful. Common AEs included hematologic toxicities, alopecia and gastrointestinal AEs. No clinically relevant interactions were observed between nintedanib and docetaxel. Twenty-six percent of patients achieved an objective response to nintedanib/docetaxel, with a median PFS of 5.7 months. However, there were two fatal events including hemoptysis, calling for a careful patient observation of patients in the future.

Clinical trials currently ongoing investigate administration of combination therapy with nintedanib in NSCLC patients. Two trials currently recruiting patients will investigate the administration of nintedanib plus docetaxel in advanced NSCLC patients [36,37]. Another Phase I study will evaluate cisplatin, docetaxel and nintedanib as induction chemotherapy for stage IB–IIIA NSCLC patients amenable for upfront surgical resection [38].

Phase II studies

The activity of single agent nintedanib was investigated in a Phase II study, which evaluated two different doses of the drug, in 73 patients with locally advanced or metastatic NSCLC. Patients were previously treated with at least one line of platinum-based chemotherapy and were randomized to receive either nintedanib 150 or 250 mg twice daily. Median PFS and OS were 6.9 and 21.9 weeks, respectively, and did not differ among treatment arms. However, patients with ECOG PS 0–1 had prolonged PFS and OS (11.6 and 37.7 weeks) compared with those with PS 2. Of note, the response rate was 46% and one durable partial response lasting 9 months was observed in a patient who received the 250 mg twice-daily dose. In terms of clinical benefit, half of the patients reported symptoms improvement (mainly cough, dyspnea, pain) as measured by the EORTC QLQ-LC13. Toxicity was easily manageable and comparable between the two doses and mainly involved nausea, vomiting, diarrhea; however, liver enzyme elevation was more frequent in the 250 mg twice-daily dose [39].

A biomarker-driven Phase II trial is currently recruiting patients. Particularly, nintedanib will be administered in NSCLC patients who have failed up to two prior chemotherapy lines and FGFR1 amplification will be evaluated as a predictor of efficacy [40].

The ongoing LUME-Lung 3 Phase I/II study is evaluating the MTD of nintedanib when added to first-line chemotherapy doublet with 3 weekly schedules of gemcitabine and cisplatin in patients with squamous lung cancer. In the Phase II part of the study, patients are randomly receiving either nintedanib or placebo in addition to the chemotherapy doublet and the efficacy of the regimen is going to be assessed [41].

Given the activity of this molecule in idiopathic pulmonary fibrosis (IPF) [42], it is hypothesized that BIBF 1120 may prevent cells from radiation-related injury in NSCLC patients undergoing radiotherapy. The National Comprehensive Cancer Network awarded a grant for a randomized Phase II trial which is going to assess nintedanib versus placebo as prophylaxis to radiation-induced pneumonitis in patients with unresectable NSCLC undergoing radiotherapy [43].

Phase III studies

The efficacy of BIBF 1120 was further tested in larger Phase III trials. The LUME-Lung 1 was a double-blind, randomized controlled trial, which assessed the efficacy and safety on nintedanib plus docetaxel as second-line therapy in 1314 NSCLC patients [9]. Specifically, 655 patients of all NSCLC histology received intravenous docetaxel 75mg/m^2 on day 1 with nintedanib 200 mg twice daily on days 2–21 every 21 days, and 659 patients received docetaxel in the same dose with placebo, until disease progression or unacceptable toxicity. Interim analysis after a median follow-up of 7.1 months revealed a PFS improvement in favor of the nintedanib arm. Particularly, the median PFS was 3.4 versus 2.7 months (hazard ratio [HR]: 0.79; 95% CI: 0.68–0.92; p = 0.0019) and all NSCLC histologies derived a PFS benefit with the addition of nintedanib. After further follow-up of 31.7 months, OS has significantly improved in the docetaxel plus nintedanib arm, however, the benefit was seen only for patients with adenocarcinoma subtype. Specifically, for patients with adenocarcinoma histology the median OS was 12.6 versus 10.3 months (HR: 0.83; 95% CI: 0.70–0.99; p = 0.0359) in favor of the nintedanib-docetaxel combination. An OS benefit was also seen for adenocarcinoma patients who progressed within 9 months after start of first-line treatment and received the docetaxel-nintedanib doublet compared with those who received docetaxel-placebo (10.9 vs 7.9 months, p = 0.0073). Of note, no statistically significant OS benefit was seen in the entire population of the study between nintedanib and placebo (10.1 vs 9.2 months, p = 0.2720) and in the non-adenocarcinoma histology (8.6 vs 8.7 months, p = 0.8907). The addition of nintedanib to docetaxel increased the disease control rate compared with docetaxel plus placebo for all patients (54 vs 41.3%; odds ratio: 1.68; 95% CI: 1.35–2.09; p < 0.0001). Regarding toxicity, grade III or IV events were more common in the nintedanib arm and mainly involved diarrhea (6.6 vs 2.6%) and reversible increases in ALT and AST values [9]. It is noteworthy that the OS benefit with the addition of nintedanib in patients with adenocarcinoma was achieved without a detriment to quality of life as reported by a study that evaluated patient-reported outcomes [44].

Another randomized, double-blind, Phase III trial assessed the efficacy and safety of second-line nintedanib or placebo added to pemetrexed in non-squamous NSCLC patients [45]. Of the 713 patients, 353 received pemetrexed 500mg/m^2 intravenously on day 1 every 21 days and nintedanib 200 mg twice daily and 360 received pemetrexed in the same dose with placebo, until disease progression or unacceptable toxicity. Of note, 8% of the patients received bevacizumab in previous treatment in both arms. The median PFS, which was the primary point of the study, was significantly higher in the nintedanib arm (4.4 vs 3.6 months; HR: 0.83; 95% CI: 0.7–0.99; p = 0.04). Better disease control rate was also seen in the nintedanib arm (61 vs 53%; odds ratio: 1.37; p = 0.039). Nonetheless, no significant OS difference was seen between the two arms (12 vs 12.7 months; HR: 1.01; 95% CI: 0.85–1.21; p = 0.8940). Importantly, the addition of nintedanib to pemetrexed resulted in a higher incidence of grade 3–4 liver enzyme elevation (ALT elevation 23 vs 7%, AST elevation 12 vs 2%) and diarrhea (3 vs 1%) compared with placebo. No difference in grade 3 hypertension, hemorrhage, thrombosis, mucositis or neuropathy was observed between the two groups [45,46].

LUME-Columbus is another randomized, double-blind, Phase III trial that will evaluate the efficacy and safety of nintedanib (or placebo) in combination with docetaxel in patients with stage IIIB/IV or recurrent, lung adenocarcinoma after first-line platinum-based chemotherapy failure. This trial is intended to enroll 800 patients [37].

The efficacy and safety profile of BIBF 1120 have been evaluated in the above-mentioned studies, which are summarized in Table 1.

Regulatory affairs

Nintedanib is marketed under the brand names OFEV® and VARGATEF® (Boehringer Ingelheim), available in 100 mg soft capsules. In the EU, it has been approved in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumor histology after first-line chemotherapy [47] in November 2014, marketed under the brand name VARGATEF, and for the treatment of IPF in January 2015, under orphan drug status, marketed under the brand name OFEV. In the USA, FDA approved nintedanib for the treatment of IPF [42] in October 2014.

Conclusion

Advanced NSCLC is a notorious disease showing moderate sensitivity to chemotherapy. Nintedanib is a novel tyrosine kinase inhibitor that targets tumor angiogenesis and is associated with improved survival in patients with lung adenocarcinoma when used in combination with docetaxel in second-line chemotherapy. However, there is still an unmet need for predictive factors in order to specify a subpopulation that would derive the maximum clinical benefit.

Expert commentary

Angiogenesis is a fundamental procedure for tumor growth and multiplication. It is therefore regarded as one of the essential hallmarks of tumorigenesis [48]. The clinical application of targeting angiogenesis in solid tumors was stressed early in 1995 by Folkman. The 'perfusion and paracrine' effect of neovascularization was explicitly described in his pioneering work.

The paracrine effect was attributed to growth factors (such as IGF, FGF, PDGF) produced by endothelial cells [49]. This paracrine effect may be a potential therapeutic target. Nintedanib exerts its activity targeting VEGFR-1, -2, -3, FGFR-1, -2, -3 and PDGFR-α, -β tyrosine kinases. The clinical benefit seen with this agent may be partly attributed to the blockage of the paracrine signaling.

Besides, another critical molecular pathway involved in tumor survival, motility, proliferation and angiogenesis is

Table 1. Nintedanib clinical studies.

Study (Year)	Phase	Tumor under study	Type of study	Patients (n)	Drug	Administration modality	MTD (mg)	Daily administration frequency	Adverse effects	Response	Ref.
Lee *et al.* (2006)	I	Advanced solid tumors	Dose escalation	39	Nintedanib	Continuous once-daily dosing	400	Once daily	Nausea, vomiting, diarrhea, abdominal pain, reversible elevation in liver enzymes, fatigue	10 SD, one prostate cancer pt PSA doubling time prolongation	[33]
Mross *et al.* (2009)	I	Advanced tumors	Accelerated titration	61	Nintedanib	Treatment with nintedanib for 4 weeks followed by 1-week washout	250	Once, twice daily	Mild to moderate (hepatic enzyme elevation, hypertension, nausea, diarrhea, vomiting)	1 CR, 2 PR	[32]
Okamoto *et al.* (2010)	I	Advanced tumors	Safety, pharmacokinetic	21	Nintedanib	Continuous daily schedule	200	Twice daily	Reversible liver-enzyme elevation	76.2% SD, median PFS 113 days	[30]
Ellis *et al.* (2010)	I	Recurrent, advanced NSCLC	Open-label, dose-escalation	26	Nintedanib + pemetrexed	Day 1: pemetrexed 500 mg/m^2 i.v., day 2–21: nintedanib	200	Twice daily	Gastrointestinal disorders, general disorders, rash	1 CR, 50% SD	[31]
Doebele *et al.* (2012)	I	Advanced NSCLC	Dose escalation	26	Nintedanib + paclitaxel + carboplatin	Day 1: paclitaxel 200 mg/m^2, carboplatin AUC = 6 mg/ml/min, day 2–21: BIBF 1120	200	Once daily	Liver enzyme elevation, thrombocytopenia, abdominal pain, rash	7 PR, 10 SD	[29]
Okamoto *et al.* (2015)	I	Previously treated NSCLC	Dose escalation	42	Nintedanib + docetaxel	Day 1: docetaxel, days 2–21: nintedanib twice daily	150 and 200	Twice daily	Hepatic enzyme elevation, neutropenia, leukopenia, fatigue, alopecia, decreased appetite	26% PR, 47% SD	[35]
Reck *et al.* (2011)	II	Relapsed NSCLC	Efficacy-safety	73	Nintedanib	Nintedanib 150 or 250 mg		Twice daily	Liver enzyme elevation more frequent in the 250 mg dose	RR46%, PFS 6.9 m, OS 21.9 m	[39]
Reck *et al.* (2014)	III	Relapsed NSCLC	Double-blind, randomized controlled	1314	Docetaxel + nintedanib/ placebo	Day 1: docetaxel 75 mg/m^2, days 2–21: nintedanib 200 mg twice daily/placebo		Twice daily	Diarrhea, transient liver enzyme elevation	PFS 3.4 vs 2.7 months ($p = 0.0019$), OS for adenocarcinoma histology 12.6 vs 10.3 months ($p = 0.0359$)	[5]
Nasser *et al.* (2013)	III	Relapsed NSCLC	Double-blind, randomized controlled	713	Pemetrexed + nintedanib/ placebo	Day 1: pemetrexed 500 mg/m^2, days 1–21: nintedanib 200 mg twice daily/placebo		Twice daily	Diarrhea, transient liver enzyme elevation	PFS 4.4 vs 3.6 months ($p = 0.04$)	[45]

AUC: Area under the curve; CR: Complete response; i.v.: Intravenous; MTD: Maximum tolerated dose; NSCLC: Non-small lung cancer; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; PSA: Prostate-specific antigen; SD: Stable disease.

mediated by the proto-oncogene tyrosine protein kinase Src. This proto-oncogene is implicated in the epithelial to mesenchymal transition (EMT), which is regarded as a molecular signature associated with aggressive clinical behavior. Importantly, EMT is a phenomenon through which cancer cells evade the chemotherapy effect [50]. Nintedanib may prevent cancer cells from EMT, inhibiting members of the Src family. EMT has been also associated with acquired resistance to the EGFR inhibitor erlotinib. Whether nintedanib could restore sensitivity to erlotinib has yet to be investigated.

Bevacizumab was the first anti-angiogenic factor used in advanced NSCLC of adenocarcinoma histological subtype, combined with carboplatin-paclitaxel. The addition of bevacizumab to the chemotherapy backbone conferred an OS benefit (HR: 0.79; p = 0.003). Bevacizumab maintenance until progression has also gained acceptance [13]. Taking the paradigm of colorectal cancer, sustaining angiogenesis inhibition despite bevacizumab failure improves outcome, impeding tumor revascularization [51]. We speculate that continuing anti-angiogenesis in NSCLC either with an antibody or a TKI such as nintedanib may be of clinical benefit. This hypothesis needs to be validated by randomized Phase III trials. Of note, LUME-Lung 1 trial included 60 patients whose disease progressed after first-line bevacizumab added to chemotherapy. The small number of this subpopulation does not permit a subgroup analysis to investigate the effect of the nintedanib in patients pretreated with bevacizumab [9].

Nevertheless, it is clear that nintedanib is the first agent targeting angiogenesis used in second-line chemotherapy in NSCLC patients which improves PFS and OS.

Despite the lack of validated predictive markers regarding angiogenesis, certain mutations may be clinically meaningful. An interventional, pilot, Phase 0 study is going to evaluate the efficacy of nintedanib in molecularly selected NSCLC patients who harbor mutations in molecules that drive angiogenesis (VEGFR1-3, PDGFR-A, PDGFR-B and FGFR1-3). Interestingly, this study will perform exome sequencing of pre- and post-treatment paired tumor in order to define potential predictive markers [41].

More exploratory and translation research studies are therefore needed to unravel the tumor angiogenesis pathway and shed light on potential predictive factors.

Five-year view

Currently, nintedanib plus docetaxel represents an available treatment option for adult patients with locally advanced, metastatic or locally recurrent NSCLC adenocarcinoma. Existing Phase I, II and III clinical trials provide evidence of efficacy for this combination regimen suggesting a reasonably safety profile with tolerable adverse effects. Nevertheless, deeper analysis is needed to address a series of issues regarding the extent and limits of nintedanib clinical efficacy.

First, the biological mechanisms that may explain the agent particular efficacy on some but not all patients are likely to be further elucidated in the forthcoming years. This step would contribute to the identification of patient subgroups that would mostly benefit from nintedanib treatment and spare those who would show treatment resistance. Such knowledge will particularly affect the planning and implementation of future studies that will likely include groups with more specific patient and disease characteristics. The magnitude of the identification of molecular signatures is clearly depicted in the results of the CheckMate 057 trial [52]. In this trial, patients with EGFR wild-type, advanced NSCLC experienced a 2.8 months OS benefit when received second-line nivolumab (a programmed cell death protein 1 immune checkpoint inhibitor) compared with those who received docetaxel (12.2 vs 9.4 months, respectively; HR: 0.73; 95% CI: 0.59–0.89; p = 0.0015). Interestingly, higher expression of programmed death-ligand 1 staining was associated with better OS. It is, therefore, essential that therapy be tailored to the patient disease unique features such as EGFR mutation status, EML4-ALK translocation, programmed death-ligand 1 staining along with the clinical status of the patient.

Second, further analysis will help to determine whether treatment with nintedanib may produce better, equal or poorer results in terms of safety profile and OS in combination with other existing agents or even as monotherapy. Existing evidence of efficacy is sufficiently robust to encourage further research within the context of second-line treatment in NSCLC.

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Key issues

- BIBF 1120 – nintedanib is a tyrosine kinase inhibitor which blocks VEGF, FGF, PDGF receptors and inhibits Fms-like tyrosine kinase 3 and members of the Src-family.
- Preclinical studies showed its antitumor activity and synergy with chemotherapy agents (doxorubicin and paclitaxel), and its eventual importance on restoring multidrug resistance.
- Despite its conjugation to glucuronic acid, the majority of BIBF 1120 metabolism is CYP450 enzyme-independent, allowing a combination with cytotoxic chemotherapy. Its metabolites are excreted via the biliary system into the feces whereas urinary excretion is minor.
- Nintedanib maximum tolerated dose is 400 mg and is administered as capsules 200 mg twice daily orally after food intake.
- Toxicity is easily manageable and mainly involves nausea, vomiting, diarrhea, abdominal pain, fatigue and liver enzymes elevation.
- In the LUME-Lung 1 study, patients with advanced non-small-cell lung cancer (NSCLC) who received second-line chemotherapy with the combination docetaxel-nintedanib showed improved progression-free survival (hazard ratio: 0.79) compared with those who received docetaxel. Patients with adenocarcinoma derived an overall survival benefit with the combination (hazard ratio: 0.83).
- The combination of nintedanib with pemetrexed is feasible in NSCLC patients receiving second-line chemotherapy.
- Many ongoing clinical trials are investigating the role of nintedanib in the treatment of advanced NSCLC. Importantly, some of them molecularly select patients who harbor certain mutations in order to define potential predictive markers.
- In the EU, it has been approved in November 2014 in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumor histology after first-line chemotherapy, marketed under the brand name VARGATEF®.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Jemal A, Bray F, Center M. Global cancer statistics. CA Cancer J Clin 2011;61:69-90
2. Molina J, Yang P, Cassivi S, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment and survivorship. Mayo Clinic Proc 2008;83(5):584-94
3. Crino L, Weder W, Van Meerbeeck J, Felip E. Early stage and locally advanced (non-metastatic) non-small-cell-lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(Suppl 5):v103-v15
4. Gridelli C, Ardizoni A, Giardiello F, et al. Second-line treatment of advanced non-small cell lung cancer. J Thorac Oncol 2008;3(4):430-40
5. Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3): iii27-39
6. Peters S, Adjei A, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7): vii56-64
7. Ettinger D, Akerley W, Borghaei H. Non-small cell lung cancer. J Nat Compr Canc Netw 2012;10:1236-71
8. Leighl N. Treatment paradigms for patients with metastatic non-small-cell lung cancer: first, second, and third-line. Curr Oncol 2012;19:S52-8
9. Reck M. 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, randomized controlled trial. Lancet Oncol 2014;15:143-55

•• **A recent multi-center randomized controlled trial with 1314 participants from 27 countries assessing the efficacy of nintedanib plus docetaxel in progression-free survival (PFS) and overall survival (OS). The effect of treatment on survival by baseline patient characteristics is presented as well as a detailed overview of adverse effects.**

10. Hanahan D, Weinberg R. The hallmarks of cancer. Cell 2000;100:57-70
11. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 1990;82:4-6
12. Ferrara N. The role of vascular endothelial growth factor in pathological angiogenesis. Breast Cancer Res Treat 1995;36:127-37
13. Sandler A, Gray R, Perry M, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. NEJM 2006;355:2542-250
14. Novello S, Scagliotti G, Rosell R, et al. Phase II study of continuous daily sunitinib dosing in patients with previously treated advanced non-small cell lung cancer. Br J Cancer 2009;3(101):1543-8
15. Scagliotti G, Novello S, von Pawel J. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced NSCLC. J Clin Oncol 2010;28(11): 1835-42
16. Paz-Ares L, Biesma B, Heigener D. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/ cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous NSCLC. J Clin Oncol 2012; 30(25):3084-92
17. Paz-Ares L, Hirsch V, Zhang L. Monotherapy administration of sorafenib in patients with NSCLC: phase III, randomized, double-blind, placebo-controlled MISSION trial. Ann Oncol 2012;23(Suppl 9):LBA33
18. Lee J, Hirsch V, Park K. Vandetanib versus placebo in patients with advanced NSCLC after prior therapy with an EGFR tyrosine kinase inhibitor: a randomized, double-blind phase III trial (ZEPHYR). J Clin Oncol 2012;30(10):1114-21
19. Garon E, Ciuleanu T, Arrieta O. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression in platinum-based therapy (REVEL): a multicenter,

double-blind, randomized phase 3 trial. Epub. Lancet 2014;384(9944):665-73

20. Perol M, Ciuleanu T, Arrieta O. REVEL: a ramdomised, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM;IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy. J Clin Oncol 2014;32(Suppl 5):LBA8006

21. Hilberg F, Roth G, Krssak M, et al. BIBF 1120: Triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68(12): 4474-782

- **A study of the BIBF 1120 preclinical profile, including its pharmacological and pharmacokinetic properties, which yields results regarding the agent's effectiveness and tolerance in animal models.**

22. Casanovas O, Hicklin D, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. Cancer Cell 2005;8:299-309

23. Berger W, Setinek U, Mohr T, et al. Evidence for a role of FGF-2 and FGF receptors in the proliferation of non-small cell lung cancer cells. Int J Cancer 1999;83: 415-23

24. Roth G, Binder R, Colbatzky F, et al. Nintedanib: From discovery to the clinic. J Med Chem 2014;58:1053-63

- **A review article summarizing existing preclinical and clinical research, including drug synthesis and metabolism, mechanism of action as well as key efficacy results from Phase III studies.**

25. Rothschild S. Clinical potential of Nintedanib for the second-line treatment of advanced non-small-cell lung cancer: current evidence. Lung Cancer: Targets and Therapy 2014;5:51-7

26. Hilberg F, Brandstetter I. Efficacy of BIBF 1120, a potent triple angiokinase inhibitor, in models of human non-small cell lung cancer is augmented by chemotherapy. Eur J cancer 2007;2:S380

27. Health ECDHaFSP. Community register of medicinal products for human use. Vargatef 2014

28. Stopfer P, Rathgen K, Bischoff D, et al. Pharmacokinetics and metabolism of BIBF 1120 after oral dosing in healthy male volunteers. Xenobiotica [serial on the Internet]. 2011

- **A study that bridges nonclinical to clinical research of BIBF 1120 pharmacokinetics and metabolism. Eight healthy male volunteers participated, receiving a single oral dose of [14C]-radiolabelled BIBF 1120.**

29. Doebele R, Conkling P, Traynor A, 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 2012;23(8):2094-102

30. Okamoto I, Kaneda H, Satoh T, et al. Phase I safety, pharmacokinetic, and biomarker study of BIBF 1120, an oral triple tyrosine kinase inhibitor in patients with advanced solid tumors. Mol Cancer Ther 2010;9(10):2825-33

31. Ellis P, Kaiser R, Zhao Y, 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 2010;16(10):2881-9

32. Mross K, Stefanic M, Gmehling D. Phase I study of the angiogenesis inhibitor BIBF 1120 in patients with advanced solid tumors. Clin Cancer Res 2010;16(1):311-19

33. Lee C, Attard G, Poupard L, et al. editors. A phase I study of BIBF 1120, an orally active triple angiokinase inhibitor (VEGFR, PDGFR, FGFR) in patients with advanced solid malignancies. ASCO Annual Meeting Proceedings; 2005

34. Eisen T, Shparyk Y, Macleod N, et al. Effect of small angiokinase inhibitor Nintedanib (BIBF 1120) on QT interval in patients with previously untreated, advanced renal cell cancer in an open-label, phase II study. Invest New Drugs 2013;31(5): 1283-93

35. Okamoto I, Miyazaki M, Takeda M, et al. Tolerability of Nintedanib (BIBF 1120) in combination with docetaxel: a phase 1 study in Japanese patients with previously treated non-small-cell lung cancer. J Thorac Oncol 2015;10(2):346-52

36. ClinicalTrials.gov. Nintedanib plus docetaxel in Japanese patients with adenocarcinoma subtype non-small cell lung cancer after failure of first line chemotherapy. Available from: https://clinicaltrials.gov/ct2/show/NCT02300298

37. ClinicalTrials.gov. LUME-Columbus: Nintedanib plus docetaxel in advanced non-small cell lung cancer with translational research. Available from: https://clinicaltrials.gov/ct2/show/NCT02231164

38. ClinicalTrials.gov. Induction study of cisplatin, docetaxel, and Nintedanib stage IB-IIIA non-small cell lung cancer (NCLC). Available from: https://clinicaltrials.gov/ct2/show/NCT02225405

39. Reck M, Kaiser R, Eschbach C, 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 2011;22(6):1374-81

- **A study of 73 patients receiving BIBF 1120, investigating the PFS and OS, as well as commonly reported adverse effects.**

40. ClinicalTrials.gov. Nintedanib in Treating Patients With Advanced Non-Small Cell Lung Cancer Who Have Failed Up to Two Previous Chemotherapy Regimens. (NCT01948141). Available from: https://clinicaltrials.gov/ct2/show/NCT01948141

41. ClinicalTrials.gov. A Phase I/II Study of Continuous Oral Treatment With BIBF 1120 Added to Standard Gemcitabine/ Cisplatin Therapy in First Line NSCLC Patients With Squamous Cell Histology. (NCT01346540). Available from: https://clinicaltrials.gov/ct2/show/NCT01346540

42. Administration USFaD. FDA News Release: FDA approves Ofev to treat idiopathic pulmonary fibrosis. 2014

43. Boehringer Ingelheim NCCN. Four researchers awarded grants to investigate effectiveness of Nintedanib in lung, colorectal, and gastrointestinal cancers [media release]. 2014

44. Novello S, Kaiser R, Mellemgaard A, et al. et al.Lung 1 trial: a randomised, double-blind, placebo-controlled, Phase III study of second-line Nintedanib in patients with advanced non-small cell lung cancer. Eur J cancer 2015;51(3):317-26

- **A study of patient-reported outcomes for symptoms and health-related QoL of patients who participated in the LUME-Lung 1 trial. The analysis provides evidence of no detrimental effect of the nintedanib addition to docetaxel on patient self-reported QoL.**

45. Nasser H, Hanna RK, Richard N, 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 2013; 31(Suppl)):abstract 8034

- **A Phase III trial investigating PFS, OS, response rate, safety and quality of life in non-squamous NSCLC patients treated with nintedanib plus pemetrexed. Nintedanib plus pemetrexed combination was identified as an efficacious treatment option with a manageable safety profile.**

46. ClinicalTrials.gov. Lume Lung 2 : Nintedanib Plus Pemetrexed Compared to Placebo Plus Pemetrexed in 2nd Line Nonsquamous NSCLC. (NCT00806819). Available from: https://clinicaltrials.gov/ct2/show/NCT00806819

47. European Commission DHaFS, Public Health. 2014

48. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144(5):646-74

49. Folkman J. Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. N Engl J Med 1995;333(26):1757-63

50. Wilson C, Nicholes K, Bustos D, et al. Overcoming EMT-associated resistance to anti-cancer drugs via Src/FAK pathway inhibition. Oncotarget 2014;5(17):7328-41

51. Masi G, Salvatore L, Boni L, et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. Ann Oncol 2015;26(4):724-30

52. Paz-Ares LG, Horn L, Borghaei H, et al. Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). J Clin Oncol 2015;33(Suppl): abstract LBA109