EXPERT OPINION

BIBF 1120/nintedanib: a new triple angiokinase inhibitor-directed therapy in patients with non-small cell lung cancer

Christian Rolfo, Luis E Raez, Giuseppe Bronte, Edgardo S Santos, Kostantinos Papadimitriou, Lucio Buffoni, Jan P van Meerbeeck & Antonio Russo†

†*University of Palermo, Palermo, Italy*

Introduction: Several new targeted agents with anti-angiogenic properties have been developed recently, including vandetanib, sunitinib, sorafenib, bevacizumab and others. Tumor development, progression, metastasis are strongly linked to angiogenesis. Targeted agents like bevacizumab, a monoclonal antibody which targets VEGF, have been fully developed in several solid tumors. These new agents strongly advocate that targeting angiogenesis is one of the best approaches for cancer therapy.

Areas covered: Those agents that target additional pro-angiogenic intracellular signaling pathways beyond VEGF signaling have also the potential to contribute to anticancer therapies. The authors present here nintedanib (BIBF 1120), a triple angiokinase inhibitor. It targets not only VEGFRs, but also FGFR and PDGFR. All the available clinical information regarding Phase I – II trials and the toxicity and efficacy of BIBF 1120 both as single agent and in combination with cytotoxic agents in non-small cell lung cancer (NSCLC) is reviewed and discussed here.

Expert opinion: Up till now, Phase I and II trials with nintedanib showed an improvement for survival of advanced NSCLC patients. Tolerability profile seems to be acceptable in these clinical trials. However, Phase III trials are mandatory to translate these findings into clinical practice. The research for predictive biomarkers could improve the success of these anti-angiogenic agents.

Keywords: anti-angiogenesis, BIBF 1120, nintedanib, non-small cell lung cancer, vascular endothelial growth factor

Expert Opin. Investig. Drugs [Early Online]

1. Introduction

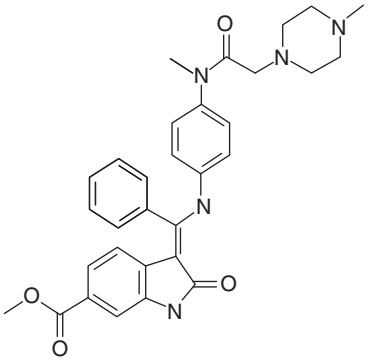
The process of angiogenesis involves the growth of new blood vessels mediated by the balance between pro-angiogenic and anti-angiogenic factors [1]. The process of tumor angiogenesis with vessel formation is crucial for the proliferation and enlargement of metastasizing cancer cells [2,3]. Some studies have shown an association between neovascularization and prognosis in various solid tumors [4,5]. Tumor vasculature shows a highly aberrant structure and function, characterized by dilated, tortuous, poorly organized and highly permeable vessels. This intratumoral microenvironment induces interstitial hypertension, hypoxia and acidosis, causing increased VEGF levels. Subsequently, chemotherapeutic drugs could not reach tumor cells and clinical effectiveness is impaired.

VEGF plays a role in both normal and cancerous cells by promoting endothelial migration and proliferation necessary for angiogenesis. There are three types of

informa healthcare

10.1517/13543784.2013.812630 © 2013 Informa UK, Ltd. ISSN 1354-3784, e-ISSN 1744-7658

Box 1. Drug summary.

Drug name	Nintedanib
Phase	Phase I/II
Indication	Non-small cell lung cancer
Pharmacology description	VEGFR tyrosine kinase inhibitor
Route of administration	Oral
Chemical structure	
	Chemical name: (*Z*)-methyl 3-((4-(*N*-methyl-2-(4-methylpiperazin-1-yl) acetamido)phenylamino)(phenyl) methylene)-2-oxoindoline-6-carboxylate
Pivotal trial(s)	[47-50]

Pharmaprojects – copyright to Citeline Drug Intelligence (an Informa business). Readers are referred to Pipeline (http://informa-pipeline.citeline.com) and Citeline (http://informa.citeline.com).

receptors for VEGF: VEGFR-1, VEGFR-2 and VEGFR-3. However, the biological effects of VEGF are mediated by VEFGR1 and VEFGR3. Instead, VEFGR-2 is believed to have a primary role in endothelial cell activation. VEGF is expressed in most cancers including lung cancer [6]. Elevated VEGF levels are associated with increased tumor aggressiveness and result in a poor prognosis [7]. The primary effect of anti-angiogenic agents is the inhibition of the abnormal blood vessel formation [8,9]. Although at present there are several anti-angiogenic agents available based on the inhibition of a single component of angiogenesis, as in the case of the antibody bevacizumab, the therapeutic results of these agents are far from optimal. The efforts of researchers are actually directed to a wide set of new agents, able to target multiple pathways implicated in angiogenesis, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and VEGF (**Figure 1**) [1,10,11].

Several PDGF receptor tyrosine kinases (TKs PDFGR) are expressed on endothelial cells and pericytes. They could control various cellular mechanisms, such as the vessel stability, the survival of endothelial cells and pericytes-endothelial cell contact [12,13]. The activation by ligands and signal transduction through PDGFR are associated with malignancy development by cell migration and proliferation and tumor angiogenesis [14,15]. FGF signaling is mediated by its TK receptors, FGF receptors (FGFRs). It is regulated by its complex expression patterns and binding specificity of the FGF ligands and receptor isoforms. FGF signaling contributes to tissue homeostasis, tissue repair, angiogenesis and inflammation (**Figure 2**). Its deregulation can have significant consequences in carcinogenesis. The activation of the FGF receptor tyrosine kinase (FGFR TKs) promotes cell proliferation and survival as well as the stimulation of angiogenesis [16,17]. The VEGF ligand regulates vascular proliferation functioning as an anti-apoptotic factor for the new vessels formed and also regulate the permeability thereof [12]. The tumor cells have the ability to escape the sustained inhibition of VEGF by regulating pro-angiogenic factors such as PDGF and FGF (**Figure 3**) [13,18-20]. A study has shown that tumor cells that are under the sustained inhibition of VEGF signaling may change VEGF to FGF production [20]. As a consequence, the development of new drugs has great relevance to block multiple pathways simultaneously. This review aims to summarize the clinical advances of nintedanib, an anti-angiogenic agent, which inhibits VEGFR, FGFR and PDFGR and has already reached Phase III trial advancement (**Box 1**).

2. New drugs designed to inhibit angiogenesis

Nintedanib comes after the market availability of several anti-angiogenic agents. The first commercially available drug with anti-angiogenic properties was bevacizumab [21]. Some properties of nintedanib resemble those of the existing agents while others differ thereof. Bevacizumab blocks the VEGF-A and is currently approved in combination with standard chemotherapy [22] for the treatment of metastatic colorectal cancer, lung (non-small cell carcinoma (NSCLC)), glioblastoma multiforme and kidney and is also indicated in Europe, in combination with chemotherapy for treatment of patients with metastatic colorectal carcinoma, lung (non-squamous), renal and breast [22]. The most common toxicities observed with bevacizumab-based therapy include hypertension, proteinuria, bleeding, fistula formation and thrombotic events [22-24]. In patients with squamous NSCLC, a severe bleeding has been described. These safety and toxicity concerns have also been observed in other small molecules with anti-angiogenic properties [23,25]. Sorafenib is a small molecule that inhibits VEGFR-2, VEGFR-3, PDGFR-v Rafm1 viral murine leukemia oncogene homolog 1 (RAF) and the stem cell factor receptor (c-kit) [26,27]. Sorafenib, an oral agent, is approved for treatment of renal cell carcinoma and hepatocellular carcinoma (HCC) [28,29]. Two Phase III trials of first-line chemotherapy (ESCAPE – paclitaxel/carboplatin and NEXUS – gemcitabine/cisplatin) alone or in combination with sorafenib failed to demonstrate clinical benefit [30,31]. An incidence of bleeding similar to those reported with bevacizumab was described in patients with squamous histology. Sunitinib, a drug similar to those mentioned above, is a small molecule

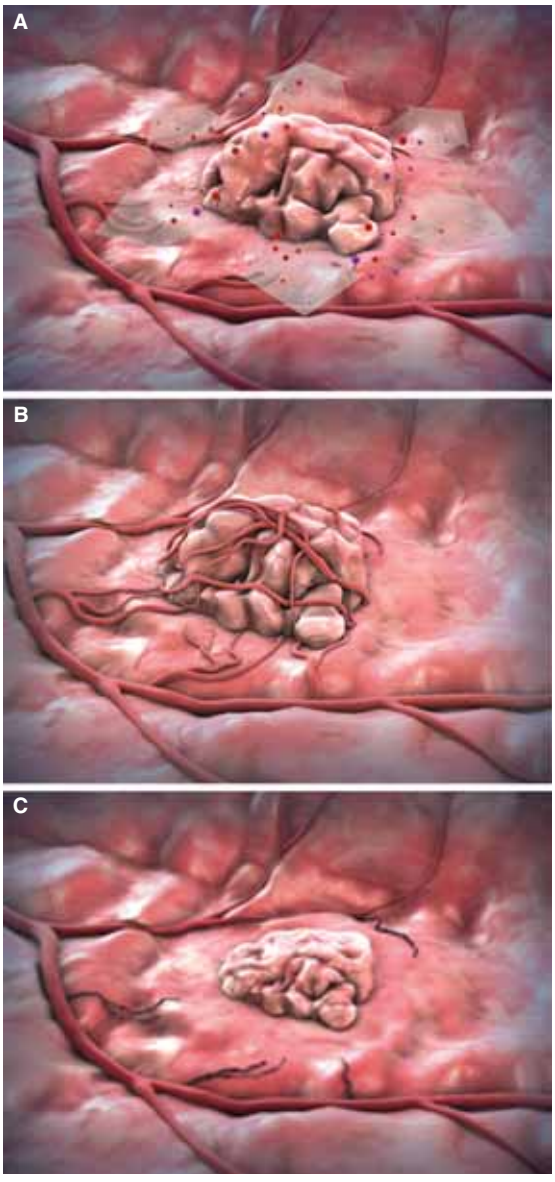


Figure 1. Development of tumor vasculature. A. Tumor cells produce pro-angiogenic factors which stimulate near blood vessel for angiogenesis. **B.** The formation of new blood vessels within the tumor tissue leads to a chaotic and disorganized vascular structure. **C.** Anti-angiogenic drugs block the vascularization of the tumor tissue.

that inhibits VEGFR, PDGFR, c-kit and fms-like tyrosine kinase 3 (Flt-3) and has indications similar to sorafenib (metastatic renal carcinoma, gastrointestinal stromal tumor (GIST) and pancreatic neuroendocrine tumors (pNET) [32,33]. Studies have suggested that Phase II single agent sunitinib has activity in pretreated patients with NSCLC. The results of these studies report that 11% (7/63) and 29% (18/63) of patients achieved stabilization of their disease for > 8 weeks [34]. Another study involved 47 patients given sunitinib continuously reported a 2% response rate (1/47) and 23% stable diseases (11/47) [35]. Finally, vandetanib and other small molecules by oral administration inhibited EGFR TK, VEGFR and RET (rearranged during transfection). Vandetanib has recently been approved for the treatment of medullary thyroid cancer [36-38]. For lung cancer patients, vandetanib alone or in combination with other agents has been studied in various randomized trials, including ZEST [39], Zeal [40], ZODIAC [41] and ZEPHYR [42]. Vandetanib did not prolong overall survival in any of these studies. For this reason, it was not approved in the USA by the Food and Drug Administration (FDA) [43].

3. Nintedanib: preclinical findings

Nintedanib is a triple angiokinase oral inhibitor that blocks the VEGFR-1, VEGFR-2 and VEGFR-3, FGFR-1, FGFR-2 and FGFR-3, PDGFR-α and β TKs (**Figure 4**). It also has activity against sarcoma viral oncogene (c-src) and Flt-3 [44]. Nintedanib is not yet approved for any indications in the USA or Europe. This molecule is considered an indolinone derivative. It is believed that the activation of the adenosine-5′-triphosphate (ATP) binding site in the kinase domain of these receptors results in the receptor dimerization and the consequent block of the angiogenic signal [44,45].

In vitro studies have demonstrated the ability of nintedanib to inhibit proliferation of HUVEC (human umbilical vein endothelial cell) stimulated by VEGF. There are also additives and inhibitory effects when combined with paclitaxel. In parallel, the fraction of cells undergoing apoptosis is increased with this combination [46]. This association was also analyzed in NSCLC cell lines H460. *In vitro* studies showed that there was a greater inhibition when nintedanib was combined with paclitaxel. *In vivo* studies with the NSCLC models have revealed that combination of BIBF 1120 with docetaxel in H460 xenografts has clear antitumor efficacy. Similar studies with xenograft models have also demonstrated that the combination of pemetrexed with nintedanib is possible and effective [46].

4. Trials with nintedanib in NSCLC

4.1 Nintedanib as single agent

In a Phase I, Mross et al. treated 51 patients affected by various advanced tumors with nintedanib dose escalation [47]. Twenty-five patients received nintedanib at the dose of 50 – 450 mg once a day and 36 patients received nintedanib at a dose of 150 – 300 mg twice daily in 4-week cycles with a week off. The most common side effects were mild or moderate. G3 toxicity was observed with different frequency for nintedanib once daily versus twice daily: irreversible liver enzyme elevation (12% grade 3 and 4% grade 4 vs 0% grade 3 and 2.8% grade 4), elevation of aspartate aminotransferase (AST) (grade 3, 8 vs 2.8%), elevated alanine aminotransferase (ALT) (grade 3, 0 vs 5.6%), γ-glutamyl elevation transpeptidase (grade 3, 4 vs 5.6%), CD4 lymphocytes decrease (grade

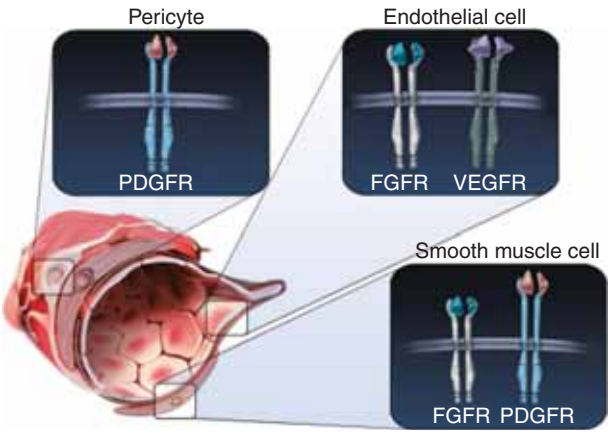


Figure 2. Receptors involved in tumor-related neoangiogenesis. Endothelial cells express FGFR and VEGFR. Smooth muscle cells express FGFR and PDGFRF. Pericytes express PDGFR.

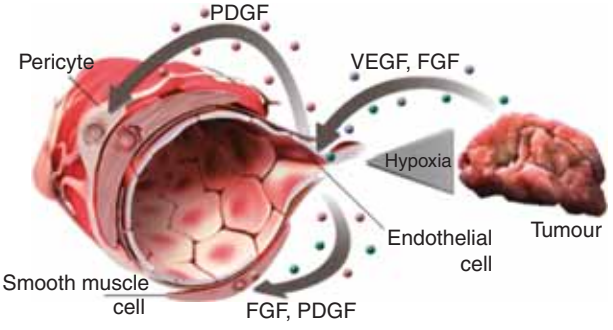


Figure 3. Mechanisms of tumor-related neoangiogenesis. Since hypoxia develops within the tumor, pro-angiogenic factors are produced to stimulate endothelial cell proliferation and pericyte regulation of angiogenesis.
FGF: Fibroblast growth factor; PDGF: Platelet-derived growth factor.

3, 16 vs 5.6%), hypertension (grade 3, 4 vs 0%), diarrhea (grade 3, 0 vs 2.8%), nausea (grade 3, 0 vs 5.6%) and vomiting (grade 3, 0 vs 2.8%).

The maximum tolerated dose (MTD) for both once- and twice-daily dosing was 250 mg. Another Phase I study in Japanese patients with advanced lung cancer found out for nintedanib a MTD of 200 mg twice daily. Twenty patients received twice-daily nintedanib at 150 mg (n = 3), 200 mg (n = 12) or 250 mg (n = 6). All dose-limiting toxicities were largely reversible elevations in liver enzymes. It reported stable disease for more than two cycles of treatment in 76% of patients (n = 16) [48].

Nintedanib has also been studied in Phase II trials in patients with locally advanced or metastatic NSCLC. To be included in this trial, patients needed to fail at least after one or two lines of chemotherapy (including a platinum scheme). Patients were randomly assigned to a dose of 150 or 250 mg of nintedanib with a mean time to progression of 6.9 weeks and no significant difference between the two study groups. Median survival was 22 weeks. Patients with Eastern Cooperative Oncology Group (ECOG) PS 0 – 1 (n = 56) had a half time to progression of 11.6 weeks and a median survival of 37.7 weeks. Forty-six percent of patients were able to stabilize their disease. The most common adverse effects reported were: nausea (57.5%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible elevation of transaminase levels: serum glutamic oxaloacetic transaminase (SGOT; 13.7%) and serum glutamic-pyruvic transaminase (SGPT) (9.6%). It is noteworthy that nintedanib continuous treatment was well tolerated, with no difference between treatment groups. The time to progression and objective response rate found in this study supported the opportunity of further studies about this drug.

4.2 Nintedanib in combination with cytotoxic agents

Nintedanib has been studied in combination with other standard chemotherapeutic regimens, such as pemetrexed or the carboplatin/paclitaxel combination. In a Phase I trial, nintedanib was combined with pemetrexed to treat recurrent or advanced NSCLC (including all histologies) cancer patients who had previously received at least one line of platinum-based therapy [49]. The aim of this study was to determine the dose escalation safety and tolerability and MTD of the combination of nintedanib with pemetrexed. Included patients could not have received prior treatment with pemetrexed. Twenty-six patients were recruited for the safety analysis. The nintedanib MTD was 200 mg twice daily, when administered for 21 days in combination with the standard dose of pemetrexed. Among the first group of seven patients, 26.9% experienced a dose-limiting toxicity (DLT). One patient received 100 mg twice daily of nintedanib, another patient received 150 mg twice daily, three patients received 200 mg twice daily (one in the original cohort patient dose escalation and two patients in the extension phase) and two patients received 250 mg twice daily. DLTs included elevated liver enzymes (3.8%), elevated AST only (3.8%), elevated ALT only (7.6%), gastrointestinal events such as vomiting (3.8%), esophageal pain (3.8%) and nausea (3.8%), fatigue (19.2%), confusion (3.8%) and anorexia (3.8%). Most DLTs occurred during the first week. All patients experienced some adverse effects during the study. Gastrointestinal problems were seen in 84.6% of patients and most consisted of nausea, vomiting, abdominal pain and diarrhea. Local reactions related to drug delivery were also reported in 76.9% of patients, that is, erythema. The most common side effects reported in order of frequency were fatigue (65.4%), nausea (61.5%), anorexia (53.8%), erythema skin (38.5%), diarrhea (34.6%) and vomiting (34.6%). One patient among the 26 who were recruited

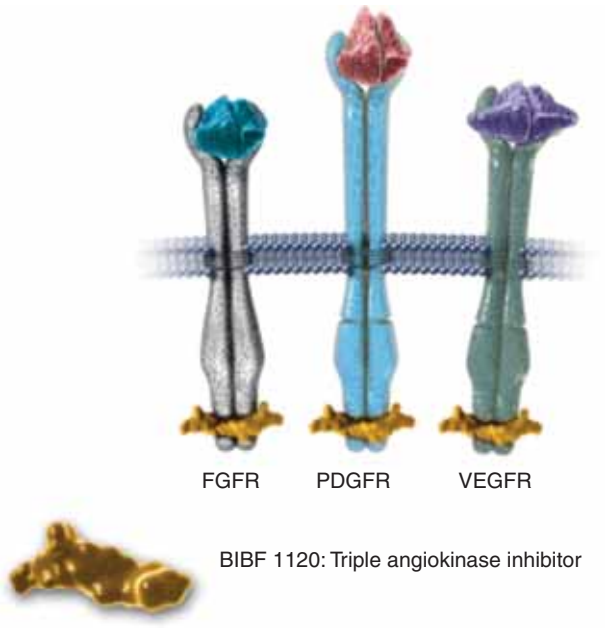


Figure 4. BIBF 1120 targets. BIBF 1120 is a multi-target tyrosine kinase inhibitor. It binds to the intracellular tyrosine kinase domain of angiogenesis-related receptors, including FGFR, PDGFR and VEGFR.

and treated with 100 mg nintedanib twice daily showed a quick complete response 44 days after beginning treatment. The authors reported that the patient was still in treatment with nintedanib single agent twice a day at the moment of publication and it had been continued for 3.5 years. Among the 26 patients treated in this group, 13 (50%) experienced stable disease as best response and 8 patients had disease progression. The median time to progression for the 26 patients treated was approximately 5.4 months. In conclusion, continued treatment with pemetrexed in combination with nintedanib was tolerable with interesting efficacy results, the combination of pemetrexed and nintedanib is a viable treatment option that requires further research.

In another Phase I study, the combination of nintedanib with carboplatin/paclitaxel was investigated. The primary objectives were to determine the safety and tolerability and nintedanib MTD in patients with untreated advanced NSCLC and ECOG PS 0 – 1 [50]. Patients with squamous cell histology were eligible for this study, but patients with cavitary lesions or necrotic tumors or evidence that the mass was near a major blood vessel were excluded. The study involved a dose escalation of nintedanib (starting at 50 mg twice daily) on days 2 – 21 of each cycle combined with carboplatin (area under the curve (AUC) = 6) and paclitaxel (200 mg/m^2) on day 1 of each 21 days cycle. Patients were treated for a minimum of four to a maximum of six cycles of combination chemotherapy with the option to continue with nintedanib in monotherapy after completion of combination therapy. Nintedanib dose was escalated from 50 mg per cohort until the MTD was determined. The MTD was defined as the dose of nintedanib to which 2 or > 6 in the cohort patients experienced DLT during the first treatment cycle. The measurement of tumor lesions was made at baseline and after every second cycle according to RECIST criteria. Twenty-five patients were included and 14 were treated at the MTD in this study. The nintedanib MTD was 200 mg twice daily in combination regimen with carboplatin/ paclitaxel. This triple combination was well tolerated. Five patients experienced DLT during the first treatment cycle including transaminases increase (2/5), thrombocytopenia (1/5), abdominal pain (1/5) and redness (1/5); these toxicities resolved after the drug was discontinued.

Ten patients received nintedanib as single agent after completion of the planned combination including two, three or up to six cycles. According to RECIST criteria, considering that 17 patients were eligible for response, 7 had partial response and 10 patients had stable disease. Initial signs of clinical efficacy were observed in patients who were in this trial.

5. Expert opinion

Several agents such as nintedanib have been developed to target angiogenesis or TKs. Some of them demonstrated clinical utility as single agent or in combination with conventional cytotoxic chemotherapy. The advantages of the drugs belonging to this class are both the opportunity of oral administration and the availability of tools for targeting resistance in the various pathways involved in cancer development and progression. However, these advantages have not yet been clearly translated into clinical benefit. For example, vandetanib is a TK inhibitor which has anti-angiogenic properties, but randomized clinical trials showed no benefit when compared with other TK inhibitors such as gefitinib. So there is a need to recognize the fact that nintedanib and other drugs could improve survival when combined with chemotherapy, but Phase III trials are necessary to clarify this topic. However, this new drug has shown its good tolerability profile even with full-dose chemotherapy regimens. This issue is mandatory to guarantee an optimal inclusion of this kind of targeted drug in the overall treatment strategies for lung cancer. According to the information available today, the toxicities of these agents are apparently acceptable but the number of patients treated in the Phase I and Phase II trials is still too small to reach a meaningful conclusion regarding both efficacy and safety. For this reason, Phase III trials could help for better knowledge of the toxicity related to these agents in advanced NSCLC patients. It is also important to highlight that in squamous lung cancers, severe bleeding was reported as observed for bevacizumab. For this reason, a particular warning is mandatory for future clinical trials with nintedanib,

since those patients with squamous histology should be excluded. Another limitation for full clinical application of nintedanib as well as the other anti-angiogenic agents is represented by the lack of predictive biomarkers for response. The identification of prognostic and predictive factors is essential to choose the best treatment option for each patient and avoid unnecessary toxicity. Various efforts have been made for defining tailored therapy. Several biomarkers were evaluated, as in the ECOG 4599 study for the approval of bevacizumab. Similarly, the authors evaluated markers such as ICAM (soluble intercellular adhesion molecule). So far, the identification of biomarkers for anti-angiogenic agents is being studied.

Acknowledgement

The authors wish to thank Dr. Gemma Sempere for the help in the narration of the manuscript.

Declaration of interest

LE Raez receives aid for scientific research and clinical studies from Boehringer Ingelheim, Lilly Oncology, Roche, Genentech and Pfizer. E Santos is a member of the Speaker Bureau of Genentech and Lilly Oncology and receives the US aid for scientific research and clinical studies from Boehringer Ingelheim. No other conflict of interest for the other authors.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Carmeliet P, Jain R. Angiogenesis in cancer and other diseases. Nature 2000;407:249-57
2. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 1990;82(1):4-6
• **A milestone analysis by Folkman about the potential of angiogenesis in cancer biology. He poses the bases for the understanding of angiogenetic mechanisms and the relative therapeutic potential of anti-angiogenic agents.**
3. Hicklin D, Ellis L. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005;23(5):1011-27
4. Weidner N. Tumoural vascularity as a prognostic factor in cancer patients: the evidence continues to grow. J Pathol 1998;184:119-22
5. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25:581-611
6. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. Oncology 2005;69(Suppl 3):4-10
7. Bremnes R, Camps C, Sirera R. Angiogenesis in non-small cell lung cancer: the prognostic impact of neoangiogenesis and the cytokines VEGF and bFGF in tumours and blood. Lung Cancer 2006;51(2):143-58
8. Jain R. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987-9
9. Giaccone G. The potential of antiangiogenic therapy in non-small cell lung cancer. Clin Cancer Res 2007;13:1961-70
10. Clement-Duchene C, Wakelee H. Antiangiogenic agents and vascular disrupting agents for the treatment of lung cancer: a review. J Thorac Oncol 2010;5:129-39
11. McKeage M, Baguley B. Disrupting established tumor blood vessels: an emerging therapeutic strategy for cancer. Cancer 2010;116:1859-71
12. Jain R, Booth M. What brings pericytes to tumor vessels? J Clin Invest 2003;112:1134-6
14. Cao Y, Cao R, Hedlund EM. R Regulation of tumor angiogenesis and metastasis by FGF and PDGF signaling pathways. J Mol Med 2008;86:785-9
• **This work highlights the role of other pathways different from that related to VEGF. It represents the basis for the interesting mechanism of multi-targeting angiogenesis by nintedanib.**
13. Erber R, Thurnher A, Katsen A, et al. Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. FASEB J 2004;18:338-40
15. Shih A, Holland E. Platelet-derived growth factor (PDGF) and glial tumorigenesis. Cancer Lett 2006;232:139-47
16. Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. Nat Rev Drug Discov 2009;8:235-53
17. Presta M, Dell'Era P, Mitola S, et al. Fibroblast growth factor/fibroblast growth factor receptor system in angiogenesis. Cytokine Growth Factor Rev 2005;16:159-78
18. Rosen LS. Clinical experience with angiogenesis signaling inhibitors: focus on vascular endothelial growth factor (VEGF) blockers. Cancer Contr 2002;9:36-44
19. Bergers G, Song S, Meyer-Morse N, et al. Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. J Clin Invest 2003;111:1287-95
20. Casanovas O, Hicklin DJ, 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
21. Ferrara N, Hillan K, Gerber H, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004;3:391-400
•• **This work represents one of the first analysis about the great therapeutic potential of bevacizumab by direct VEGF inhibition.**
22. Avastin® (bevacizumab) [package insert]. Genentech, Inc, South San Francisco, CA; 2009
23. Herbst R. Toxicities of antiangiogenic therapy in non-small-cell lung cancer. Clin Lung Cancer 2006;8:S23-30

24. Spigel D, Hainsworth J, Yardley D, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol 2010;28:43-8

25. Scagliotti G, Novello S, Von P, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. J Clin Oncol 2010;28:1835-42

26. Wilhelm S, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099-109

27. NEXAVAR (sorafenib) tablets, oral [package insert]. Bayer Healthcare Pharmaceuticals Inc, Wayne, NJ; 2009

28. Escudier B, Eisen T, Stadler W, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27:3312-18

29. Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90

30. Scagliotti G, Novello S, von Pawel J, Reck M. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non–small-cell lung cancer. JCO 2010;28(11):835-42

31. Paz-Ares LG, Biesma B, Heigener D, et al. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. J Clin Oncol 2012;30:25):3084-92

32. Heng D, Kollmannsberger C. Sunitinib. Recent Results Cancer Res 2010;184:71-82

33. SUTENT® (sunitinib malate) capsules, oral [package insert]. Pfizer Inc, New York, NY; 2010

34. Socinski M, Novello S, Brahmer J, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. J Clin Oncol 2008;26:650-6

35. 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;101:1543-8

36. United States Federal Drug Administration (FDA): FDA approves new treatment for rare form of thyroid cancer. Vandetanib is first drug approved for medullary thyroid cancer. 2013.Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm250168.htm

37. Mitsudomi T. Advances in target therapy for lung cancer. Jpn J Clin Oncol 2010;40:101-6

43. AstraZeneca Oncology 2009. Vandetanib (Zactima™). Available from: http://www.astrazeneca.com/Media/Press-releases/Article/20091028–AstraZeneca-withdraws-regulatory-submissions-for-Zact [Accessed 29 April 2013]

38. Wells S, Robinson B, Gagel R, et al. [Abstract OC-021]. Presented at the 14th International Thyroid Conference; 11 – 16 September 2010; Paris, France

39. Natale R, Thongprasert S, Greco F, et al. Vandetanib versus erlotinib in patients with advanced non-small cell lung cancer (NSCLC) after failure of at least one prior cytotoxic chemotherapy: a randomized, double-blind phase III trial (ZEST) [abstract 8009]. J Clin Oncol 2009;27:409s

40. De Boer R, Arrieta O, Gottfried M, et al. Vandetanib plus pemetrexed versus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer (NSCLC): a randomized, double-blind phase III trial (ZEAL) [abstract 8010]. J Clin Oncol 2009;27:409s

41. Herbst RS, Sun Y, Eberhardt WE, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. Lancet Oncol 2010;11:619-26

42. Lee J, Hirsh V, Park K, et al. Vandetanib versus placebo in patients with advanced non–small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: a randomized . double-blind phase III trial (ZEPHYR). J Clin Oncol 2010;28:7525

44. Hilberg F, Roth G, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68:4774-82

•• **In this work, the mechanism of BIBF 1120 is clearly described. The role of multi-targeting of angiogenesis-related pathways is explained to clarify the antitumor activity of this new drug.**

45. Roth G, Heckel A, Colbatzky F, et al. Design, synthesis, and evaluation of indolinones as triple angiokinase inhibitors and the discovery of a highly specific 6-methoxycarbonyl-substituted indolinone (BIBF 1120). J Med Chem 2009;52:4466-80

46. 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: C7-03. J Thoracic Oncol 2007;2(8):S380

• **A preclinical model is used in this work to show the synergism of nintedanib with chemotherapy as a new interesting strategy for NSCLC treatment.**

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

•• **This is one of the first clinical trials which investigated the antitumor activity of nintedanib.**

48. 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

49. Ellis PM, 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

50. Doebele RC, Conkling P, Traynor AM, 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

Affiliation

Christian Rolfo[1], Luis E Raez[2], Giuseppe Bronte[3], Edgardo S Santos[4], Kostantinos Papadimitriou[5], Lucio Buffoni[6], Jan P van Meerbeeck[7] & Antonio Russo[†8]

[†]Author for correspondence

[1]Antwerp University Hospital, Oncology Department, Phase I – Early Clinical Trials Unit, Edegem, Belgium

[2]Memorial Cancer Institute, Memorial Health Care System, Thoracic Oncology Program, Pembroke Pines, FL, USA

[3]University of Palermo, Department of Surgical and Oncology Sciences, Section of Medical Oncology, Palermo, Italy

[4]Lynn Cancer Institute, Thoracic Oncology, Boca Raton, Florida, USA

[5]Antwerp University Hospital, Oncology Department, Edegem, Belgium

[6]San Giovanni Battista Molinette Hospital, Department of Medical Oncology, Turin, Italy

[7]Ghent University Hospital, Department of Respiratory Medicine, Ghent, Belgium

[8]University of Palermo, Palermo, Italy

E-mail: lab-oncobiologia@usa.net