

Profile of nintedanib in the treatment of solid tumors: the evidence to date

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Abstract: Angiogenesis is an essential process for tumor growth and metastasis, and remains a promising therapeutic target process in cancer treatment for several cancer types. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), was the first antiangiogenic agent approved for cancer therapy. Novel antiangiogenic agents, such as sunitinib, sorafenib, pazopanib, or vandetanib that target additional proangiogenic signaling pathways beyond VEGF, have also been approved for the treatment of various malignant diseases. While most of these agents are approved in combination with cytotoxic chemotherapy for indications including metastatic colorectal cancer, non-small-cell lung cancer, breast cancer, renal cell carcinoma (RCC), and gastric cancer, some are used as approved monotherapy for advanced RCC, hepatocellular carcinoma and medullary thyroid cancer. Major challenges to the success of antiangiogenic therapy include associated toxicity risks, limitation of efficacy through the possible development of resistance and induction or promotion of metastatic progression. Nintedanib (formally known as BIBF 1120) is a triple angiokinase inhibitor of VEGF, fibroblast growth factor, platelet-derived growth factor signaling with lesser activity against RET, Flt-3, and Src. Through this unique targeting profile nintedanib has demonstrated significant antitumor activity in several tumor types in preclinical studies. Nintedanib has also shown promising clinical efficacy in combination with docetaxel and has been approved for treating patients with locally advanced and metastatic non-small-cell lung cancer in Europe. Nintedanib has also been found to be clinically promising in terms of efficacy and safety in several other solid tumors including ovarian cancer (Phase III), RCC (Phase II), and prostate cancer (Phase II). This review article provides a comprehensive summary of the preclinical and clinical efficacy of nintedanib in the treatment of solid tumors.

Keywords: nintedanib, BIBF 1120, angiogenesis, VEGF, tyrosine kinase inhibitors

Introduction

Angiogenesis, the process of new blood vessel development from existing vasculature, is a hallmark of cancer progression and metastasis that has long been considered an attractive therapeutic target.¹ Tumor angiogenesis is a complex process that represents a highly regulated yet disturbed balance between proangiogenic and antiangiogenic mechanisms.² Among several proangiogenic signaling molecules, vascular endothelial growth factor (VEGF) is considered to be one of the most important factors involved in tumor angiogenesis.³ VEGF is frequently highly expressed in human solid cancers and plays a fundamental role in tumor-mediated blood vessel growth by mediating vasculogenesis, angiogenic remodeling, angiogenic sprouting, and vascular permeability.³⁻⁵ Thus, initial antiangiogenic therapy attempts have largely focused on inhibiting VEGF signaling. Bevacizumab, a monoclonal antibody that blocks angiogenesis by binding VEGF-A (a ligand for VEGFR1 and VEGFR2), was the first antiangiogenic

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agent approved in 2004 that showed clinical efficacy in combination with chemotherapy in some solid tumors including metastatic colorectal cancer (CRC),⁶ non-small-cell lung cancer (NSCLC),⁷ breast cancer,⁸ and renal cell carcinoma (RCC).⁹ Since then, several antiangiogenic agents, such as sunitinib,¹⁰ sorafenib,¹¹ pazopanib,¹² vandetanib,¹³ axitinib,¹⁴ regorafenib,¹⁵ aflibercept,¹⁶ cabozantinib,¹⁷ and ramucirumab¹⁸ that target VEGF signaling and/or some additional proangiogenic signaling activity have been approved for the treatment of various malignant diseases. These antiangiogenic agents, either as monotherapy or in combination with chemotherapy, generally have only provided limited clinical benefits in some tumor types. Furthermore, in certain advanced metastatic cancers, VEGF inhibition alone was insufficient to prevent progression, induced resistance and in some cases may have contributed to increased invasion and metastasis.^{19,20} One of the main reasons for the limited and transient response of the anti-VEGF therapies is that tumor angiogenesis is regulated by multiple pathways that are able to compensate for each other when single pathways are inhibited. The fibroblast growth factor (FGF) and its receptors (FGFR1/2/3),²¹ platelet-derived growth factor (PDGF), and its receptors (PDGFR α and PDGFR β),²² epidermal growth factor and its receptor,²³ angiopoietin-2,²⁴ placenta-derived growth factor,²⁵ and neuropilin²⁶ are key components within the main signaling pathways that provide potential escape mechanisms from anti-VEGF therapy leading to resistance development and facilitate resumption of tumor growth.²⁷

The FGF/FGFR signaling axis plays an important role in tissue homeostasis, tissue repair, angiogenesis, and inflammation. Deregulation of FGF/FGFR signaling through genetic modification or over-expression of its ligands/receptors has been observed to promote cell proliferation, survival, and tumor angiogenesis in numerous tumor settings including pancreatic cancer, prostate cancer, and some squamous cell carcinomas.^{28,29} Several preclinical studies demonstrated that inhibition of FGF/FGFR signaling has antiproliferative, proapoptotic, and antiangiogenic effects, supporting the validity of this signaling axis as a potential therapeutic target. PDGF is another important growth factor that can be crucial for tumor growth and progression. PDGF itself is a potent mitogen in both normal and tumor cells,³⁰ but it also has significant angiogenic effects on endothelial cells. PDGF/PDGFR signaling has been shown to promote cell division,^{31,32} cell migration,³³ and angiogenesis.³⁴ In addition, recruitment of pericytes such as vascular smooth muscle cells by PDGF is essential for maintenance of tumor angiogenesis.³⁵ The PDGF/PDGFR signaling has been overactive in several malignancies such as brain tumor,

sarcomas, prostate cancer, liver cancer, NSCLC, breast cancer, and CRC^{36,37} and therapeutic targeting of this pathway reduced tumor growth in many tumor types.³⁷⁻³⁹

As multiple proangiogenic factors contribute to tumor angiogenesis, and the fact that inhibition of one angiogenic signaling pathway induces compensatory mechanisms leading to the development of resistance,⁴⁰⁻⁴² more recent therapeutic strategies have focused on developing multi-targeted tyrosine kinase receptors (TKIs) that have the ability to block multiple signaling pathways simultaneously, but at the same time maintain some selectivity profile of kinases in terms of safety and tolerability. This review summarizes the antitumor profile of nintedanib, a triple angiokinase inhibitor, which targets proangiogenic signaling of VEGFR, FGFR, and PDGFR.

Nintedanib: advantages and mechanism of action

The first commercially available antiangiogenic drug was bevacizumab, a monoclonal antibody against VEGF-A.⁴³ Bevacizumab is currently approved in combination with standard chemotherapy for the treatment of several cancers including metastatic CRC,⁶ NSCLC,⁷ and RCC.^{6,7,19} While bevacizumab demonstrates some promising antitumor activity, its clinical use may also be limited by its side-effect profile that includes hypertension, proteinuria, bleeding, thrombotic events, and hemorrhage.^{44,45} Efforts beyond bevacizumab have focused on a second class of antiangiogenic agents, namely small molecules that are orally available and have the ability to target multiple TKIs. Most of these broad-spectrum TKIs such as sunitinib, sorafenib, pazopanib, vandetanib have complex efficacy data, but in many cases the use of these drugs is associated with a significant increase in the incidence and risk of side effects.⁴⁶⁻⁴⁸ Most of these TKIs that affect multiple kinases have lower specificity toward some of their therapeutic targets, particularly at the FGF/FGFR axis, requiring higher doses for efficacy.⁴⁹ Therefore, these TKIs have increased risk for on-target toxicities (such as hypertension, skin toxicity, and diarrhea) and presumed off-target toxicities (such as cardiac impairment).^{49,50}

Nintedanib is a next generation, oral, and potent triple angiokinase inhibitor that inhibits the proangiogenic pathways mediated by VEGFR1/2/3 (IC₅₀ 13–34 nmol/L), FGFR1/2/3 (IC₅₀ 37–108 nmol/L), and PDGFR α / β (IC₅₀ 59–65 nmol/L) to a high degree of specificity (Figure 1). Nintedanib competitively binds to the ATP binding-pocket of these receptors, resulting in interference with receptor dimerization and blocking intracellular signaling critical for the proliferation and survival of angiogenesis-related endothelial cells, pericytes, and vascular smooth muscle cells (Figure 2). Nintedanib also inhibits some

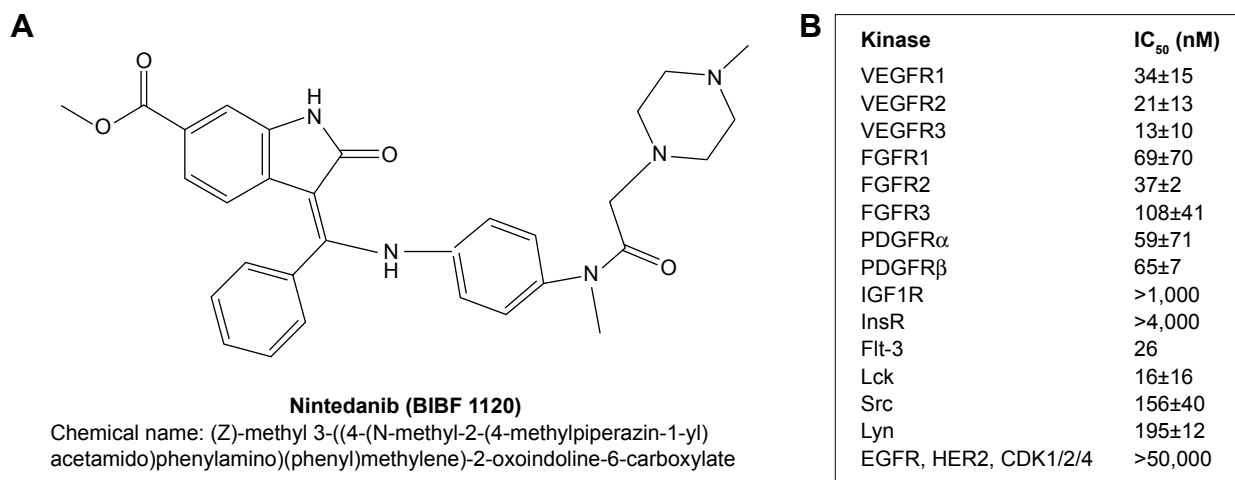


Figure 1 Summary of nintedanib.

Notes: (A) Molecular structure of nintedanib. (B) In vitro kinase inhibition profile of nintedanib (IC₅₀). Data presented as mean \pm standard error of at least three determinations.

Abbreviations: VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; IGF1R, insulin-like growth factor 1 receptor; InsR, insulin receptor; Flt-3, fms-like tyrosine protein kinase 3; Lck, lymphocyte-specific tyrosine kinase; Src, proto-oncogene tyrosine protein kinase src; Lyn, tyrosine-protein kinase lyn; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; CDK, cyclin-dependent kinase.

non-receptor kinases such as Fms-like tyrosine protein kinase (Flt-3, IC₅₀ 26 nmol/L), proto-oncogene ret (Ret, IC₅₀ 35 nmol/L), lymphocyte-specific tyrosine kinase (Lck, IC₅₀ 16 nmol/L), tyrosine-protein kinase lyn (Lyn IC₅₀ 195 nmol/L), and proto-oncogene tyrosine protein kinase src (Src, IC₅₀ 156 nmol/L)^{51,52} (Figure 1). In addition, nintedanib has recently been approved for the treatment of idiopathic pulmonary fibrosis based on results from the replicate Phase III trials involving 1,066 patients from 24 countries.⁵³ Nintedanib is thus the first targeted treatment for idiopathic pulmonary fibrosis, indicating the therapeutic potential of TKIs in non-malignant diseases.

A major challenge in the success of VEGF signaling blocking antiangiogenic therapy is the development of resistance in the primary tumor, probably due to induction of tumor escape mechanisms through upregulated FGFR and PDGFR signaling.^{54–56} This mechanism of the development of antiangiogenic drug resistance provides a potential rationale for efficacy of nintedanib, which can prevent tumor growth and metastasis via its triple inhibition of VEGFR, FGFR and PDGFR, and also provide a therapeutic alternative for patients with intrinsic and acquired resistance to single or dual target antiangiogenic drugs.

Nintedanib: preclinical studies to date

In vitro studies demonstrated that nintedanib treatment inhibited the proliferation of VEGF-stimulated human umbilical vein endothelial cells and human skin microvascular endothelial cells. Nintedanib also inhibited the proliferation of PDGF-stimulated smooth muscle cells and pericytes.⁵²

Although Kutluk Cenik et al⁵⁷ showed that nintedanib has no antiproliferative activity on selected lung and pancreatic cancer cell lines, recent reports suggest that nintedanib effects are not generally limited to stromal cells as it also differentially inhibited the proliferation of hepatocellular carcinoma (HCC) cells⁵⁸ and pancreatic ductal adenocarcinoma (PDAC) cells.⁵⁹ Tai et al⁵⁸ demonstrated that nintedanib treatment caused a significant antiproliferative effect in a panel of four HCC cell lines (PLC5, Hep3B, SK-Hep1, and HuH7) and one hepatoblastoma cell line (Hepg2). Awasthi et al⁵⁹ demonstrated that nintedanib not only inhibited the proliferation of human umbilical vein endothelial cells, fibroblast WI-38 cells and pancreatic cancer stromal cells, but it also inhibited the proliferation of human PDAC cells (AsPC-1, BxPC-3, MIA PaCa-2, and Panc-1) and murine PDAC cells PanO2.

In vivo, nintedanib demonstrated potent antitumor effects in all human tumor xenografts reported to date, including NSCLC, RCC, CRC, ovarian cancer, prostate cancer, and PDAC.^{52,57,59} More importantly, nintedanib treatment augmented the antitumor response of standard cytotoxic agents. In NSCLC xenografts (H460 cells), nintedanib treatment caused synergistic antitumor effects in combination with cytotoxic agents docetaxel or pemetrexed.⁶⁰ Kutluk Cenik et al⁵⁷ demonstrated significant antitumor activity of nintedanib monotherapy and in combination with standard cytotoxic chemotherapy in several xenograft models of lung and pancreatic cancer.⁵⁷ Recently, Awasthi et al⁵⁹ demonstrated that nintedanib significantly enhanced gemcitabine response in pancreatic cancer: net local tumor growth compared to

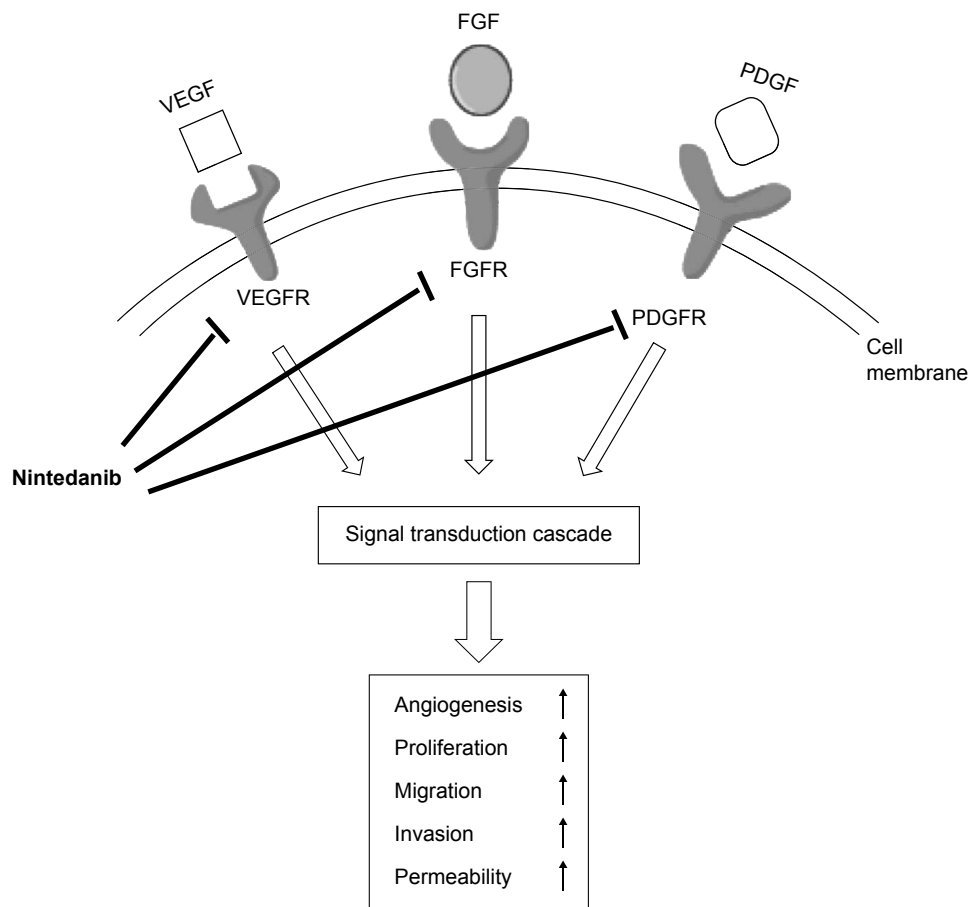


Figure 2 Triple angiokinase inhibition mechanism of nintedanib targeting tumor angiogenesis.

Abbreviations: VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor.

controls (100%) was $60.8\% \pm 10.5\%$ in the gemcitabine group, $-2.1\% \pm 9.9\%$ after nintedanib monotherapy and $-12.4\% \pm 16\%$ after gemcitabine plus nintedanib combination therapy. In addition, this study demonstrated that compared with controls, the increase in median animal survival was 56% with gemcitabine ($P=0.036$), 94% for nintedanib ($P=0.004$) and 138% after gemcitabine + nintedanib ($P=0.001$).⁵⁹ In human tumor xenografts, intratumoral antitumor mechanism of nintedanib involves reduced microvessel density, pericyte coverage, vessel permeability, tumor perfusion, and induced hypoxia, as well as inhibition of phosphatidylinositol 3-kinase (PI3K)-AKT and mitogen-activated protein kinase (MAPK) signaling pathways.^{52,57,59}

Nintedanib: clinical studies to date

The clinical pharmacokinetic profile studies of nintedanib demonstrated that it is rapidly absorbed as its maximum plasma concentrations occur within 1–3 hours after oral administration.^{61,62} The terminal half-life of nintedanib was observed to be ~13–19 hours.^{61,62} The first Phase I dose-

escalation study with single agent nintedanib therapy was reported in 61 patients with different advanced solid tumors.⁶² Twenty-five patients received nintedanib 50–450 mg once daily (od) and 36 patients received nintedanib 150–300 mg twice daily (bid) in 4-week cycles with a week off. The most common drug-related adverse events (AEs) were mild to moderate; grade 3 or more AEs for nintedanib od vs bid occurring in >5% patients were reversible hepatic enzyme elevation (12% grade 3 and 4% grade 4 vs 0% grade 3 and 2.8% grade 4), increase in aspartate aminotransferase (AST; grade 3, 8% vs 2.8%), increase in alanine aminotransferase (ALT; grade 3, 0% vs 5.6%), increase in γ -glutamyl transpeptidase (grade 3, 4% vs 5.6%), decrease in CD-4 lymphocyte (grade 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 tolerable dose (MTD) of nintedanib was defined as 250 mg for both od and bid dosing.⁶² In another Phase I dose-escalation study, 21 Japanese patients with advanced refractory solid tumors were treated with bid nintedanib doses of 150 mg

(n=3), 200 mg (n=12), or 250 mg (n=6).⁶³ This study reported that the dose-limiting grade 3 or 4 toxicity elevation of liver enzymes occurred in 3 of 12 patients at 200 mg bid and 3 of 6 patients at 250 mg bid dose. Stable disease (SD) was reported in 76.2% of patients (n=16). The MTD of nintedanib in this study was determined to be 200 mg bid.

Nintedanib in NSCLC

In NSCLC patients, two Phase I dose-escalation studies have been conducted investigating nintedanib in combination with a standard chemotherapy regimen. The first study investigated the MTD of continuous nintedanib oral treatment in combination with standard-dose pemetrexed (500 mg/m²) in patients who had been previously treated with one platinum-based chemotherapy regimen.⁶⁴ In this study, one patient achieved a complete response after 44 days for more than 3 years; otherwise, the best overall response was SD in 50% patients (n=13). The second trial investigated the safety, tolerability, and MTD of nintedanib in combination with carboplatin and paclitaxel in patients with advanced NSCLC who were previously untreated.⁶⁵ In these two Phase I studies, the recommended dose of nintedanib was determined as 200 mg bid when used in combination with the mentioned standard chemotherapy regimens of NSCLC. The most frequent AEs in these studies were comparable to the nintedanib monotherapy trials.

A Phase II double-blind trial evaluated the efficacy of nintedanib monotherapy (150 mg bid, n=36 or 250 mg bid, n=37) in patients with relapsed, advanced NSCLC (any histology) with an Eastern Cooperative Oncology Group performance status 0–2. This study reported a median progression free survival (PFS) of 6.9 weeks, the median overall survival (OS) was 21.9 weeks, and SD was observed in 46% of the patients (Table 1). In 56 patients with Eastern Cooperative Oncology Group performance status 0–1, median PFS was 11.6 weeks with a median OS of 37.7 weeks. Most commonly reported drug-related AEs included nausea, diarrhea, vomiting, anorexia, and abdominal pain.⁶⁶

A Phase III, double-blind, randomized trial of nintedanib (200 mg, bid, n=565) or placebo (n=569) on days 2–21, in combination with docetaxel (75 mg/m² on day 1) in patients with previously treated NSCLC (LUME-Lung 1 trial), reported that median PFS was significantly improved in the docetaxel plus nintedanib group compared with the docetaxel plus placebo group (3.4 months vs 2.7 months, hazard ratio (HR) 0.79, *P*=0.0019). The median OS was also significantly improved in the docetaxel plus nintedanib group compared with docetaxel alone group (12.6 months vs 10.3 months;

Table 1 Summary of key efficacy and safety results from Phase II and III studies with nintedanib in patients with NSCLC

Study	Setting	Regimen	Median PFS	Median OS	Most common AEs
Phase II ⁶⁶	Advanced NSCLC, previously treated	Nintedanib 150 mg (bid, n=36) or 250 mg (bid, n=37)	6.9 weeks	21.9 weeks	Nausea, diarrhea, vomiting, anorexia, abdominal pain
Phase III ⁶⁷ LUME-lung 1	Advanced NSCLC, previously treated	Nintedanib (200 mg, bid, 2–21 days) + docetaxel (75 mg/m ² , day 1), n=565 or placebo + docetaxel (75 mg/m ² , day 1), n=569	3.4 months vs 2.7 months, <i>P</i> =0.0019 (nintedanib vs placebo)	12.6 months vs 10.3 months, <i>P</i> =0.0359 (nintedanib vs placebo arm)	The more common AEs in the nintedanib vs placebo: diarrhea (42.3% vs 21.8%), increase in ALT (28.5% vs 8.4%), increase in AST (22.5% vs 6.6%), nausea (24.2% vs 18%), vomiting (16.9% vs 9.3%)
Phase III ⁶⁸ LUME-lung 2	Advanced NSCLC or nonsquamous histology, after relapse or failure of first-line chemotherapy	Nintedanib (200 mg, bid, 2–21 days) + pemetrexed (500 mg/m ² , day 1), n=353 or placebo + pemetrexed (500 mg/m ² , day 1), n=360	4.4 months vs 3.6 months, <i>P</i> =0.0435 (nintedanib vs placebo)	12.2 months vs 12.7 months, <i>P</i> =0.7921 (nintedanib arm vs placebo arm)	Nintedanib vs placebo: grade 3/4 AEs (increase in liver enzymes and gastrointestinal events; 58.5% vs 42.3%), serious AEs (30% vs 32.8%), grade 5 AEs (9.8% vs 12%)

Abbreviations: AEs, adverse events; bid, twice daily; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression free survival.

Table 2 Summary of key efficacy and safety results from Phase II and III studies with nintedanib in solid tumors other than NSCLC

Study	Setting	Regimen	Median PFS/PFS rate	Median OS	Most common AEs
Phase II ⁶⁹	Ovarian cancer, previously treated	Nintedanib 250 mg (bid, n=43) or placebo (n=40) continuous for 36 weeks	PFS rate at 36 weeks: 16.3% vs 5%, P=0.06 (nintedanib vs placebo)	NR	Nintedanib vs placebo: grade 3/4 AEs were similar (34.9% vs 27.5%, P=0.49)
Phase III ⁷⁰ LUME-ovar I	Advanced epithelial ovarian cancer, previously untreated	Standard first-line chemotherapy (carboplatin and paclitaxel) followed by nintedanib (200 mg, bid) up to 120 weeks, or placebo plus chemotherapy	PFS: 17.3 months vs 16.6 months, P=0.0239 (nintedanib vs placebo arm)	NR	Nintedanib vs placebo: major AEs: gastrointestinal symptoms, hematologic symptoms
Phase II ⁷¹	Advanced clear cell renal cell carcinoma (RCC), previously untreated	Nintedanib (200 mg, bid, 4 week cycle; n=64) or sunitinib (50 mg od, 4 weeks on 2 weeks off cycle; n=32)	PFS: 8.44 months vs 8.38 months, P=0.56 (nintedanib vs sunitinib)	20.37 months vs 21.22 months, P=0.63 (nintedanib vs sunitinib)	Nintedanib and sunitinib: diarrhea (61% vs 50%), nausea (38% vs 34%), fatigue (both 25%), vomiting (16% vs 22%), dermatologic events (8% vs 47%), hypertension (3.1% vs 15.6%), hand-foot syndrome (0% vs 31.3%), stomatitis (0% vs 31.3%)
Phase II ⁷²	Advanced and unresectable hepatocellular carcinoma (HCC), pooled analysis of two randomized trials	Nintedanib (200 mg, bid; n=125) or sorafenib (400 mg, bid; n=63) continuously in 28-day cycle	PFS: 3.7 months vs 3.9 months (nintedanib vs sorafenib groups)	11.4 months vs 11 months (nintedanib vs sorafenib group)	Nintedanib vs sorafenib: diarrhea (10% vs 6%), fatigue (7% vs 2%), anemia (7% vs 6%), increased AST (8% vs 13%), increased ALT (6% vs 8%), thrombocytopenia (5% vs 8%), skin reaction (1% vs 6%), rate of grade \geq 3 AEs (62% vs 87%), AEs leading to dose-reduction (19% vs 51%)
Phase II ⁷³	Metastatic castration-resistant prostate cancer (CRPC); primary endpoint \geq 20% decline in the PSA	Nintedanib 150 mg, bid or nintedanib 250 mg, bid	PFS: 73.5 days vs 76 days; decline in PSA: 0% vs 11.1% (nintedanib 150 mg vs 250 mg)	NR	Gastrointestinal disorders, asthenia, hypertension, and reversible transaminase. Serious AEs were 20% vs 24.4% in nintedanib 150 mg vs 250 mg
Phase II ⁷⁴	Advanced castration-resistant prostate cancer (CRPC)	Nintedanib (250 mg, bid) or afatinib (40 mg, od) or alternating sequential 7-day nintedanib and afatinib (70 mg, od, Combi70, which was reduced to 40 mg od, Combi40)	PFS rate at 12 weeks: 26% nintedanib group, 0% afatinib, and Combi40 groups	NR	Diarrhea, nausea, vomiting, and lethargy
Phase III ⁷⁵	Advanced colorectal cancer (CRC), previously treated	Repeated courses of alternating 7-day treatment periods. First with nintedanib (250 mg, bid) then afatinib (50 mg, od), n=46	PFS: 1.9 months; stable disease: 43.5% (20 patients)	5.5 months	Diarrhea (80.4%), asthenia (47.8%), nausea (43.5%), rash (41.3%)
Phase III ^{76,77}	Metastatic colorectal cancer, previously untreated	Phase I: Nintedanib (200 mg or 150 mg, bid) + mFOLFOX6 q2w; n=15 Phase II: Nintedanib (200 mg, bid) + mFOLFOX6 (q2w), n=85 or bevacizumab (5 mg/kg, q2w) + mFOLFOX6 (q2w), n=41	PFS: 10.5 months vs 15.4 months in nintedanib vs bevacizumab groups	NR	Nintedanib vs bevacizumab: diarrhea (77.6% vs 68.3%), nausea (70.6% vs 58.5%), asthenia (55.3% vs 61%), neutropenia (47.1% vs 36.6%), vomiting (45.9% vs 34.1%), decreased appetite (31.8% vs 41.5%), constipation (18.8% vs 46.3%), serious AEs: (37.6% vs 53.7%)

Abbreviations: AE, adverse events; bid, twice daily; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression free survival; od, once daily; NR, not reported; q2w, once every two weeks.

HR 0.83, $P=0.0359$) for all patients with adenocarcinoma histology. In the total study population, median OS in the docetaxel plus nintedanib group and docetaxel alone group was 10.1 and 9.1 months (HR 0.94, $P=0.2720$), respectively. Nintedanib plus docetaxel had a manageable safety profile as AEs more common in the combination group than in the docetaxel alone group included diarrhea (42.3% vs 21.8%), increases in ALT (28.5% vs 8.4%), increase in AST (22.5% vs 6.6%), nausea (24.2% vs 18%), and vomiting (16.9% vs 9.3%) (Table 1). Most of these AEs were manageable by symptom management and/or dose reduction.⁶⁷ Based on the positive results of this study of 1,300 patients in 27 countries, the European Union granted approval for nintedanib in combination with docetaxel for use in patients with locally advanced, metastatic, or locally recurrent NSCLC with adenocarcinoma histology and progression after first-line chemotherapy. Another Phase III study (LUME-Lung 2) trial investigated the efficacy and safety of nintedanib (200 mg, bid on 2–21 days) in combination with standard pemetrexed (500 mg/m² on day 1) compared with pemetrexed alone (500 mg/m² on day 1) in patients with advanced or recurrent nonsquamous NSCLC after relapse or failure of first-line chemotherapy. In this study, patient enrollment was halted after 713 patients based on a pre-defined futility analysis of investigator-assessed PFS by an independent data monitoring committee. This decision was based on the likelihood that the primary endpoint of centrally assessed PFS would not be met, and was not safety related. Interestingly, a subsequent analysis of the 713 patients who were enrolled, demonstrated that the primary end-point of centrally reviewed PFS was met even though the study was stopped prematurely. This analysis showed that median PFS was significantly improved in the pemetrexed plus nintedanib group compared with pemetrexed alone (4.4 vs 3.6 months, HR 0.83, $P=0.0435$). There was no difference in OS between the two treatment groups (12.2 vs 12.7 months, HR 1.03, $P=0.7921$) and overall response rates were also comparable (9.1% vs 8.3%). There was a higher incidence of grade 3/4 AEs (increase in liver enzymes and gastrointestinal events, overall 58.5% vs 42.3%), serious AEs were 30% vs 32.8% and grade 5 AEs were 9.8% vs 12% in the nintedanib arm vs placebo (Table 1).⁶⁸ A Phase II study (a biomarker-driven study: FGFR1 amplification as predictive of efficacy) of nintedanib in advanced squamous cell lung cancer patients who have failed up to two prior chemotherapy regimens is currently ongoing (NCT01948141). Another placebo-controlled, Phase III trial of nintedanib plus docetaxel in patients with stage IIIB/IV or recurrent adenocarcinoma NSCLC after

failure of first line chemotherapy is also ongoing (LUME-Columbus, NCT02231164).

Nintedanib in ovarian cancer

In a Phase II double-blind, randomized trial of 83 patients who had just completed chemotherapy for relapsed ovarian cancer with evidence of response but at high risk of further early recurrence, patients were randomized to receive either nintedanib 250 mg (n=43) or placebo (n=40), bid, continuously for 36 weeks. The PFS rates at 36 weeks were 16.3% and 5% in the nintedanib and placebo groups, respectively (HR 0.65, 95% CI: 0.42–1.02, $P=0.06$). Grade 3 or 4 AEs were similar between the nintedanib group and placebo (34.9% vs 27.5%, $P=0.49$) (Table 2). This study concluded that nintedanib is well tolerated and it is associated with a potential improvement in survival.⁶⁹

In a Phase III study (LUME-Ovar 1 or AGO-OVAR 12), nintedanib 200 mg bid was added to standard first-line chemotherapy (carboplatin and paclitaxel) followed by nintedanib maintenance therapy for a maximum of 120 weeks as first-line treatment in patients with advanced epithelial ovarian cancer. This study demonstrated a significant improvement in median PFS in the nintedanib plus chemotherapy group compared with placebo/chemotherapy alone (17.3 vs 16.6 months, HR 0.84, 95% CI: 0.72–0.98, $P=0.0239$) (Table 2). In a subgroup analysis, a more pronounced PFS benefit was observed with nintedanib compared with the placebo arm in patients with <1 cm postsurgical residual tumor deposits (27.1 vs 20.8 months, HR 0.75, 95% CI: 0.61–0.92, $P=0.005$). This study is still ongoing.⁷⁰ Three Phase II trials of nintedanib are currently ongoing: one with and without metronomic dose of cyclophosphamide in advanced ovarian cancer (NCT01610869), one in combination with first line chemotherapy with interval debulking surgery in patients with ovarian cancer (NCT01583322), and another in bevacizumab resistant, persistent, or recurrent epithelial ovarian cancer (NCT01669798).

Nintedanib in renal cell carcinoma

The efficacy and safety of nintedanib (200 mg, bid, given in 4 week cycle, n=64) was assessed in a Phase II study of previously untreated advanced RCC patients and compared with the standard of care agent sunitinib (50 mg od, 4 weeks on, 2 weeks off schedule, n=32) as first-line systemic therapy. No significant difference in median PFS was observed between nintedanib and sunitinib treated groups (8.44 vs 8.38 months, HR 1.16, 95% CI: 0.71–1.89, $P=0.56$). Also, no significant difference was observed between the two therapy

groups in terms of median OS (20.37 vs 21.22 months, HR 0.92, 95% CI: 0.54–0.156, $P=0.63$) or 9 month PFS (43% vs 45%, $P=0.85$). The overall incidence of AE (any grade) was similar between nintedanib and sunitinib groups (90.6% vs 93.8%). However, grade 3 or more AEs occurred in 47% of patients after nintedanib compared with 56% after sunitinib. Most common AEs of all grades after nintedanib compared to sunitinib included diarrhea (61% vs 50%), nausea (38% vs 34%), fatigue (both 25%), and vomiting (16% vs 22%). However, dermatologic AEs (8% vs 47%) and other common AEs associated with antiangiogenic agents such as hypertension (3.1% vs 15.6%), hand–foot syndrome (0% vs 31.3%), and stomatitis (0% vs 31.3%), were less common in nintedanib treated patients compared with sunitinib therapy (Table 2).⁷¹

Nintedanib in HCC

Two Phase II studies evaluated the efficacy and safety of nintedanib (200 mg, bid) in comparison with sorafenib (400 mg, bid) continuously in 28-day cycle, in patients with unresectable, advanced HCC in Europe (NCT0100434003) and Asia (NCT00987935). Pooled analysis of these two trials (180 patients) in Caucasian and Asian patients showed similar efficacy between nintedanib and sorafenib therapy groups in terms of median time to progression (TTP; 3.7 vs 3.9 months, HR 1.31, 95% CI: 0.89–1.91), median OS (11.4 vs 11 months, HR 0.91, 95% CI: 0.65–1.29), and overall response rates (4% vs 5%). The most frequent (>5% of patients in any group) grade ≥ 3 AEs after nintedanib compared to sorafenib included diarrhea (10% vs 6%), fatigue (7% vs 2%), anemia (7% vs 6%), increased AST (8% vs 13%) and ALT (6% vs 8%), thrombocytopenia (5% vs 8%), and skin reaction (1% vs 6%). However, the rates of grade ≥ 3 AEs (62% vs 87%) and AEs leading to dose reduction (19% vs 51%) were lower in the nintedanib group compared to sorafenib (Table 2).⁷²

Nintedanib in prostate cancer

Two doses of nintedanib (150 and 250 mg, bid) were evaluated in a randomized Phase II study in metastatic castration-resistant prostate cancer patients after progression with docetaxel.⁷³ The primary endpoint, prostate-specific antigen (PSA) response rate ($\geq 20\%$ decline in PSA from baseline), was 0% in the nintedanib 150 mg group and 11.1% in the nintedanib 250 mg group ($P=0.12$). However, nintedanib at 250 mg showed at least 50% PSA reduction in 5.6% patients and the rate of PSA increase in this group was significantly decelerated on treatment vs before treatment ($P=0.002$). The median PFS was similar between the two groups (73.5 vs 76 days, $P=0.3$). AEs included gastrointestinal disorders,

asthenia, hypertension, and reversible transaminase elevation. The incidence of serious AEs for nintedanib 150 mg vs 250 mg, were 20% vs 24.4% (Table 2).⁷³

Another Phase II study evaluated nintedanib and afatinib, an ErbB family blocker, in advanced castration-resistant prostate cancer patients; dosing included nintedanib (250 mg, bid, $n=27$), afatinib (40 mg od, $n=13$), or alternating sequential 7-day nintedanib (250 mg, bid) and afatinib (70 mg od; Combi70), which was later termed Combi40 ($n=10$) because the afatinib dose was reduced to 40 mg od due to AEs. The primary end-point of the study, the progression-free rate at 12 weeks was 26% for nintedanib and 0% for the afatinib and Combi40 groups (Table 2). However, the median TTP was 31 days (95% CI: 29–84) for nintedanib monotherapy, 29 days (95% CI: 29–54) for afatinib monotherapy, and 57 days (95% CI: 29–78) for Combi40. The median PFS results were the same as for median TTP. Two patients had a $\geq 50\%$ decline in PSA, one each in the nintedanib and the Combi40 groups. The most common drug-related AEs were diarrhea, nausea, vomiting, and lethargy; the majority of patients (>90%) in each group had at least one therapy-related AE. Rash was more frequent with afatinib and elevation in transaminase was more frequent with nintedanib monotherapy. The frequency of therapy-related AEs did not increase in Combi40 compared with monotherapy.⁷⁴

Nintedanib in CRC

In a Phase II study an alternating regimen of nintedanib (250 mg, bid) and then afatinib (50 mg, od) was evaluated in patients with advanced pretreated CRC. In this study, the best response was SD in 20 patients (43.5%) but no objective responses were observed. Seven patients (15.2%) remained progression-free for ≥ 16 weeks. Median PFS was 1.9 months; median OS was 5.5 months. The most common AEs were diarrhea (80.4%), asthenia (47.8%), nausea (43.5%), and rash (41.3%) (Table 2).⁷⁵ In another Phase II study, nintedanib plus mFOLFOX6 compared to bevacizumab plus mFOLFOX6 were evaluated in 126 patients with previously untreated metastatic CRC. The primary endpoint of this study was the kaplan-meier (KM) estimate of PFS at 9 months, which was 62.1% for the nintedanib regimen and 70.2% for the bevacizumab regimen; a numerical difference in PFS between treatments was -8.1% (95% CI: -27.8 to 11.5). The results for best confirmed overall response were 63.5% (95% CI: 52.4–73.7) for the nintedanib and 56.1% (95% CI: 39.7–71.5) for the bevacizumab group. SD frequency was lower in the nintedanib than in the bevacizumab group (27.1% vs 36.6%). The final analysis of this study demonstrated that the

median PFS was 10.5 months in the nintedanib group (95% CI: 9.4–12.4) and 15.4 months in the bevacizumab group (95% CI: 9.6–18.9), which contrasted with a median PFS at the time of the interim analysis (nintedanib: 10.6 months, bevacizumab: 9.2 months). The most frequent AEs (>40% in either group) in the nintedanib vs bevacizumab groups were diarrhea (77.6% vs 68.3%), nausea (70.6% vs 58.5%), asthenia (55.3% vs 61%), neutropenia (47.1% vs 36.6%), vomiting (45.9% vs 34.1%), decreased appetite (31.8% vs 41.5%), and constipation (18.8% vs 46.3%). Incidences of AEs leading to discontinuation of nintedanib or bevacizumab, with or without discontinuation of mFOLFOX, were 27.1% for nintedanib and 31.7% in the bevacizumab group. The overall incidence of serious AEs was lower for the nintedanib group than for the bevacizumab group (37.6% vs 53.7%) (Table 2).^{76,77} A double-blind, randomized, Phase III study of nintedanib vs placebo in refractory CRC is currently ongoing (NCT02149108). Another Phase I/II study of nintedanib in combination with capecitabine in treating patients with refractory metastatic CRC is currently ongoing (NCT02393755).

Nintedanib in breast cancer

In a Phase I study, the combination of nintedanib (150 mg, bid) with a standard preoperative treatment for breast cancer (weekly 80 mg/m² paclitaxel, followed by adriamycin plus cyclophosphamide) was evaluated in HER-2-negative breast cancer patients.⁷⁸ At this dose level, the observed toxicity was not different from that reported with paclitaxel alone therapy. The dose-limiting toxicity was transaminase elevation. The dose intensity of both initial drugs, nintedanib and paclitaxel, was 99.9% and 97.4%, respectively. Despite the low number of patients (n=8), the efficacy at this dose level was very promising with a pathological complete response of 50%. Based on these trial data, a randomized Phase II study of docetaxel with or without nintedanib in patients receiving a second-line of chemotherapy for neoadjuvant HER-2-negative breast cancer patients is ongoing (NCT01658462). Another Phase II study of nintedanib monotherapy for patients with metastatic HER2-negative inflammatory breast cancer is also ongoing (NCT02389764).

Based on promising efficacy and safety results of nintedanib in the above-mentioned solid tumors, nintedanib is currently under investigation in several other solid tumors including thyroid cancer (NCT01788982), neuroendocrine tumors (NCT02399215), cervix cancer (NCT02009579), endometrial cancer (NCT01225887), esophagogastric cancer (NCT02234596), urothelial carcinoma (NCT02278978), and glioblastoma (NCT01666600).

Conclusion

Increased understanding of the complexity of tumor angiogenesis pathways indicated the importance of multitargeted antiangiogenic agents to increase tumor response and overcome or delay resistance development. By simultaneous targeting of VEGF, FGF, and PDGF signaling, nintedanib may offer a better approach for the treatment of several solid tumors. The clinical efficacy of nintedanib in combination with docetaxel in NSCLC was recognized by its approval in the European Union. Nintedanib also demonstrated rather encouraging clinical efficacy and tolerability data in patients with different solid tumors, and several additional clinical studies are currently ongoing. There is a good possibility that nintedanib will be approved for at least some of these tumor types in the near future. However, more understanding of nintedanib's molecular mechanism of action and identifying molecular biomarkers to predict nintedanib response is highly desired to maximize clinical benefits.

Disclosure

The authors report no conflicts of interest in this work.

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