PHASE I STUDY OF AFATINIB (BIBW 2992), AN ERBB FAMILY BLOCKER PLUS NINTEDANIB (BIBF 1120), A TRIPLE ANGIOKINASE INHIBITOR, IN PATIENTS WITH ADVANCED SOLID TUMOURS

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ABSTRACT (UPDATED)

Background: Inhibiting multiple signalling pathways with the combination of afatinib, an oral irreversible ErbB Family Blocker, and nintedanib, an oral triple angiokinase inhibitor of vascular endothelial growth factor receptor, platelet-derived growth factor receptor and fibroblast growth factor receptor may lead to better efficacy.

Methods: This Phase I study used a modified 3+3 design to determine the maximum tolerated dose (MTD) of afatinib given once a day (q.d.) continuous with dose escalating from 10 to 40 mg in combination with fixed-dose nintedanib (200 mg twice a day (b.i.d.) reduced to 150 mg b.i.d. after protocol amendment) in a 28-day cycle. When ≥2 out of 3–6 patients experienced a dose-limiting toxicity (DLT) at a given dose level, the same dose was then explored using afatinib intermittently (every other week) with dose escalation up to 40 mg. Secondary endpoints were safety, efficacy, pharmacokinetics (PK) and circulating tumour cells (CTCs) analysis. Treatment continued until disease progression or intolerability.

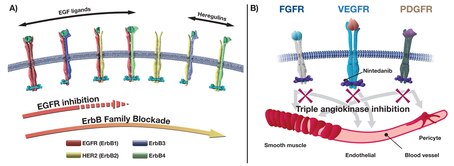
Results: Forty-five patients with heavily pretreated advanced solid tumours were included: 26 men; median age 56 years (range 37–73); main cancer types: Non-small cell lung, colorectal, breast, melanoma and ovary. Main drug-related adverse events were diarrhoea, asthenia, nausea, vomiting and transaminase elevation. Two MTDs were established: Afatinib 40 mg q.d. (intermittent) with nintedanib 150 mg b.i.d. and afatinib 30 mg q.d. (continuous) with nintedanib 150 mg b.i.d. **(Table 3)**. Antitumour activity was observed with partial responses (RECIST) in two patients (triple-negative breast cancer, and head and neck squamous cell carcinoma) and stable disease in 27 patients (lasting >12 weeks in 11 patients). PK data showed no drug–drug interaction. CTC analysis is also presented **(Table 4)**.

Conclusion: At MTD the combination of afatinib with nintedanib showed a manageable safety profile and evidence of antitumour activity in different heavily pretreated tumour types.

INTRODUCTION

- Cancer cells use multiple pathways for proliferation; therefore, targeting more than one signalling pathway may overcome anti-apoptotic/resistance mechanisms and result in increased cell death
- Preclinical models demonstrated synergistic tumour growth inhibition with the combination of afatinib (BIBW 2992), an ErbB Family Blocker,[1,2] and nintedanib (BIBF 1120), a triple angiokinase inhibitor,[3] when compared with either single agent alone[4] **(Figure 1)**

Figure 1. Mechanism of action of afatinib, an ErbB Family Blocker (A) and nintedanib, a triple angiokinase inhibitor (B)



EGF(R) = epidermal growth factor (receptor); HER = human epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; VEGFR = vascular endothelial growth factor receptor; PDGFR = platelet-derived growth factor receptor.

- Two Phase II studies combining afatinib and nintedanib, one in hormone-refractory prostate cancer[5] and one in advanced colorectal cancer[6] using different dosing schedules, showed manageable safety profiles
- Here, we report data from a Phase I study evaluating a new dosing schedule

OBJECTIVES

- **Primary endpoint:** To determine the maximum tolerated dose (MTD) of the combination of afatinib and nintedanib administered concomitantly
- **Secondary endpoints:** Safety, efficacy, pharmacokinetics (PK) and circulating tumour cells (CTCs) analysis

METHODS

Main eligibility criteria

- Confirmed histological or cytological diagnosis of advanced solid tumours not amenable to established treatments
- Men/women patients aged ≥18 years
- Life expectancy of ≥3 months
- Eastern Cooperative Oncology Group performance status 0 or 1
- Adequate organ function
- No significant gastrointestinal tract or cardiovascular disease, or pre-existing interstitial lung disease, or active infection
- No untreated or symptomatic brain metastases
- No prior EGFR or HER2 inhibitor or anti-angiogenic agent within the last 4 weeks
- No anticoagulation, except low-dose heparin and/or heparin flush
- Written informed consent

Study design

- Phase I, open-label, dose-escalation study using a modified 3+3 design
  - Two schedules of afatinib q.d. were explored in combination with a fixed dose of nintedanib b.i.d.
  - ***Continuous schedule:*** afatinib was given orally q.d. (dose escalation from 10 to 40 mg) concomitantly with nintedanib given orally b.i.d. continuously
  - When ≥2 out of 3–6 patients experienced a dose-limiting toxicity (DLT) at a given dose level, the same dose level was then explored using afatinib intermittently every other week
  - ***Intermittent schedule:*** afatinib was given orally q.d., every other week (dose escalation up to 40 mg) with nintedanib given orally b.i.d. continuously
- The MTD was defined as the highest dose of afatinib (continuous or intermittent) and nintedanib at which <2/6 patients experienced a DLT. The MTD could be defined for a continuous and/or an intermittent dosing schedule of afatinib
- Nintedanib was initially administered at 200 mg b.i.d. but no MTD was determined. After protocol amendment, the dose was reduced to 150 mg b.i.d. and a second dose-escalation phase was conducted starting with afatinib at 30 mg q.d.
- One treatment cycle was 28 days

DLTs (according to Common Terminology Criteria for Adverse Events (CTCAE))

- Grade 4 neutropenia that is uncomplicated lasting for >7 days
- Grade 3/4 neutropenia of any duration associated with fever >38.5°C
- Platelets <25,000/µL or Grade 3 with bleeding requiring transfusion
- Grade ≥3 non-haematological AEs (except well-controlled nausea/vomiting or diarrhoea)
- Grade ≥2: Decrease in cardiac left ventricular function; worsening of renal function; diarrhoea, or vomiting or nausea persisting for ≥7 days, despite supportive treatment
- Drug-related liver toxicity except GGT:
  - AST/ALT/ALP >5 x ULN if total bilirubin ≤1.5 x ULN
  - AST/ALT/ALP >2.5 x ULN if associated with total bilirubin >1.5 x ULN
  - ALP ≥10 x ULN in patients with Grade 2 ALP (>2.5–5 x ULN) at baseline
- Grade ≥2 drug-related AEs leading to treatment interruption ≥14 consecutive days

AE = adverse events; GGT = gamma-glutamyltransferase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; ULN = upper limit of normal.

Safety

- Adverse events (AEs) were evaluated according to National Cancer Institute CTCAE v. 3.0

Efficacy

- Response assessment according to Response Evaluation Criteria In Solid Tumors (RECIST 1.1)

PK

- Samples were collected immediately before the morning drug administration on Days 1, 8, 15, 22 and 28 (Cycle 1) and Days 42 and 56 (Cycle 2). Afatinib and nintedanib drug concentrations were determined by validated high-performance liquid chromatography – tandem mass spectrometry assays

CTCs

- For determination of CTCs, 7.5 mL blood samples were drawn in CellSave® Blood Collection tubes (Veridex, Raritan, NJ, USA) at baseline and at Days 15, 30 and 60
  - The samples were analyzed with CellSearch® (Veridex, Raritan, NJ, USA) and reported as number of CTCs in 7.5 mL of blood
  - Patients were categorized as having either unfavourable (≥5 CTCs/7.5 mL) or favourable (<5 CTCs/7.5 mL) CTC counts. This dichotomous cut-off has been previously defined in several studies with cancer patients[7,8]

RESULTS

- From October 2009 to January 2012, a total of 45 patients with metastatic solid tumours were recruited into the study at a single site in France
- Patient demographics are presented in **Table 1**
- The majority (73%) of patients received at least four prior chemotherapy lines

Table 1. Summary of patient demographic and disease characteristics

Characteristic	Patients N=45
Age, years Median (range)	56.0 (37–73)
Gender, % Male/female	58/42
Eastern Cooperative Oncology Group performance status, % 0/1	31/69
Tumour type, n (%) Colon Non-small cell lung cancer Ovary Breast Melanoma Head and neck squamous cell carcinoma Pancreas Neuroendocrine Other*	9 (20) 6 (13) 6 (13) 5 (11) 4 (9) 3 (7) 2 (4) 2 (4) 8 (18)
Afatinib administration, n (%) Continuous Intermittent	26 (58) 19 (42)

*Other tumour types include one patient each with Ewing sarcoma, unknown primary, biliary, bladder, pleura, thyroid, oesophagus and kidney.

Safety

Time on treatment

- Overall median time on treatment was 60 days (range 7–174)
- Ten patients received treatment for ≥90 days

DLT assessment in Cycle 1 and determination of the MTD

- **Table 2** shows the dose-escalation cohorts
- Overall, there were 12 DLTs reported in eight patients receiving afatinib in a continuous schedule and five DLTs in four patients receiving afatinib in an intermittent schedule

Table 2. Dose escalation and patients with DLTs (first cycle)

Cohort number	Afatinib dose (mg q.d.)/ schedule	Nintedanib (mg b.i.d.)	Patients entered/ evaluable	Patients with DLT	DLT (CTCAE grade)
1	10/C	200	3/3	0	
2	20/C	200	3/3	0	
3	30/C	200	8/7	3	1. G3 diarrhoea 2. G3 transaminase elevation/diarrhoea 3. G3 diarrhoea
4	40/C	200	3/3	3	1. G3 diarrhoea 2. G3 transaminase elevation 3. G3 transaminase elevation/G2 creatinine increase
5	30/I	200	6/5	2	1. G3 diarrhoea/G2 creatinine increase 2. G3 transaminase elevation
6	40/I	200	6/5	2	1. G3 dehydration 2. G4 transaminase elevation
7	40/C	150	3/3	2	1. G3 diarrhoea/dehydration/renal failure 2. G3 renal failure
8	40/I	150	7/6	0	MTD
9	30/C	150	6/6	0	MTD

C = continuous; G = Grade; I = intermittent.

→ Two MTDs were determined: Nintedanib 150 mg b.i.d. and afatinib 30 mg q.d. continuously or 40 mg q.d. every other week

Overall safety

- The most frequently observed AEs are depicted in **Table 3**
- There were no Grade 5 treatment-related AEs
- Nine and eight patients discontinued afatinib and nintedanib due to AEs, respectively
- After dose reduction of nintedanib from 200 mg b.i.d. to 150 mg b.i.d., no Grade >2 transaminase elevations were reported

Table 3. Main treatment-related AEs (≥20% incidence)

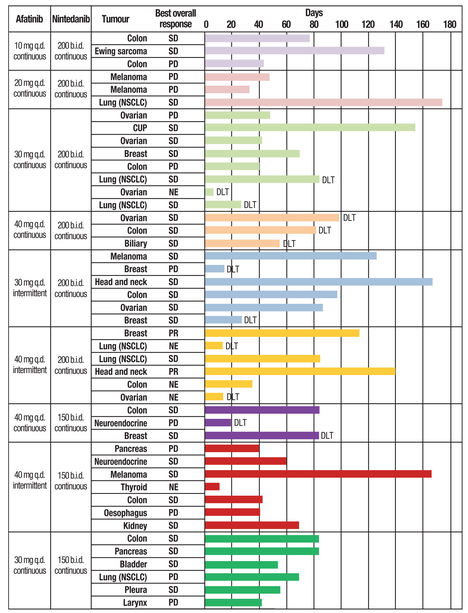
	Grade 1	Grade 2	Grade 3	Grade 4	All grades*
Number of patients, n (%)	**44 (100)**	**44 (100)**	**44 (100)**	**44 (100)**	**44 (100)**
Diarrhoea	9 (20)	15 (34)	19 (43)	0	43 (98)
Nausea	23 (52)	6 (14)	0	0	29 (66)
Asthenia	10 (23)	15 (34)	3 (7)	0	28 (64)
Vomiting	14 (32)	13 (30)	0	0	27 (61)
Decreased appetite	14 (32)	7 (16)	4 (9)	0	25 (57)
Folliculitis	19 (43)	4 (9)	0	0	23 (52)
Epistaxis	17 (39)	0	0	0	17 (39)
Rhinitis	16 (36)	1 (2)	0	0	17 (39)
Dry skin	16 (36)	0	0	0	16 (36)
ALT increased	7 (16)	3 (7)	5 (11)	0	15 (34)
AST increased	7 (16)	3 (7)	3 (7)	0	13 (30)
Hypokalaemia	6 (14)	0	4 (9)	1 (2)	11 (25)
Cytolytic hepatitis	4 (9)	5 (11)	2 (5)	0	11 (25)
Rash	10 (23)	0	0	0	10 (23)
Mucosal inflammation	6 (14)	4 (9)	0	0	10 (23)
Dehydration	0	4 (9)	5 (11)	0	9 (20)

*There were no Grade 5 treatment-related AEs.

Efficacy

- Partial responses per RECIST 1.1 were observed in one patient with triple negative breast cancer and in one patient with head and neck squamous cell carcinoma **(Figure 3)**; both patients were in Cohort 6 (intermittent afatinib 40 mg q.d. with 200 mg nintedanib b.i.d.) **(Figure 2)**
- Stable disease was reported in 27 patients (lasting >12 weeks in 11 patients)
- The disease control rate assessed by complete/partial response + stable disease was 64%
- The waterfall plot shows best percent change from baseline in tumour target lesions **(Figure 4)**

Figure 2. Dose-escalation scheme, DLTs, treatment duration and best overall response



SD = stable disease; PD = progressive disease; NSCLC = non-small cell lung cancer; CUP = cancer of unknown primary; NE = not evaluable; PR = partial response.

Figure 3. Partial response (–58% change in tumour lesions) in patient with squamous cell carcinoma of the epiglottis (head and neck squamous cell carcinoma)

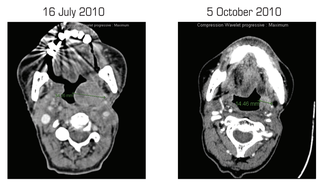
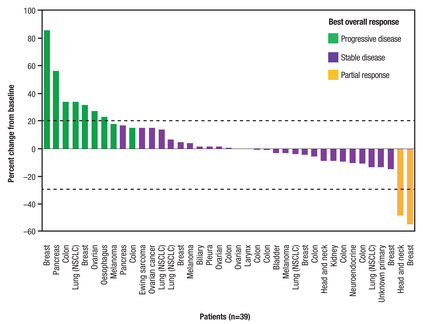


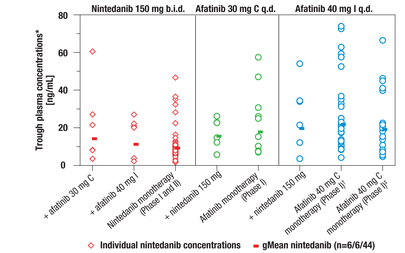
Figure 4. Waterfall plot of target lesions: Best percent change from baseline and best overall response



PK

- PK analysis showed no drug–drug interaction between either dosing schedule of afatinib and nintedanib **(Figure 5)**

Figure 5. Individual and geometric mean (gMean) plasma concentration–time values of afatinib and nintedanib (MTD cohorts)



*At 336 h (Day 15). †From meta-analysis of afatinib in Phase I studies. ‡From afatinib monotherapy arm in another Phase I study analyzing the nintedanib/afatinib combination. gMean = geometric mean.

CTCs

- At baseline, there were 10 (26%) patients with an unfavourable CTC count (≥5 CTCs). After 1 month of treatment, only four (12%) patients had an unfavourable CTC count **(Table 4)**
- Most patients with SD lasting ≥12 weeks had a favourable CTC count both at baseline and throughout the study

Table 4. Exploratory CTC analyses

	Day 0	Day 15	Day 30	Day 60
Patients*, n	40	40	40	40
CTC samples, n	39	37	34	21
<5 CTC, n (%)	29 (74.4)	31 (83.8)	30 (88.2)	16 (76.2)
≥5 CTC, n (%)	10 (25.6)	6 (16.2)	4 (11.8)	5 (23.8)
Patients* with stable disease ≥12 weeks	9	9	9	9
CTC samples, n	9	8	9	9
<5 CTC, n (%)	9 (100)	8 (100)	9 (100)	8 (88.9)
≥5 CTC, n (%)	0	0	0	1 (11.1)

*Excluding patients with non-epithelial tumours.

CONCLUSIONS

- The MTDs were defined as afatinib 40 mg q.d. every other week plus nintedanib 150 mg b.i.d. or afatinib 30 mg q.d. continuously plus nintedanib 150 mg b.i.d.
- At the MTDs, the AEs of afatinib combined with nintedanib were generally mild-to-moderate and manageable
- PK analysis suggests no drug–drug interactions between afatinib and nintedanib
- Antitumour activity was observed, with two partial responses and a disease control of 64% in this heavily pretreated patient population

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