Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-005364-14	**Synopsis No.:**
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Title of trial:	A phase I-II study of BIBF 1120 and Folfox compared to Bevacizumab and Folfox in first line metastatic colorectal cancer patients
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study conducted in 27 centres in 5 countries in Western Europe (Belgium, France, Germany, Italy, and Spain)
Publication (reference):	Data from the interim report [U12-1098-01], dated 27 Jan 2012, were published: Van Cutsem E, Prenen H, Guillen-Ponce C, et al. Eur J Cancer 2011;47 (Suppl 2):8-9 [P11-11862]
Clinical Phase:	I/II
Objectives:	The primary objective of this study was to evaluate the progression-free survival (PFS) rate at 9 months of nintedanib in combination with a modified FOLFOX regimen (mFOLFOX6) compared to mFOLFOX6 combined with bevacizumab in first line patients with metastatic colorectal cancer (CRC). Secondary efficacy objectives were to determine overall survival, PFS, overall response rate, resection rate, and tumour shrinkage. In addition, safety, the appropriate dose of nintedanib in combination with mFOLFOX6, and the pharmacokinetic characteristics of nintedanib (and clinically relevant metabolites) and of the components of mFOLFOX6 (5-fluorouracil [5-FU], and oxaliplatin) were to be determined. Exploratory investigations of biomarkers that might be used to predict response to anti-angiogenic treatments were performed (and reported separately).
Methodology:	This was a multicentre open-label, randomised, parallel-group, phase I/II trial to determine the maximum tolerated dose (MTD) then to assess safety, efficacy and pharmacokinetics. Patients were randomised 2:1 to nintedanib:bevacizumab, each in addition to mFOLFOX6. Treatment could continue until disease progression or start of a new anticancer therapy. Patients who discontinued all study medications for reasons other than progressive disease were to be followed-up until they died, progressed, or received other anticancer therapy. After a follow-up visit 28 days after the last dose of trial medication, visits were performed as scheduled for all patients in the trial. After disease progression,

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Methodology (continued):	patients were to be followed up at 90-day intervals to assess vital status. During Phase I of the trial, the first 12 to 18 patients randomised to nintedanib were treated with nintedanib in accordance with a standard 3+3 dose escalation design to determine the maximum tolerated dose (MTD) for nintedanib (150 mg or 200 mg twice daily [b.i.d.]) administered with mFOLFOX6. Efficacy, safety, and pharmacokinetics were also assessed. For all patients, the Phase II part of the trial comprised the period from the start of Phase I until the last patient had died, progressed, received other anticancer therapy, or been lost to follow-up. Safety, efficacy, and pharmacokinetics were assessed during Phase II. The patients in nintedanib group were treated with the recommended dose determined in phase I part.
No. of patients:	
planned:	entered: 120 (80 into the nintedanib group; 40 into the bevacizumab group)
actual:	enrolled: 136 (enrolled = screened) entered: 128 (entered = randomised) Treatment nintedanib plus mFOLFOX6: entered: 86 treated: 85 analysed (for primary endpoint): 85 analysed for nintedanib MTD: 12 analysed for pharmacokinetics: 13 for Phase I; 65 for Phase II Treatment bevacizumab plus mFOLFOX6: entered: 42 treated: 41 analysed (for primary endpoint): 41
Diagnosis and main criteria for inclusion:	Patients with confirmed, unresectable, metastatic CRC who had not yet received first-line therapy were eligible to participate.
Test product:	nintedanib capsules
dose:	150 mg b.i.d. or 200 mg b.i.d.
mode of admin.:	Oral
batch no.:	[redacted]

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Reference therapy:	Bevacizumab
dose:	5 mg/kg every other week
mode of admin.:	Intravenous (i.v.) infusion
batch no.:	[redacted]
Additional therapy:	Both nintedanib and bevacizumab were administered in combination with mFOLFOX6 (oxaliplatin, leucovorin, and 5-FU), given every other week.
dose:	Oxaliplatin: 85 mg/m² infusion over 2 hours *l*-leucovorin 200 mg/m^2 or *d,l*-leucovorin 400 mg/m² infusion over 2 hours 5-FU: 400 mg/m² bolus and 2400 mg/m² continuous infusion over 46 hours
mode of admin.:	i.v.
batch no.:	Not available; commercially available products supplied at the study sites were used.
Duration of treatment:	11 to 12 months, until disease progression or non-tolerable toxicity
Criteria for evaluation:	
Efficacy/clinical pharmacology:	Efficacy: Tumour response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. The primary efficacy endpoint was PFS rate at 9 months, estimated using the Kaplan-Meier (KM) method. Other endpoints included overall survival, PFS, objective response rate, overall response rate, resection rate, and tumour shrinkage. Levels of carcinoembryonic antigen (CEA) were measured. Eastern Cooperative Group (ECOG) performance status was assessed. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires EORTC-QLQ-30 and EORTC-QLQ-CR38. Exploratory investigations of biomarkers that might be used to predict response to anti-angiogenic treatments were performed, but not reported in this clinical trial report. Pharmacokinetics: Standard pharmacokinetic (PK) characteristics of nintedanib and its metabolites,

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Efficacy/clinical pharmacology (continued):	oxaliplatin, and 5-FU were assessed to determine the effect (if any) of co-administration of mFOLFOX6 with nintedanib in Phase I of the study. In addition, trough concentrations of nintedanib and its metabolites were assessed during the Phase II part of the study).
Safety:	Assessment of the MTD was based on dose-limiting toxicity (DLT) during the first 2 treatment cycles for patients in the dose escalation phase. Adverse events (AEs), laboratory safety, and vital signs were assessed for all treated patients.
Statistical methods:	All analyses were performed on the treated set (all patients documented to have taken at least 1 dose of the trial drug). The nintedanib patients treated in the dose escalation part of the study and included in the assessment of the MTD were referred to as the MTD set. All data were summarised using descriptive statistics. No formal statistical testing was planned. For the primary efficacy endpoint, the Kaplan-Meier (KM) PFS rate and asymptotic 95% confidence interval (CI) in each group and the difference between the groups were determined. The sample size chosen assumed a 'pick the winner' approach in a superiority trial, assuming nintedanib patients would have a median PFS of 13.5 months and bevacizumab would have a median PFS of 11 months. The number of patients in each group gave a >70% probability of correctly picking nintedanib as 'the winner'. Overall survival was evaluated using the KM method. An unblinded interim analysis was performed 9 months after the last patient entered the trial [U12-1098-01]. The main analysis of the trial described in this report was planned to take place once follow-up to a maximum of 12 months after the last patient had entered the trial was concluded. No adjustment for multiplicity was done as the analyses were of an exploratory nature. The analysis of standard PK parameters was performed according to the Sponsor's standard procedures. In addition, there was an exploratory analysis of the effect of nintedanib on the PK of oxaliplatin and 5-FU.

SUMMARY – CONCLUSIONS:

Efficacy/clinical pharmacology results:	The analyses described below were based on the status at database lock (02 Jan 2012) for the main analysis of this study. <u>Disposition</u> The mean duration on trial (the period from informed consent to trial

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Efficacy/clinical pharmacology results (continued):

termination) was 10.5 months (standard deviation [SD] 6.1) overall and was similar for the nintedanib (10.3 months, SD 5.6) and bevacizumab (10.8 months, SD 7.0) groups.

A total of 97.7% of patients in the nintedanib group discontinued nintedanib and 95.1% discontinued bevacizumab. Fewer patients discontinued nintedanib due to other AEs (21.2%) than discontinued bevacizumab (26.8%). All patients in both groups discontinued oxaliplatin and approximately 98% in both groups discontinued 5-FU. In total, 94.1% of nintedanib patients and 87.8% of bevacizumab patients discontinued from the trial.

Demographic and baseline characteristics

The demographic and baseline characteristics were generally balanced between the groups. Overall, the mean age was 62.8 years; more than half of the patients were male (52.4%). One patient had a level 2 ECOG score (bevacizumab group); all other patients had an ECOG score of 0 or 1.

Oncology history was generally balanced between the groups. Sigmoid colon was most frequently reported as the primary site region (29.4%). For almost half the patients, the differentiation grade was moderate (49.2%), and most had stage IV tumours (80.2%). Local and lymphogenous recurrences were, respectively, reported for 23.8% and 19.8% of patients. Metastatic sites were most commonly reported in the liver (83.3%), lung (36.5%), and distant lymph nodes (25.4%). More than half the patients had previous surgery for colon cancer (58.7%).

Efficacy

For the nintedanib group, the PFS KM estimate at 9 months was 62.1% vs. 70.2% for the bevacizumab group using Peto's variance estimate; difference between treatments -8.1% (95% CI: -27.8, 11.5).

The effect of nintedanib on the PFS KM estimate at 9 months was consistent across all subgroups (i.e. by sex, age <70 years vs. ≥70 years, lactate dehydrogenase level normal vs. abnormal, ECOG score 0 vs. ≥1, tumour site rectal vs. non-rectal, and differentiation grade well or moderate vs. other) and the results were comparable with those of the bevacizumab subgroups.

Results for best confirmed overall responses were similar in the 2 groups (63.5%, 95% CI: 52.4, 73.7 for the nintedanib group; 56.1%, 95% CI: 39.7, 71.5 for the bevacizumab group). The incidence of a confirmed objective response

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Efficacy/clinical pharmacology results (continued):	(complete and partial responses) was higher in the nintedanib than in the bevacizumab group (63.5% vs. 56.1%). Stable disease was less frequent in the nintedanib than in the bevacizumab group (27.1% vs. 36.6%). The median duration of confirmed objective response was 8.2 months for nintedanib patients (range: 1.5 - 17.3 months) and 12.4 months for bevacizumab patients (range: 1.7 - 21.4 months). KM estimates of median overall survival could not be calculated because the number of deaths was insufficient. The frequencies of resection were 15.3% in the nintedanib group and 22.0% in the bevacizumab group. The rate of complete resection (R0) was 7.1% for the nintedanib group and 17.1% for the bevacizumab group. KM estimates of resection rates were 22.4% (95% CI: 10.7, 34.0) for the nintedanib group and 24.5% (95% CI: 16.6, 32.4) for the bevacizumab group. Median PFS was 10.5 months in the nintedanib treatment group (95% CI: 9.4, 12.4) and 15.4 months in the bevacizumab treatment group (95% CI: 9.6, 18.9). <u>Phase I pharmacokinetics</u> Concomitant administration of 200 mg b.i.d. nintedanib for 15 days did not change the pharmacokinetics of oxaliplatin or the pharmacokinetics of 5-FU, both components of mFOLFOX6. Concomitant administration of mFOLFOX6 did not change the pharmacokinetics of nintedanib, BIBF 1202 and BIBF 1202-glucuronide. <u>Phase II pharmacokinetics</u> During long term treatment of patients with metastatic CRC with 200 mg b.i.d. nintedanib in combination with mFOLFOX6, trough plasma concentrations of nintedanib, BIBF 1202, and BIBF 1202-glucuronide remained stable over the observed treatment period.
Safety results:	<u>MTD</u> The MTD was 200 mg b.i.d. <u>Treatment exposure</u> Mean treatment exposure was similar in the 2 groups (nintedanib: 236.1 days; bevacizumab: 225.8 days). The median number of cycles of 5-FU completed by patients in the nintedanib and bevacizumab groups were, respectively, 14 vs. 13 and 10 vs. 9 for oxaliplatin. In the first 6 months of the study, 65.9% of

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nintedanib patients completed 12 cycles of 5-FU in vs. 63.4% of bevacizumab patients; 32.9% vs. 17.1% completed 12 cycles of oxaliplatin.

Adverse events

All patients had at least 1 AE. Incidences of AEs leading to discontinuation of nintedanib /bevacizumab (with or without discontinuation of mFOLFOX6) were lower in the nintedanib group (27.1%) than in the bevacizumab group (31.7%). The incidence of AEs considered by investigators to be related to study medication was comparable in both groups (nintedanib 98.8% vs. bevacizumab 97.6%). The incidence of pre-specified significant AEs was similar in the BIBF 1120 group (8.2%) and in the bevacizumab group (9.8%).

The frequencies of AEs by system organ class (SOC) as well as by preferred term were generally comparable in the 2 groups. The most frequently reported AEs were gastrointestinal disorders (nintedanib: 95.3%; bevacizumab: 95.1%), general disorders and administration site conditions disorders (89.4%; vs. 90.2%), nervous system disorders (89.4% vs. 85.4%), blood and lymphatic system disorders (61.2% vs. 41.5%), infections and infestations (47.1% vs. 48.8%), metabolism and nutrition disorders (47.1% vs. 58.5%), skin and subcutaneous tissue disorders (36.5% vs. 58.5%), respiratory, thoracic and mediastinal disorders (36.5% vs. 58.5%), vascular disorders (31.8% vs. 46.3%), musculoskeletal and connective tissue disorders (24.7% vs. 36.6%), and psychiatric disorders (17.6% vs. 36.6%). All other AEs by SOC were reported for fewer than 30% of patients in either treatment group.

The most frequently reported AEs by preferred term (incidence >40% in either group) were diarrhoea (nintedanib: 77.6% vs. bevacizumab: 68.3%), nausea (70.6% vs. 58.5%), asthenia (55.3% vs. 61.0%), 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%).

AEs by severity

Most patients had events of CTCAE grade 3/4/5 (nintedanib: 88.2%, bevacizumab: 95.1%). In both groups, the most common grade 3/4/5 AEs were neutropenia (nintedanib 32.9% vs. bevacizumab 24.4%), diarrhoea (15.3% vs. 12.2%), neurotoxicity (14.1% vs. 9.8%), paraesthesia (12.9% vs. 12.2%), and asthenia (10.6% vs. 9.8%).

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Safety results (continued):

AEs of special interest

At least 1 AE of special interest was reported for all patients in both groups. The most common events according to user-defined categories were fatigue (nintedanib 83.5% vs. bevacizumab 85.4%), diarrhoea (77.6% vs. 68.3%), peripheral neuropathies (72.9% vs. 63.4%), and nausea (70.6% vs. 58.5%). AEs with a difference in incidence between groups of >10% were nausea and vomiting (all more frequent for patients in the nintedanib group) and bleeding and rash (more frequent for patients in the bevacizumab group).

Serious AEs

The overall incidence of SAEs was lower for the nintedanib group (37.6%) than for the bevacizumab group (53.7%). The frequencies of SAEs by SOC and by preferred term were generally comparable in the 2 groups within most SOCs and for most preferred terms. The most common SAEs by SOC (>5% in either group) were gastrointestinal disorders (nintedanib: 14.1%; bevacizumab: 29.3%), infections and infestations (9.4% vs. 9.8%), general disorders and administration site conditions (8.2% vs. 2.4%), respiratory, thoracic and mediastinal disorders (7.1% vs. 0.0%), and blood and lymphatic system disorders (3.5% vs. 7.3%). The most common SAEs by preferred term (>2 patients on nintedanib or >1 patient on bevacizumab) were pyrexia (5.9% vs. 0.0%), pulmonary embolism (4.7% vs. 0.0%), diarrhoea (3.5% vs. 7.3%), intestinal obstruction (3.5% vs. 7.3%), and abdominal pain (2.4% vs. 4.9%).

Five patients died during the on-treatment period (2 nintedanib patients; 3 bevacizumab patients). The SAEs leading to death were sepsis, intestinal perforation, hepatic failure and renal failure (all reported by the same nintedanib patient) and aggravated condition (1 nintedanib patient). In the bevacizumab group, the SAEs leading to death were intestinal perforation, intestinal obstruction, and general deterioration of physical health (reported for 1 bevacizumab patient each). In both groups, the most frequent reason for seriousness was hospitalisation or prolonged hospitalisation (nintedanib: 37.6%; bevacizumab: 48.8%).

<u>Other safety parameters</u>

There were no clinically meaningful differences between groups with respect to change from baseline in laboratory parameters. Deteriorations in laboratory parameters, including liver enzymes, were reversible. There were no clinically noteworthy changes in vital signs.

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Conclusions:

The MTD for nintedanib in combination with the mFOLFOX6 chemotherapy in first line metastatic CRC patients was 200 mg b.i.d.

The phase II component of this study was not powered to determine a statistically significant difference between nintedanib and bevacizumab. The primary endpoint was the KM estimate of PFS at 9 months. A numerical difference in PFS at 9 months favoured bevacizumab over nintedanib at the final analysis (-8.1%, 95% CI: -27.8, 11.5), as it had at the interim analysis. This trend was consistent with median PFS observed at the time of the final analysis (nintedanib: 10.5 months; bevacizumab: 15.4 months) and differed from median PFS at the time of the interim analysis (nintedanib: 10.6 months; bevacizumab: 9.2 months). Post-hoc sensitivity analyses indicate that PFS was impacted by censoring rules and higher resection rate for bevacizumab patients and it may limit the robustness of the conclusion.

Nintedanib administered in combination with mFOLFOX6 showed a favourable safety profile that was consistent with previous findings for nintedanib.

There were no marked effects on the pharmacokinetics of oxaliplatin, 5-FU, nintedanib, and the metabolites BIBF 1202 and BIBF 1202-glucuronide during long term treatment with 200 mg b.i.d. nintedanib in combination with mFOLFOX6 in patients with metastatic CRC.

In conclusion, in the 1199.51 study, superiority of nintedanib over bevacizumab as first line combination therapy with mFOLFOX6 was not demonstrated either at the interim or at the main analysis. However, the combination therapy of nintedanib plus mFOLFOX6 showed a favourable safety profile compared with bevacizumab in combination with mFOLFOX6.