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:		**EudraCT No.:** 2008-006831-10	**Synopsis No.:**
Name of active ingredient: Nintedanib (BIBF 1120)		**Page:** 1 of 15	
Module:		**Volume:**	
Report date: 03 NOV 2014	**Trial No. / Doc. No.:** 1199.15 (LUME Ovar 1 / AGO-OVAR 12) / c03055581-01	**Date of trial:** From 09 DEC 2009 to 29 APR 2013 (interim database lock for primary PFS analysis; trial is ongoing)	**Date of revision:** Not applicable

Title of trial:	Multicenter, randomised, double-blind Phase III trial to investigate the efficacy and safety of BIBF 1120 in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in patients with advanced ovarian cancer
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre, multinational trial conducted in 281 centres in 22 countries
Publication (reference):	Du Bois A, Kirstensen G, Ray-Coquard I, et al. AGO-OVAR 12: a randomized placebo-controlled GCIG/ENGOT-intergroup phase III trial of standard frontline chemotherapy +/- nintedanib for advanced ovarian cancer. 18th Int Mtg of the European Society of Gynaecological Oncology (ESGO), Liverpool, 19 - 22 Oct 2013 Int J Gynecol Cancer 2013. 23(8) (Suppl 1):7-8.
Clinical phase:	III
Objectives:	The primary objective of this trial was to evaluate whether nintedanib (BIBF1120), added to standard chemotherapy with paclitaxel and carboplatin for 6 courses and subsequently in monotherapy, is more effective in prolonging progression-free survival (PFS) than placebo in combination with standard chemotherapy of carboplatin/paclitaxel in patients with advanced epithelial ovarian cancer, defined as Fédération Internationale de Gynécologie et d'Obstétrique (FIGO stages) IIB-IV, after primary debulking surgery. A secondary aim was to obtain survival data, safety information, and information on quality of life in patients treated with nintedanib in combination with paclitaxel and carboplatin and with subsequent nintedanib monotherapy.
Methodology:	Two-arm, randomised, double-blind, placebo-controlled, parallel-group comparison of nintedanib plus chemotherapy versus placebo plus chemotherapy.

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No. of patients:	
planned:	Entered: 1300 patients (nintedanib: 867 patients; placebo: 433 patients)
actual:	Enrolled (i.e. screened): 1503 patients Entered (i.e. randomised): 1366 patients Treated: 1352 patients *Nintedanib (in addition to standard first-line therapy with paclitaxel and carboplatin):* Entered (i.e. randomised): 911 patients Treated: 902 patients Analysed (for primary endpoint): 911 patients *Placebo (in addition to standard first-line therapy with paclitaxel and carboplatin):* Entered (i.e. randomised): 455 patients Treated: 450 patients Analysed (for primary endpoint): 455 patients Please note that patients who received carboplatin/paclitaxel only (12 patients in the nintedanib groups and 5 patients in the placebo group) were assigned to their randomised treatment and are included above.
Diagnosis and main criteria for inclusion:	Patients with histologically proven epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer of advanced stage (FIGO stage IIB to IV), who had either prior debulking surgery or, if debulking surgery was considered not appropriate, diagnosis confirmed by histology and no planned surgery prior to disease progression
Test product:	Nintedanib soft gelatine capsule (in addition to standard first-line therapy with paclitaxel and carboplatin)
dose:	200 mg twice daily (bid) with stepwise dose reductions to 150 mg bid or 100 mg bid (according to the protocol-defined dose reduction scheme) if required
mode of admin.:	Oral
batch no.:	[redacted]

Reference therapy:	Placebo soft gelatine capsule (in addition to standard first-line therapy with paclitaxel and carboplatin)
dose:	Not applicable
mode of admin.:	Oral
batch no.:	[redacted]
Concomitant therapy:	Paclitaxel
dose:	175 mg/m^2 of body surface area administered once (on Day 1) of a 3-week treatment course (if necessary the dose could be reduced to 135 mg/m^2)
mode of admin.:	Intravenous infusion (over 3 hours)
batch no.:	[redacted]
Concomitant therapy:	Carboplatin
dose:	Calculated according to glomerular filtration rate (GFR) with a target dose area under the curve (AUC) of 5 mg/mL·min or 6 mg/mL·min (if necessary, a dose reduction to AUC 4 mg/mL·min was allowed)
mode of admin.:	Intravenous infusion (over 30 to 60 min) administered once (on Day 1) of a 3-week treatment course
batch no.:	[redacted]

Duration of treatment:

All patients were to be treated with standard combination chemotherapy (paclitaxel and carboplatin) every 21 days for 6 courses. Nintedanib/placebo was administered as an oral daily dose of 200 mg in the morning and 200 mg in the evening after a meal, except on the days of intravenous administration of chemotherapy. Combination therapy was supposed to start after wound healing and within 4 to 10 weeks after debulking surgery. If i.v. chemotherapy treatment was indicated to commence prior to 4 weeks after surgery, nintedanib/placebo was to be started in Course 2.

Oral treatment with nintedanib / placebo was to continue uninterruptedly as monotherapy after completion of 6 courses of combination chemotherapy, for a maximum duration of 120 weeks after randomisation, unless progression of the disease occurred earlier.

Criteria for evaluation:

Efficacy:

Primary endpoint:

The primary endpoint was PFS as assessed by the investigator according to modified Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST, [R09-0262]) and additional clinical criteria. PFS was calculated as the time from randomisation to the date of disease progression, or to the date of death, whichever occurred first.

The primary analysis of PFS was to be performed when approximately 753 patients had experienced a PFS event, i.e. disease progression as determined by the investigator or death. This time point defined the interim database lock (iDBL) date for primary PFS analysis, which was derived as 29 April 2013. Only data collected until iDBL for primary analysis are summarised herein.

Key secondary endpoint:

- PFS, based on investigator assessment, as for the primary endpoint, with the exception that progressive disease for the key secondary endpoint could only be declared based on modified RECIST 1.1 criteria

Efficacy (continued):	*Secondary endpoints* • Overall survival (OS) • Time to tumour marker "progression" (CA-125) • Objective response in patients with surgeon's assessment of macroscopic residual tumour after surgery (objective tumour response defined as either complete response [CR] or partial response [PR] in patients with at least 1 target lesion reported at baseline) • Patient reported outcome and health-related quality of life measured bystandardised questionnaires: Change in abdominal/gastro-intestinal symptoms over time (scale composite of items 31 to 37 of the EORTC QLQ-OV28) and change of the Global Health Status/ QoL scale score (composite of items 29 and 30 of the EORTC QLQ-C30) over time A final analysis of efficacy will be performed approximately 60 months after the last patient has entered the trial. At that point of time, overall survival will be analysed. The analysis of PFS as assessed by the investigator will also be updated.
Safety:	Safety was assessed based on the incidence and intensity of adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and changes in safety laboratory parameters and vital signs. Data collected until iDBL for primary PFS analysis (29 April 2013) were included herein.
Statistical methods:	The primary analysis was the analysis of PFS as assessed by the investigator according to modified Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST, [R09-0262]) and additional clinical criteria. The stratified log-rank test was used for PFS to test for the effect of nintedanib at the 2-sided alpha-level of 0.05. Stratification factors at randomisation were the amount of residual tumour after surgery (no residual tumour [= 0 cm] vs. macroscopic residual disease [>0 cm]), FIGO stage (IIB - III vs. IV), and the carboplatin target dose applied at the site (AUC 5 mg/mL·min vs. AUC 6 mg/mL·min).

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SUMMARY – CONCLUSIONS:

Efficacy results:

Disposition, demographics and baseline characteristics

Overall, 1366 patients were randomised 2:1 to receive either nintedanib (911 patients) or placebo (455 patients), in addition to standard chemotherapy of carboplatin and paclitaxel in both groups. A total of 902 patients in the nintedanib arm and 450 patients in the placebo arm were treated; all of the treated patients had at least 1 course of chemotherapy. Twelve patients in the nintedanib arm and 5 patients in the placebo arm received carboplatin/paclitaxel only; they were assigned to their randomised treatment arm.

At iDBL for primary PFS analysis, 203 patients (14.9% of randomised patients) had completed the maximal allowed treatment duration of 120 weeks (nintedanib: 14.8%; placebo: 14.9%), and 208 patients (15.2% of randomised patients) were still on treatment in the monotherapy phase of the study (nintedanib: 14.8%; placebo: 16.0%). A total of 1144 patients (83.7% of randomised patients) had permanently discontinued last study medication (nintedanib: 84.2%; placebo: 82.9%). All patients had discontinued chemotherapy with paclitaxel/carboplatin and 1127 patients (82.5% of randomised patients) had permanently discontinued nintedanib/placebo (nintedanib: 82.9%; placebo: 81.8%).

The demographics and baseline conditions of patients were balanced across the treatment arms. All patients were female in this study of ovarian cancer. The mean (SD) age was 57.3 (11.1) years. The vast majority of patients were White / Caucasian (White / Caucasian: 90.9%; Black: 1.0%; Asian: 1.0%; missing: 7.1%). The majority of patients came from European countries (Europe: 83.4%; North America: 15.7 %; Australia/New Zealand: 1.0%). The majority of randomised patients had very advanced disease, with FIGO classification of IIIC or IV at diagnosis (77.5%). Overall, 86.7% of patients were diagnosed with epithelial ovarian cancer, 7.4% of patients with primary peritoneal carcinoma, and 5.6% of patients with fallopian tube carcinoma. The oncological history of patients was similar between treatment arms. Almost all patients (99.5%) had had prior tumour debulking surgery.

Efficacy results (continued):

Primary endpoint: PFS as assessed by the investigator according to the modified RECIST (version 1.1) criteria and other clinical data

Progression was to be determined by the investigators based on the modified RECIST (version 1.1) criteria. If there was no unequivocal progressive disease (PD) on imaging, PD could be diagnosed if there was CA-125 "progression" (defined as CA-125 ≥2x nadir in case nadir value >ULN or CA-125 ≥2x ULN in case nadir value ≤ULN) and clinical criteria for malignant bowel obstruction (MBO) were fulfilled.

At iDBL, a total of 752 patients (nintedanib: 486 patients [53.3%]; placebo: 266 patients [58.5%]) experienced an event contributing to the primary endpoint PFS (including 23 deaths without evidence of progression and 22 patients with the criteria for CA−125 tumour marker "progression" and MBO criteria both fulfilled in the absence of or earlier than RECIST 1.1 progression). The addition of nintedanib to carboplatin/paclitaxel chemotherapy resulted in a statistically significant prolongation of PFS compared with placebo plus chemotherapy; the hazard ratio (HR) was 0.84 ([95% CI 0.72, 0.98]; p = 0.0239). Median PFS was 17.2 months in the nintedanib arm and 16.6 months in the placebo arm.

Further analyses concerning the primary endpoint

Sensitivity analyses for the primary endpoint were a proportional hazards model, a stepwise regression analysis (with selection of covariates), an analysis replacing actual with scheduled imaging dates, an analysis using originally entered Interactive voice response system/ interactive web-based response system (IXRS) data only, and an analysis where patients with subsequent other anticancer therapies were not censored but counted as having experienced PD. The results of the different sensitivity analyses were all consistent with the primary PFS analysis, confirming the robustness of the results.

Efficacy results (continued):

A further sensitivity analysis based on central independent review by independent radiologists and oncologists confirmed the result of the primary endpoint analysis. The median PFS time was 19.5 months in the nintedanib group and 16.8 months in the placebo group (HR: 0.86; [95% CI 0.74, 1.01]; p=0.0682). The overall number of patients with PFS events based on central independent review (668 patients) was lower than the number of patients with PFS events based on the investigators' assessment (752 patients), which reflects that only the latter, as primary endpoint, triggered the iDBL.

There was no evidence that the treatment effect varied in any of the pre-specified subgroups apart from the subgroup by FIGO stage. Efficacy was more pronounced in patients with FIGO IIB-III than in patients with FIGO IV (IIB-III vs. IV; subgroup-by-treatment interaction p = 0.0391). To allow for a comparison with the results of the ICON7 trial, subgroups according to the ICON7 classification of high risk and non-high risk were analysed in a post-hoc exploratory analysis. High risk was defined as FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery. Progression free survival was prolonged in patients with non-high risk according to ICON7 (HR: 0.72; [95% CI 0.57, 0.90]). In patients with a high risk according to ICON7, no benefit regarding PFS was observed (HR: 0.95; [95% CI 0.78, 1.15]).

Key secondary endpoint

The key secondary endpoint was PFS by modified RECIST version 1.1 only (investigator assessment). Overall, 480 patients (52.7%) in the nintedanib arm and 265 patients (58.2%) in the nintedanib arm had a PFS event based on investigators' RECIST assessments. Nintedanib showed a statistically significant prolongation of PFS compared with placebo (HR: 0.83 [95% CI 0.72, 0.97], p = 0.0186) corroborating the results for the primary endpoint. Median PFS was 18.3 months in the nintedanib arm and 16.6 months in the placebo arm.

Efficacy results (continued):

Other secondary endpoints

Overall survival data at iDBL were not mature. Until iDBL, 190 patients (20.9%) in the nintedanib group and 93 patients (20.4%) in the placebo group had had an OS event. The HR of nintedanib vs. placebo was 0.99 ([95% CI 0.77, 1.27]; p = 0.9060). Median OS was 34.0 months in the nintedanib group and 32.8 months in the placebo group.

Tumour marker progression (PFS CA-125) included serological (CA-125) "progression", death, and progression by RECIST 1.1. Until iDBL, 463 patients (50.8%) in the nintedanib group and 257 patients (56.5%) in the placebo group had events classified as PFS CA-125. Median PFS CA-125 was greater in the nintedanib group (16.5 months) than in the placebo group (13.9 months) with a HR of nintedanib vs. placebo of 0.88 ([95% CI 0.76, 1.03]; p = 0.1096).

Objective tumour response was defined as either complete response or partial response in patients with at least 1 target lesion reported at baseline. Objective tumour response based on investigator assessment occurred in 259 patients (74.0% of the patients with at least 1 baseline target lesion) in the nintedanib arm and 125 patients (70.2% of the patients with at least 1 baseline target lesion) in the placebo arm. The odds ratio of nintedanib vs. placebo was 1.20 ([95% CI 0.79, 1.79], p = 0.3894).

Patient reported outcome and health-related quality of life were evaluated based on change in abdominal/gastro-intestinal symptoms over time (scale composite of items 31 to 37 of the EORTC QLQ-OV28) and on change of the Global Health Status/QoL scale score (composite of items 29 and 30 of the EORTC QLQ-C30) over time. The post-baseline mean score was determined up to Day 1 of Week 61, which was the nearest nominal assessment time to the median follow-up time (of 62 weeks).

Efficacy results (continued):	For QLQ-OV28, the adjusted mean (SE) post-baseline score in abdominal/gastrointestinal symptoms was 24.53 (0.49) in the nintedanib group and 19.34 (0.64) in the placebo group leading to an adjusted mean difference (SE) between treatment groups of 5.19 (0.72) in favour of placebo ([95% CI 3.78, 6.59]; p<0.0001). For the global health/QoL, the adjusted mean (SE) post-baseline value (nintedanib: 68.82 [0.49]; placebo: 70.68 [0.65]) was increased compared with the mean baseline value in both treatment groups, i.e. global health status had on average improved. The adjusted mean difference (SE) between treatment groups (nintedanib vs. placebo) was -1.86 (0.76) (95% CI -3.35; -0.36; p = 0.0149) indicating a greater improvement in score with placebo than with nintedanib. About half of the patients in both treatment groups showed an improved score for abdominal/gastrointestinal symptoms (nintedanib: 50.5%; placebo: 54.0%) and more than 60% of patients experienced an improvement in global health/QoL (60.5% vs. 66.1%). Worsening in summary scales was experienced by a greater proportion of patients in the nintedanib arm than in the placebo arm (abdominal/gastrointestinal symptoms: 34.3% vs. 23.9%; global health/QoL: 26.8% vs. 21.5%).
Safety results:	*Exposure* All of the treated patients had at least 1 course of chemotherapy. The mean (SD) number of chemotherapy courses was 5.5 (1.3) in the nintedanib arm and 5.8 (1.0) in the placebo arm. The majority of patients completed 6 courses where both carboplatin and paclitaxel were administered (nintedanib: 83.0%; placebo: 88.4%). The median duration of nintedanib/placebo treatment (chemotherapy combination period and extended monotherapy period) was 12.5 months in the nintedanib arm (range 0 to 29 months) and 13.5 months in the placebo arm (range 0 to 28 months).

Safety results (continued):

The vast majority of patients continued oral therapy into the extended monotherapy period (nintedanib: 80.8% of randomised patients; placebo: 85.5% of randomised patients). The median time on extended monotherapy, excluding the duration of chemotherapy combination therapy, was 11.4 months in the nintedanib arm (range 0 to 24 months) and 11.1 months in the placebo arm (range 0 to 24 months). Median duration of treatment with study medication, i.e. nintedanib/placebo and/or carboplatin and/or paclitaxel, was 13.6 months in the nintedanib arm (range 1 to 30 months vs. 14.9 months in the placebo arm (range 1 to 29 months).

Adverse events (AE)

Almost all patients had at least 1 AE during the trial (nintedanib: 99.7%; placebo: 98.7%). The most common AEs (occurring in >50% of patients treated with nintedanib during the on-treatment period) were diarrhoea (nintedanib: 77.5%; placebo: 25.8%), nausea (65.0% vs. 52.4%), and alopecia (57.5% vs. 61.8%). Adverse events considered drug-related by the investigator were more common with nintedanib (83.3%) than with placebo (51.1%) but in line with the known safety profile of nintedanib, paclitaxel, and carboplatin. The proportions of patients with CTCAE grade 3 AEs (47.9% vs. 41.8%) and CTCAE grade 4 AEs (29.8% vs. 21.6%) were greater in the nintedanib arm than in with placebo arm. In total, 3.2% of patients in the nintedanib arm and 3.6% of patients in the placebo arm had AEs that led to death (CTCAE grade 5); most were attributed to disease progression including 1.3% of patients in each treatment arm who were reported with an AE of malignant neoplasm progression. A greater proportion of patients experienced serious AEs in the nintedanib arm (41.7%) than in the placebo arm (34.4%). Furthermore, the frequency of patients with AEs leading to permanent discontinuation of investigational drug (nintedanib/placebo) was higher in the nintedanib arm than in the placebo arm (nintedanib 23.6% vs. placebo 15.1%), as was the frequency of patients with AEs leading to dose reduction of investigational drug (nintedanib: 50.6 vs. placebo: 6.9%).

Safety results (continued):

Adverse events of special interest

Search categories, based on 'medical concepts' integrating all preferred terms (PTs) considered to represent similar clinical conditions, were used for comparison of AEs of special interest. These search categories were based on Standardized MedDRA Queries (SMQs) or, if SMQs were not available, on newly created special search categories (SSC).

The most common events during the on-treatment period were gastrointestinal AEs. The percentage of patients with such events was greater in the nintedanib arm than in the placebo arm (diarrhoea [SSC]: 77.5% vs. 25.8%; nausea [SSC]: 65.0% vs. 52.4%; vomiting [SSC]: 45.0% vs. 28.0%; abdominal pain [SSC]: 44.0% vs. 36.7%). The proportion of patients with diarrhoea of CTCAE grade 3/4/5 was 21.6% in the nintedanib arm compared with 2.0% in the placebo arm. Grade 3/4/5 events of vomiting were reported for 3.1% vs. 2.4% of patients, grade 3/4/5 events of nausea for 4.0% vs. 3.1% of patients, and grade 3/4/5 events of abdominal pain for 5.1% vs. 2.9%. The frequency of patients with diarrhoea and other abdominal AEs was not notably different between patients treated with carboplatin AUC 6 and those treated with AUC 5 in both treatment arms.

As expected with the chemotherapy regimen of carboplatin and paclitaxel used as standard backbone therapy, haematotoxicity AEs were common. These AEs occurred in a greater proportion of patients in the nintedanib arm than in the placebo arm; the increased incidence was most notable for thrombocytopenia (SSC; nintedanib: 40.7%; placebo: 23.1%), while the incidence of neutropenia was only slightly greater with nintedanib than with placebo (SSC; 57.3% vs. 51.1%). Furthermore, anaemia was reported for a greater proportion of patients in the nintedanib than in the placebo arm (SSC; 43.6% vs. 34.7%; grade 3/4/5: 14.0% vs. 7.1%). The differences in frequencies of patients between treatment arms were more pronounced for grade 3/4/5 haematotoxicity, especially for grade 3/4/5 thrombocytopenia (18.3% vs. 6.7%) and grade 3/4/5 anaemia (14.0% vs. 7.1%). The treatment difference was less pronounced for grade 3/4/5 neutropenia (44.1% vs. 37.6%).

Safety results (continued):

The frequency of patients with grade 3/4/5 thrombocytopenia was markedly greater in both treatment arms in patients treated at AUC 6 (SSC; nintedanib: 30.4%; placebo: 11.3%) compared with patients treated at AUC 5 (SSC; 12.6% vs. 4.5%). The same applied to grade 3/4/5 anaemia (SSC; AUC 6: 20.8% vs. 12.0%, AUC 5: 10.8% vs. 4.9%) and grade 3/4/5 neutropenia (SSC; AUC 6: 55.7% vs. 46.5%; AUC 5: 38.7% vs. 33.4%).

Febrile neutropenia (SSC) was reported for 3.2% of patients treated with nintedanib (grade 3/4/5: 3.1%) and 2.2% of patients treated with placebo (grade 3/4/5: 2.2%). Sepsis (SSC) of CTCAE grade3/4/5 was reported for 1.3% of patients in the nintedanib group and 0.4% of patients in the placebo group. Fatal sepsis (SSC) was reported for 3 patients in the nintedanib arm (0.3%) vs. 2 patients in the placebo arm (0.4%). A fatal infection (SMQ) was reported for 4 patients in the nintedanib arm (0.4%) and 4 patients in the placebo arm (0.9%).

The proportion of patients with bleeding events (SMQ) of grade 1/2 was 16.5% in the nintedanib arm and 11.3% in the placebo arm; this was primarily due to a greater proportion of patients with the PT epistaxis in the nintedanib group. The proportion of patients with grade 3/4/5 bleeding events was below 1% and identical in both treatment groups.

Fatigue was common in both treatment arms (SSC; nintedanib: 59.3%; placebo: 58.7%). The percentage of patients with grade 3/4/5 fatigue 7.2% in the nintedanib arm and 2.9% in the placebo arm.

Within the SSC ‘specific liver related investigations (tailored), AEs were reported for a greater percentage of patients in the nintedanib arm (30.3%) than in the placebo arm (13.3%); the difference was most pronounced for grade 3/4/5 AEs (16.0% vs. 2.7%). Grade 4 events were scarce and grade 5 events did not occur. In both treatment arms, the majority of patients recovered from the events. Few patients permanently discontinued investigational product due to an AE in this search category (nintedanib: 0.6%; placebo: 0.7%). By PT, an increase in ALT was reported for 28.7% vs. 10.9% of patients and an increase in AST was reported for 24.4% vs. 9.1% of patients. Concomitant increases of transaminases together with bilirubin increases were rare.

Safety results (continued):

Perforations (gastrointestinal [SMQ] and non-gastrointestinal perforations [SSC]) were reported for 2.8% of patients in the nintedanib arm vs. 1.6% in the placebo arm during the on-treatment period. Gastrointestinal perforations (SMQ) were reported for 2.2% vs. 0.7% of patients. A fatal perforation AE was reported for 1 patient in each treatment arm. Eight patients in the nintedanib arm and 2 patients in the placebo arm (considering the 2:1 randomisation: ratio 8:4) experienced a gastrointestinal perforation event outside the on-treatment period (including the period between debulking surgery and start of oral therapy, the screening period, and the pre-trial period between debulking surgery and signing of informed consent).

Hypertension (SMQ) occurred in a greater percentage of patients treated with nintedanib than with placebo (14.4% vs. 5.6%). The majority of AEs were of CTCAE grade 2 (grade 2: 6.9% vs. 2.9%; grade 3: 4.3% vs. 0.4%; grade 4: 0.4% vs. 0%).

Regarding cardiac, arterial thromboembolic AEs (SMQ) and venous thromboembolic AEs (SMQ), only minimal numerical imbalances in the proportion of patients with such AEs were observed. There was no imbalance between treatment groups regarding the percentage of patients with fatal cardiac AEs/AEs of sudden death. Myocardial infarction (SMQ) was reported for 1.4% of patients in the nintedanib arm and 0.9% of patients in the placebo arm. Cardiac arrhythmia (SMQ) was observed in 8.2% vs. 6.7% of patients.

The frequency of patients with arterial thromboembolism (SMQ) was slightly higher in the nintedanib arm than in the placebo arm (1.0% vs. 0.4%). Venous thromboembolism (SMQ) was slightly less common with nintedanib than with placebo (3.7% vs. 4.9%).

Safety results (continued):	*Adverse events during the extended monotherapy period* With the exception of AEs primarily related to cytotoxic chemotherapy (e.g. alopecia, neutropenia, anaemia and thrombocytopenia), the most commonly reported AEs by PT during the extended monotherapy period were similar to those reported in the overall on-treatment period, but on a substantially reduced level of frequency of patients and intensity. At least 1 AE during the extended monotherapy period was reported for 87.8% of patients in the nintedanib group and 76.9% of patients in the placebo group. The frequency of patients with SAEs was comparable in the 2 treatment arms (19.4% vs. 21.1%). The proportion of patients with AEs of CTCAE grades 3 to 5 was lower compared with the combination chemotherapy period in both treatment arms; however, the proportion of patients with AEs of CTCAE grades 3 to 5 was still greater in the nintedanib group (33.3%) than in the placebo group (22.6%). The most commonly reported AEs were diarrhoea (SSC; nintedanib: 46.6% vs. placebo: 8.7%, grade 3/4/5: 10.1% vs. 0.3%), nausea (SSC; 24.5% vs. 10.5%, grade 3/4/5: 1.4% vs. 1.0%), vomiting (SSC; 20.1% vs. 6.4%, grade 3/4/5: 1.0% vs. 0.8%), abdominal pain (SSC; 25.7% vs. 18.5%, grade 3/4/5: 1.8% vs. 1.3%), and ALT increased (PT; 11.4% vs. 3.6%; grade 3/4/5: 4.9% vs. 0.5%), and specific liver related investigations (tailored) (SSC; 13.5% vs. 5.7%, grade 3/4/5: 5.3% vs. 1.0%). Adverse events reflecting grade 3/4/5 haematotoxicity (other than anaemia, which may be also e.g. tumour-related) were almost absent in the monotherapy period, and no remarkable difference was observed between the treatment groups.
Conclusions:	The addition of nintedanib to carboplatin/paclitaxel chemotherapy resulted in a statistically significant prolongation of PFS compared with placebo plus chemotherapy (HR 0.84 ([95% CI 0.72, 0.98]; p = 0.0239). Median PFS was 17.2 months in the nintedanib arm and 16.6 months in the placebo arm. Nintedanib added to carboplatin and paclitaxel for first line treatment of ovarian cancer, showed a manageable safety profile, in particular for the carboplatin dose AUC 5. Long-term treatment with nintedanib is feasible, and in most patients especially the prolonged monotherapy was well tolerated.