



Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial

Andreas du Bois, Gunnar Kristensen, Isabelle Ray-Coquard, Alexander Reuss, Sandro Pignata, Nicoletta Colombo, Ursula Denison, Ignace Vergote, Jose M del Campo, Petronella Ottevanger, Martin Heubner, Thomas Minarik, Emmanuel Sevin, Nikolaus de Gregorio, Mariusz Bidziński, Jacobus Pfisterer, Susanne Malander, Felix Hilpert, Mansoor R Mirza, Giovanni Scambia, Werner Meier, Maria O Nicoletto, Line Bjørge, Alain Lortholary, Martin Oliver Sailer, Michael Merger, Philipp Harter, on behalf of the AGO Study Group led Gynecologic Cancer Intergroup (GCIg)/ European Network of Gynaecologic Oncology Trials Groups (ENGOT) Intergroup Consortium

Summary

Lancet Oncol 2016; 17: 78–89

Published Online

November 15, 2015

[http://dx.doi.org/10.1016/S1470-2045\(15\)00366-6](http://dx.doi.org/10.1016/S1470-2045(15)00366-6)

See [Comment](#) page 9

Kliniken Essen Mitte, Essen, Germany (Prof A du Bois MD, P Harter MD); Department of Gynecologic Oncology and Institute for Cancer Genetics and Informatics, Oslo University Hospital, and Oslo University, Oslo, Norway (Prof G Kristensen PhD); Centre Leon Berard and University of Lyon, Lyon, France (Prof I Ray-Coquard MD); Coordinating Center for Clinical Trials, Marburg, Germany (A Reuss MSc); National Cancer Institute of Naples, Naples, Italy (S Pignata MD); University of Milan Bicocca, Milan, Italy (Prof N Colombo MD); European Institute of Oncology Milan, Milan, Italy (Prof N Colombo); Health + Life Gesundheitsmanagement GmbH, Vienna, Austria (U Denison MD); University Hospitals Leuven, Leuven, Belgium (Prof I Vergote MD); Vall d'Hebron University Hospital Barcelona, Barcelona, Spain (J M del Campo MD); UMC St Radboud Nijmegen, Nijmegen, Netherlands (P Ottevanger PhD); West German Tumor Center, Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany (M Heubner MD); National Institute of Oncology, Bratislava, Slovakia (T Minarik PhD); Centre François Baclesse, Comité Uro-Gynécologie, Caen, France (E Sevin MD); Department of Gynecology, University Hospital, Ulm, Germany (N de Gregorio MD); Faculty of Health Science, University of

Background Angiogenesis is a target in the treatment of ovarian cancer. Nintedanib, an oral triple angiokinase inhibitor of VEGF receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor, has shown activity in phase 2 trials in this setting. We investigated the combination of nintedanib with standard carboplatin and paclitaxel chemotherapy in patients with newly diagnosed advanced ovarian cancer.

Methods In this double-blind phase 3 trial, chemotherapy-naïve patients (aged 18 years or older) with International Federation of Gynecology and Obstetrics (FIGO) IIB–IV ovarian cancer and upfront debulking surgery were stratified by postoperative resection status, FIGO stage, and planned carboplatin dose. Patients were randomly assigned (2:1) via an interactive voice or web-based response system to receive six cycles of carboplatin (AUC 5 mg/mL per min or 6 mg/mL per min) and paclitaxel (175 mg/m²) in addition to either 200 mg of nintedanib (nintedanib group) or placebo (placebo group) twice daily on days 2–21 of every 3-week cycle for up to 120 weeks. Patients, investigators, and independent radiological reviewers were masked to treatment allocation. The primary endpoint was investigator-assessed progression-free survival analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01015118.

Findings Between Dec 9, 2009, and July 27, 2011, 1503 patients were screened and 1366 randomly assigned by nine study groups in 22 countries: 911 to the nintedanib group and 455 to the placebo group. 486 (53%) of 911 patients in the nintedanib group experienced disease progression or death compared with 266 (58%) of 455 in the placebo group. Median progression-free survival was significantly longer in the nintedanib group than in the placebo group (17.2 months [95% CI 16.6–19.9] vs 16.6 months [13.9–19.1]; hazard ratio 0.84 [95% CI 0.72–0.98]; *p*=0.024). The most common adverse events were gastrointestinal (diarrhoea: nintedanib group 191 [21%] of 902 grade 3 and three [$<1\%$] grade 4 vs placebo group nine [2%] of 450 grade 3 only) and haematological (neutropenia: nintedanib group 180 [20%] grade 3 and 200 (22%) grade 4 vs placebo group 90 [20%] grade 3 and 72 [16%] grade 4; thrombocytopenia: 105 [12%] and 55 [6%] vs 21 [5%] and eight [2%]; anaemia: 108 [12%] and 13 [1%] vs 26 [6%] and five [1%]). Serious adverse events were reported in 376 (42%) of 902 patients in the nintedanib group and 155 (34%) of 450 in the placebo group. 29 (3%) of 902 patients in the nintedanib group experienced serious adverse events associated with death compared with 16 (4%) of 450 in the placebo group, including 12 (1%) in the nintedanib group and six (1%) in the placebo group with a malignant neoplasm progression classified as an adverse event by the investigator. Drug-related adverse events leading to death occurred in three patients in the nintedanib group (one without diagnosis of cause; one due to non-drug-related sepsis associated with drug-related diarrhoea and renal failure; and one due to peritonitis) and in one patient in the placebo group (cause unknown).

Interpretation Nintedanib in combination with carboplatin and paclitaxel is an active first-line treatment that significantly increases progression-free survival for women with advanced ovarian cancer, but is associated with more gastrointestinal adverse events. Future studies should focus on improving patient selection and optimisation of tolerability.

Funding Boehringer Ingelheim.

Introduction

Ovarian cancer is the fifth most common cause of cancer-related death among women in Europe¹ and has one of the lowest cancer survival rates,^{2,3} with one study estimating a 5-year survival of just 36.1%.⁴ Standard treatment for advanced ovarian cancer involves surgical

resection and chemotherapy with carboplatin and paclitaxel.⁵ Despite high proportions of patients achieving a response with standard first-line chemotherapy,^{6–8} most women relapse. So far, addition of a third drug has only led to additional toxic effects, without improved outcome.^{9–16}

Research in context

Evidence before this study

Before the start of the study in 2009 and after data cutoff (April 29, 2013), we searched PubMed and abstracts submitted to international clinical oncology meetings using the keywords "ovarian cancer" and anti-angiogenic drugs that have been clinically assessed in this indication: "bevacizumab", "trebananib", "aflibercept", "pazopanib", and "cediranib" to identify publications that focused on anti-angiogenic treatment options for patients with ovarian cancer. Identified trials were reviewed and confirmed that targeting angiogenesis is effective at prolonging progression-free survival in patients with ovarian cancer, showing the key part that angiogenesis plays in ovarian tumour progression. Although anti-angiogenic drugs are being investigated in a first-line setting, selection of patients most likely to benefit from these treatments remains controversial, and there remains an unmet need in patients with ovarian cancer. Encouraging early-phase clinical activity of nintedanib in patients with ovarian cancer, including a favourable tolerability profile in combination with carboplatin and paclitaxel, provided further support for this trial.

Angiogenesis has a key role in ovarian tumour progression¹⁷ and anti-angiogenic drugs are being actively investigated in the first-line setting. Bevacizumab, an anti-VEGF monoclonal antibody, in combination with standard chemotherapy followed by bevacizumab maintenance has shown superior progression-free survival compared with standard chemotherapy alone.^{18–20} Furthermore, an overall survival benefit was noted in a subgroup analysis of the phase 3 ICON7 trial^{19,20} in patients considered to have high-risk tumours (International Federation of Gynecology and Obstetrics [FIGO] stage IV, or FIGO stage III if residual tumour after debulking surgery was >1.0 cm). By contrast, the ICON collaborators^{19–21} did not report any significant benefit in the complementary subgroup of non-high-risk patients with FIGO stage up to III and no or minimum macroscopic residual tumour of less than or equal to 1 cm maximum diameter. The AGO-OVAR 16 phase 3 trial²² of the tyrosine kinase inhibitor pazopanib as maintenance therapy, which preferentially included patients with absent or limited macroscopic tumour and excluded patients with progressive disease during initial chemotherapy or persisting bulky tumours after chemotherapy, showed that pazopanib was effective in these patients.

Nintedanib is a potent, oral inhibitor of the VEGF receptors (VEGFRs) 1–3, fibroblast growth factor receptors (FGFRs) 1–3, and platelet-derived growth factor receptors (PDGFRs) α and β , with anti-angiogenic activity.²³ Tolerability of nintedanib in combination with carboplatin and paclitaxel at a dose of 200 mg twice daily has been established in two phase 1 studies.^{24,25} In a

Added value of this study

This is, to our knowledge, the first phase 3 trial of nintedanib in ovarian cancer. In this trial, the addition of nintedanib to the standard first-line chemotherapy regimen of carboplatin and paclitaxel significantly increased progression-free survival compared with placebo in women with advanced ovarian cancer. The effect of nintedanib treatment seemed greatest in patients without characteristics known to be associated with a high risk for early disease progression, mostly shown by a lower postoperative tumour burden. We judged efficacy noted in this post-hoc subgroup analysis to be clinically meaningful. Treatment with nintedanib was accompanied by an increase in gastrointestinal adverse events.

Implications of all the available evidence

This is the fourth phase 3 trial of anti-angiogenic first-line therapy of advanced ovarian cancer to show a significant improvement in progression-free survival compared with placebo, further confirming the importance of angiogenesis in disease progression in patients with advanced ovarian cancer. Further studies of nintedanib are needed to help define its role in the management of ovarian cancer.

randomised, placebo-controlled phase 2 trial of post-chemotherapy maintenance therapy with nintedanib in patients with relapsed ovarian cancer, nintedanib was well tolerated and improved progression-free survival.²⁶

Here, we report the findings of a phase 3 trial (AGO-OVAR 12), in which we investigated the combination of nintedanib with standard carboplatin and paclitaxel chemotherapy in patients with newly diagnosed advanced ovarian cancer.

Methods

Study design and participants

We did an international, cooperative, randomised, double-blind, placebo-controlled, phase 3 trial of standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer. Eligible patients were at least 18 years old, with histologically confirmed FIGO stage IIB–IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, who had either had previous debulking surgery or, if debulking surgery in stage IIIC was intraoperatively not amenable to maximal cytoreduction or in stage IV was deemed inappropriate, had diagnosis confirmed by histology and no planned surgery before disease progression, with a life expectancy of at least 6 months. Chemotherapy was scheduled within 10 weeks after surgery. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower and adequate haematological, hepatic, and renal function.

Exclusion criteria included borderline tumours or non-epithelial tumours; planned surgery within

Jan Kochanowski, Kielce, Poland (Prof M Bidziński MD); Gynecologic Oncology Center, Kiel, Germany (Prof J Pfisterer MD); University Hospital, Department of Oncology, Lund, Sweden (S Malander MD); Universitäts-Klinik Schleswig-Holstein (UKSH) Campus Kiel, Department of Gynecology and Obstetrics, Kiel, Germany (Prof F Hilpert MD); Rigshospitalet-Copenhagen University Hospital, Department of Oncology, Copenhagen, Denmark (M R Mirza MD); Università Cattolica del Sacro Cuore Policlinico Gemelli, Rome, Italy (Prof G Scambia MD); Evangelisches Krankenhaus, Department of Gynecology and Obstetrics, Duesseldorf, Germany (Prof W Meier MD); Istituto Oncologico Veneto Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Oncologia Medical, Padova, Italy (M O Nicoletto MD); Haukeland Universitetssykehus, Bergen, Norway (Prof L Bjørge PhD); Centre Catherine de Sienne, Nantes, France (A Lortholary MD); and Boehringer Ingelheim, Ingelheim, Germany (M O Sailer PhD, M Merger MD)

Correspondence to: Prof Andreas du Bois, Kliniken Essen-Mitte, Department of Gynecology and Gynecologic Oncology, 45136 Essen, Germany prof.dubois@googlemail.com

124 weeks after randomisation, including interval debulking; other malignancy diagnosed within the past 5 years; brain metastases; history of a major thromboembolic event; known coagulopathy or bleeding disorder; substantial cardiovascular disease; serious infections (including hepatitis B or C and HIV), in particular if requiring antibiotic, antiviral, or antifungal treatment; glomerular filtration rate less than 40 mL/min (estimation by Cockcroft-Gault sufficient); neutrophil count less than 1.5×10^9 cells per L or absolute neutrophil count greater than 1.5×10^9 cells per L only achieved with induction or granulocyte-colony stimulating factor; platelets less than 100×10^9 cells per L; haemoglobin less than 90 g/L; proteinuria Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher; total bilirubin greater than the upper limit of normal (ULN); alanine aminotransferase or aspartate aminotransferase, or both, greater than $2.5 \times$ ULN; and prothrombin time or activated partial thromboplastin time greater than 50% deviation from normal limits in the absence of anticoagulation. The appendix (p 35–37) includes a full list of eligibility criteria.

See Online for appendix

Patients with planned surgery (including delayed debulking surgery) were excluded, as were those with uncontrolled hypertension or known state of hypercoagulability or bleeding disorder. Gastrointestinal disorders that might interfere with the absorption of the study drug were also excluded. Patients with bowel resection of large burden of tumour were not excluded, but those included in the trial within fewer than 4 weeks after surgery were to receive the first course of chemotherapy without nintedanib.

All patients provided written informed consent before enrolment. The trial conformed to the Declaration of Helsinki, Good Clinical Practice guidelines, and was approved by the ethics committee for each participating centre. An independent data safety monitoring board reviewed safety data during the study.

Randomisation and masking

Patients were randomly assigned (2:1) via a third-party interactive voice or web-based response system to nintedanib (Boehringer Ingelheim, Ingelheim, Germany) or placebo. Randomisation was done in blocks and was stratified by macroscopic complete resection versus incomplete resection, FIGO stage IIB–III versus IV, and carboplatin starting dose of AUC 5 mg/mL per min versus AUC 6 mg/mL per min.

Patients, investigators, and independent radiological reviewers were masked to treatment allocation. Access to the randomisation codes was controlled and documented. All people directly involved in the undertaking and analysis of the trial had no access to the treatment allocation before final database lock. Participating sites and study groups are listed in the appendix (p 1–11).

Procedures

Patients were given either nintedanib 200 mg starting dose or placebo administered orally, twice daily on days 2–21 of every 3-week cycle for up to 120 weeks. Nintedanib or placebo were added to six cycles of paclitaxel 175 mg/m² and carboplatin (AUC 5 mg/mL per min or 6 mg/mL per min; both allowed because of variation in international practice; dose to be chosen by the treating clinician before the start of treatment), both given intravenously on day 1 of a 21-day cycle. We planned to treat patients for up to 120 weeks or until occurrence of unacceptable toxic effects; withdrawal of consent; or diagnosis of disease progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, or by raised CA-125 (Gynecological Cancer Intergroup criteria) in conjunction with clinical malignant bowel obstruction. Malignant bowel obstruction was diagnosed on the basis of new or worsening abdominal pain, nausea, vomiting, abdominal distension, constipation, or diarrhoea, or a combination thereof, in the absence of evidence of metabolic or electrolyte abnormalities, or concomitant drugs leading to these symptoms.

We did radiological assessments of disease by CT or MRI at baseline and every 6 months thereafter until progression. Imaging (CT or MRI) was scheduled for weeks 25, 49, 61, 73, 97, and 121. Between 12 and 18 months, during which time disease progression was anticipated to occur in most patients, imaging was done every 3 months. Every patient had a clinical and gynaecological examination on every scheduled visit. The same examination was repeated at subsequent visits. Serum CA-125 was assessed at baseline and every 3 months thereafter until progression. Upon clinical evidence suggestive of progression or CA-125 progression, radiological assessments and clinical investigations were done. Imaging data were reassessed by a masked independent review committee.

Adverse events were monitored continuously and graded according to the National Cancer Institute CTCAE version 3.0. Adverse events were also grouped into special search categories by pooling Medical Dictionary for Regulatory Activities preferred terms. In the event of any potentially drug-attributable toxic effects (appendix p 40–42), the nintedanib or placebo dose was initially reduced from 200 mg twice daily to 150 mg twice daily and, if necessary, further reduced to 100 mg twice daily. Interruptions of nintedanib or placebo treatment were allowed; if treatment was interrupted for more than 21 days in a patient and the treating clinician intended to restart treatment, agreement had to be obtained from the study chair. Health-related quality of life (HRQoL) was assessed by European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire-core 30 (QLQ-C30) and ovarian cancer-specific quality-of-life questionnaire (OV-28). HRQoL was assessed before cycles 1, 3, and 5 of chemotherapy and every 12–24 weeks thereafter until disease progression.

Outcomes

The primary endpoint was progression-free survival, defined as the interval between the date of randomisation and investigator-assessed disease progression defined by RECIST version 1.1, or by raised CA-125 in conjunction with malignant bowel obstruction, or death from any cause. Secondary endpoints included progression-free survival by imaging and RECIST only; overall survival, defined as the interval between the date of randomisation and death from any cause; time to tumour marker progression (CA-125); incidence and intensity of adverse events; and HRQoL. The HRQoL endpoints stated in the protocol were the change in abdominal or gastrointestinal symptoms (EORTC QLQ-OV 28, composite of items 31–37) and global health status and quality-of-life scale (EORTC QLQ-C30, composite of items 29 and 30). A full list of secondary endpoints is provided in the appendix (p 39).

Statistical analysis

We planned to recruit 1300 patients over 18 months, anticipating 753 progression-free survival events after an additional 18 months of follow-up, which would produce 90% power for a log-rank test with a two-sided significance level 0.05 if the underlying hazard ratio (HR) is 0.783 (corresponding to a median progression-free survival of 18 months in the placebo group *vs* 23 months in the nintedanib group). The sample size calculation was done using EAST-5 software (version 5.1).

The primary endpoint of progression-free survival was analysed in the intention-to-treat population using a two-sided log-rank test stratified for randomisation strata. Progression-free survival distribution, including median progression-free survival, was estimated using the Kaplan-Meier method. HRs and corresponding 95% CIs were estimated using a stratified Cox proportional hazards model. Log cumulative hazard plots were visually inspected to check the proportional hazards assumption. Sensitivity analyses included progression-free survival according to independent central review of imaging and clinical data, an analysis replacing the actual imaging times by scheduled imaging times, an analysis counting the start of subsequent treatment as progression, and an exploration of proportional hazards. Sensitivity analyses were based on the Kaplan-Meier method, stratified log-rank test, and Cox proportional hazards model. Preplanned subgroup analyses were done in cohorts defined by randomisation strata.

The secondary endpoints of progression-free survival by imaging and modified RECIST only and time to tumour marker progression (CA-125) were analysed in the intention-to-treat population using the same methods as for the primary endpoint. Median overall survival for eligible patients was estimated to be about 45 months and planned follow-up for overall survival is 60 months from randomisation. Hence, overall survival data are pending and will be the subject of a separate publication.

Changes in the HRQoL endpoints were assessed in the patients with available quality-of-life data. We used a longitudinal modelling approach based on mixed-effects growth curve models with the mean profile over time for each endpoint described by a piecewise linear model adjusted for the stratification factors used at randomisation. The treatment effect was estimated as the mean difference between the treatment group mean scores, together with 95% CIs and associated *p* values on the basis of a *t* statistic with degrees of freedom calculated with the Kenward-Roger method.²⁷

The safety population was defined as all patients who received at least one dose of study medication (chemotherapy, nintedanib, or placebo). Dose intensity was calculated as the dose administered divided by the dose expected until time of study treatment discontinuation. All statistical analyses were done using SAS version 9.2 or higher.

This trial is registered with ClinicalTrials.gov, number NCT01015118.

Role of the funding source

The funder of the study was involved in development of the trial protocol. Decisions regarding content were made by the academic principal investigator (AdB) of the leading academic group in consultation with the trial steering committee (appendix p 38), which included one representative of each participating academic study group and the funder. Data collection was organised by the funder. Data were gathered by the investigators and analysed by an independent academic statistical team (Coordinating Center for Clinical Trials, Marburg, Germany) of the AGO Study Group, within the academic intergroup consortium; an independent analysis was done also by the funder. AdB, AR, MOS, and MM had full access to the primary raw data after study closure. Boehringer Ingelheim provided writing support. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 9, 2009, and July 27, 2011, 1503 patients were screened and 1366 randomly assigned by nine study groups in 22 countries: 911 to the nintedanib group and 455 to the placebo group (figure 1). 890 patients in the nintedanib group received at least one dose of nintedanib, 736 of whom received extended monotherapy. 445 patients in the placebo group received at least one dose of placebo, 389 of whom received extended monotherapy. Baseline characteristics were well balanced between groups (table 1). 48 (4%) of 1366 patients did not undergo surgery for ovarian cancer (35 [4%] in the nintedanib group: nine FIGO stage IIIC and 26 FIGO stage IV; 13 [3%] in the placebo group: four FIGO stage IIIC and nine FIGO stage IV). 693 (53%) of 1318 patients who underwent debulking surgery had no macroscopic residual disease

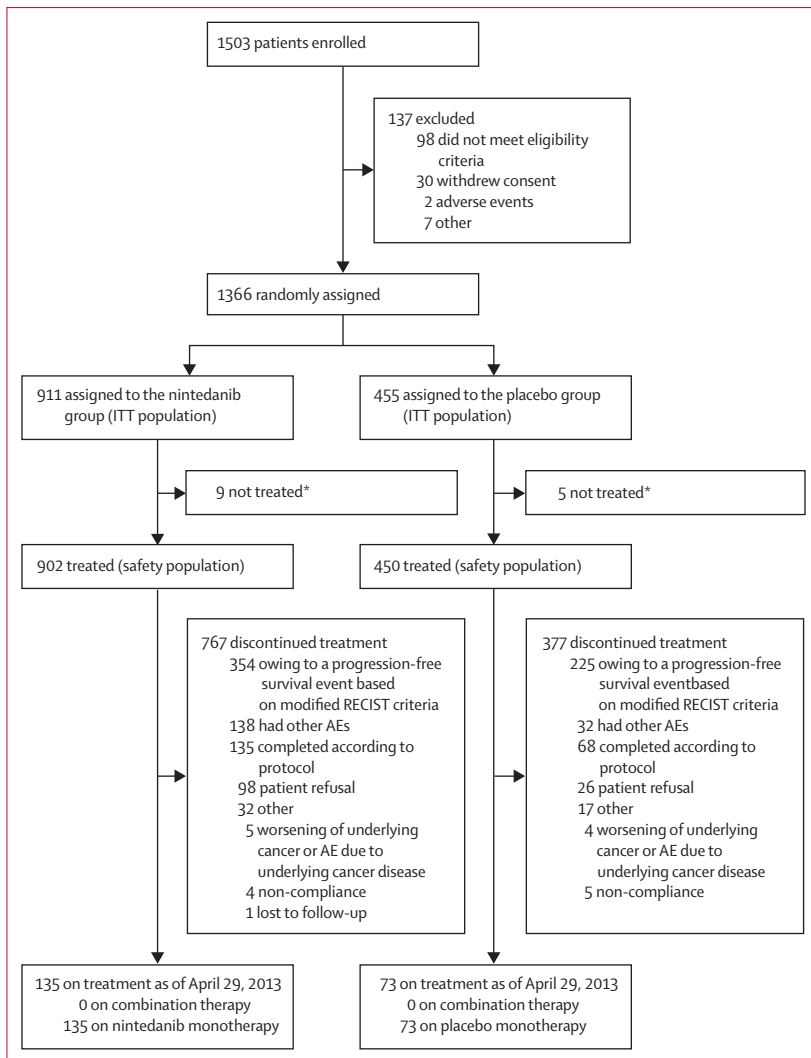


Figure 1: Trial profile

AE=adverse event. ITT=intention to treat. RECIST=Response Evaluation Criteria in Solid Tumors. *Reasons for the 14 patients not treated were worsening of underlying cancer or adverse event due to underlying cancer disease in two, other AE in one, non-compliance with protocol in four, patient refusal in six, and other in one.

(nintedanib 463 [53%] of 876; placebo 230 [52%] of 442). Nine untreated patients assigned to nintedanib and five assigned to placebo did not receive at least one dose of study drug and were excluded from the safety analyses; thus, 902 patients randomly assigned to nintedanib and 450 to placebo were included in the safety population. A further 12 patients in the nintedanib group and five in the placebo group received chemotherapy only and were excluded from analyses of exposure to nintedanib or placebo. The median interval from surgery to start of treatment was 37.0 days (IQR 30.0–46.0) in the nintedanib group versus 36.5 days (30.0–45.0) in the placebo group. At data cutoff (April 29, 2013), 767 (85%) of 902 patients in the nintedanib group and 377 (84%) of 450 in the placebo group had discontinued all study treatment (figure 1).

The mean number of carboplatin and paclitaxel courses was 5.5 (SD 1.3) in the nintedanib groups and 5.8 (1.0) in the placebo group. In the nintedanib group, 778 (86%) of 902 patients received all six planned courses, compared with 413 (92%) of 450 in the placebo group. Overall, the mean dose intensity of carboplatin was 93.3% (SD 11.7) in the nintedanib group and 96.8% (9.5) in the placebo group. For patients planned to receive AUC 5 mg/mL per min, completion of six courses of chemotherapy was achieved by 545 (89%) of 613 in the nintedanib group and the mean carboplatin dose intensity was 95.4% (SD 10.3). For patients planned to receive AUC 6 mg/mL per min, completion of six courses of chemotherapy was achieved by 233 (81%) of 289 in the nintedanib group and the mean carboplatin dose intensity was 88.8% (SD 13.3). The overall mean cumulative dose of carboplatin was 29.1 mg/mL per min (SD 8.3) in the nintedanib group and 30.5 mg/mL per min (6.0) in the placebo group (analysed by AUC cohort, for nintedanib vs placebo: AUC 5 mg/mL per min, 28.1 mg/mL per min vs 28.8 mg/mL per min, AUC 6 mg/mL per min, 31.2 mg/mL per min vs 34.0 mg/mL per min).

The median duration of treatment was 12.5 months (range 0–29) with nintedanib and 13.5 months (0–28) with placebo. The mean dose intensity of nintedanib was 89.1% (SD 18.1) and of placebo it was 98.5% (11.9). The mean cumulative dose of nintedanib was 133.8 g (SD 92.3) and of placebo it was 168.0 g (98.8). 460 (52%) of 890 patients who received nintedanib had at least one dose reduction of nintedanib, whereas 38 (9%) of the 445 patients who received placebo had at least one dose reduction of placebo.

After a median observation period of 22.4 months (IQR 21.8–27.7), 486 (53%) of 911 patients in the nintedanib group had experienced disease progression or death compared with 266 (58%) of 455 in the placebo group. Log-cumulative hazard plots showed no signs of a violation of the proportional hazards assumption. Median progression-free survival was 17.2 months (95% CI 16.6–19.9) in the nintedanib group and 16.6 months (13.9–19.1) in the placebo group (HR 0.84, 95% CI 0.72–0.98; stratified log-rank $p=0.024$; figure 2). The sensitivity analysis for progression-free survival by independent central review, which was based on 668 progression-free survival events, showed consistency with these results (median progression-free survival 19.5 months [95% CI 16.7–22.0] in the nintedanib group vs 16.8 months [14.9–20.8] in the placebo group; HR 0.86, 95% CI 0.74–1.01; $p=0.068$). Further consistency was noted with the secondary endpoint of progression-free survival measured by imaging and modified RECIST (median progression-free survival 18.3 months [95% CI 16.6–20.7] in the nintedanib group vs 16.6 months [13.9–19.6] in the placebo group; HR 0.83, 95% CI 0.72–0.97; stratified log-rank $p=0.019$). Median time to tumour marker progression was 16.5 months (IQR 10.1–28.5) in the nintedanib group compared with 13.9 months (8.6–30.4) in the placebo group (HR 0.88 [95% CI 0.76–1.03]; $p=0.11$).

Figure 3 shows preplanned and post-hoc subgroup analyses of progression-free survival. Progression-free survival was greater in the nintedanib group than in the placebo group for patients who had been planned to receive a carboplatin dose of AUC 5 mg/mL per min, but not AUC 6 mg/mL per min. Progression-free survival was also improved in the nintedanib group compared with the placebo group for patients with FIGO stage IIB–III disease, but not for those with FIGO stage IV disease. No significant differences were noted in subgroups according to the presence of macroscopic residual tumour.

In a post-hoc analysis, we compared non-high-risk versus high-risk subgroups as defined in ICON7¹⁹. Overall, 527 (39%; 355 in the nintedanib group and 172 in the placebo group) of 1366 patients were in the high-risk or high tumour burden subgroup, defined as either FIGO stage III and postoperative macroscopic residual tumour of over 1 cm diameter, or FIGO stage IV; whereas 839 (61%; 556 in the nintedanib group and 283 in the placebo group) of 1366 patients were in the non-high-risk or low tumour burden subgroup, defined as FIGO stage III and postoperative residuals 1 cm or smaller, or FIGO stage II. In the non-high-risk subgroup, median progression-free survival was 27.1 months (95% CI 22.1–28.5) in patients in the nintedanib group versus 20.8 months (16.8–23.0) in those in the placebo group (HR 0.74 [95% CI 0.61–0.91]). No significant difference in progression-free survival was noted between the nintedanib and placebo groups for the high-risk subgroup (HR 0.99 [95% CI 0.80–1.24]). Kaplan-Meier plots for the subgroup analyses are shown in the appendix (p 12–19).

899 (>99%) of 902 patients in the nintedanib group and 444 (99%) of 450 in the placebo group experienced an adverse event of any grade. Grade 3 or worse adverse events occurred in 730 (81%) of 902 patients in the nintedanib group compared with 301 (67%) of 450 in the placebo group (table 2). For both nintedanib and placebo groups, the incidence and severity of adverse events was worse with the combination of carboplatin and paclitaxel (any grade: 898 [>99%] of 902 in the nintedanib group and 442 [98%] of 450 in the placebo group; grade ≥ 3 : 685 [76%] and 263 [58%]) compared with the maintenance period (any grade: 646 [88%] of 736 vs 299 [77%] of 389; grade ≥ 3 : 245 [33%] of 736 vs 88 [23%] of 389).

Diarrhoea, nausea, vomiting, and decreased appetite were more frequent with nintedanib than with placebo (table 2). Onset of diarrhoea occurred within the initial 2 months of treatment in 470 (67%) of 699 patients with diarrhoea in the nintedanib group and 69 (59%) of 117 patients with diarrhoea in the placebo group (table 3). 147 of 195 patients in the nintedanib group and nine of nine patients in the placebo group with grade 3 diarrhoea experienced one such episode only (table 3), and 145 (74%) of those in the nintedanib group and four (44%) of those in the placebo group were able to continue the

	Nintedanib group (n=911)	Placebo group (n=455)
Age (years)	58.0 (23–84)	58.0 (21–79)
Ethnic origin		
White	822 (90%)	420 (92%)
Asian	9 (1%)	4 (1%)
African-American or African	10 (1%)	4 (1%)
Missing	70 (8%)	27 (6%)
Primary tumour type		
Ovary	781 (86%)	403 (89%)
Primary peritoneal	72 (8%)	29 (6%)
Fallopian tube	55 (6%)	22 (5%)
Missing	3 (<1%)	1 (<1%)
Stage at diagnosis*		
FIGO IIB	94 (10%)	43 (9%)
FIGO III	594 (65%)	300 (66%)
FIGO IV	221 (24%)	111 (24%)
Histological findings†		
Serosus	659 (72%)	320 (70%)
Clear cell	22 (2%)	12 (3%)
Undifferentiated	22 (2%)	10 (2%)
Endometrioid	78 (9%)	40 (9%)
Mucinous	25 (3%)	12 (3%)
Other	104 (11%)	60 (13%)
Histological grade		
Well differentiated	70 (8%)	33 (7%)
Moderately differentiated	157 (17%)	96 (21%)
Poorly differentiated or undifferentiated	576 (63%)	267 (59%)
Not assessable or missing	108 (12%)	59 (13%)
ECOG performance status‡		
0	542 (59%)	293 (64%)
1	334 (37%)	149 (33%)
2	25 (3%)	12 (3%)
Geographical region		
Europe	751 (82%)	388 (85%)
Australia or New Zealand	12 (1%)	1 (<1%)
USA or Canada	148 (16%)	66 (15%)
Macroscopic residual postoperative tumour		
No	463 (51%)	230 (51%)
Yes	448 (49%)	225 (49%)
Small or large bowel, or both, removed or resected		
No	659 (72%)	330 (73%)
Yes	252 (28%)	125 (27%)
Carboplatin dose		
AUC 5 mg/mL per min	620 (68%)	311 (68%)
AUC 6 mg/mL per min	291 (32%)	144 (32%)

Data are median (range) or number (%). Some percentages do not add up to 100 because of rounding. FIGO=International Federation of Gynecology and Obstetrics. ECOG=Eastern Cooperative Oncology Group. *Data missing for two patients in the nintedanib group and one in the placebo group. †Data missing for one patient in each group. ‡Data missing for ten patients in the nintedanib group and one in the placebo group.

Table 1: Demographics and baseline characteristics

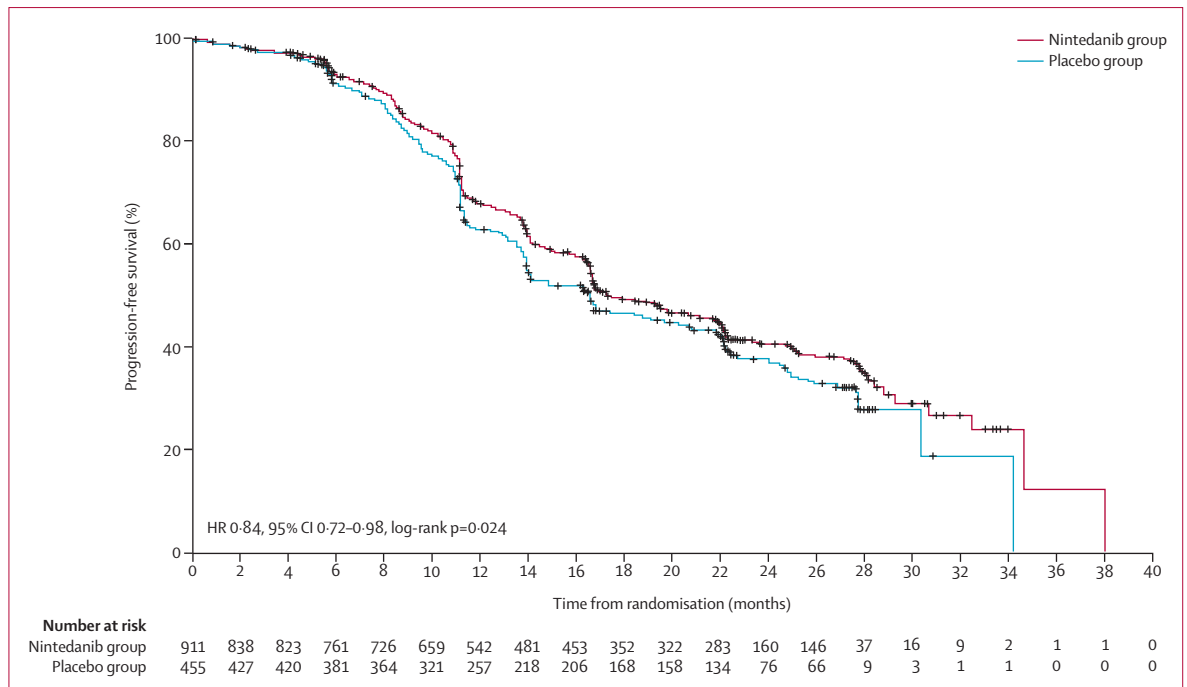


Figure 2: Progression-free survival
 Investigator-assessed analysis was stratified by (1) macroscopic residual postoperative tumour (yes vs no); (2) International Federation of Gynecology and Obstetrics stage (IIB–III vs IV); and (3) carboplatin concentration (AUC 5 mg/mL per min vs 6 mg/mL per min). p value was calculated using the two-sided stratified log-rank test. HR and 95% CI were calculated using the stratified Cox regression model. Crosses indicate censoring. HR=hazard ratio.

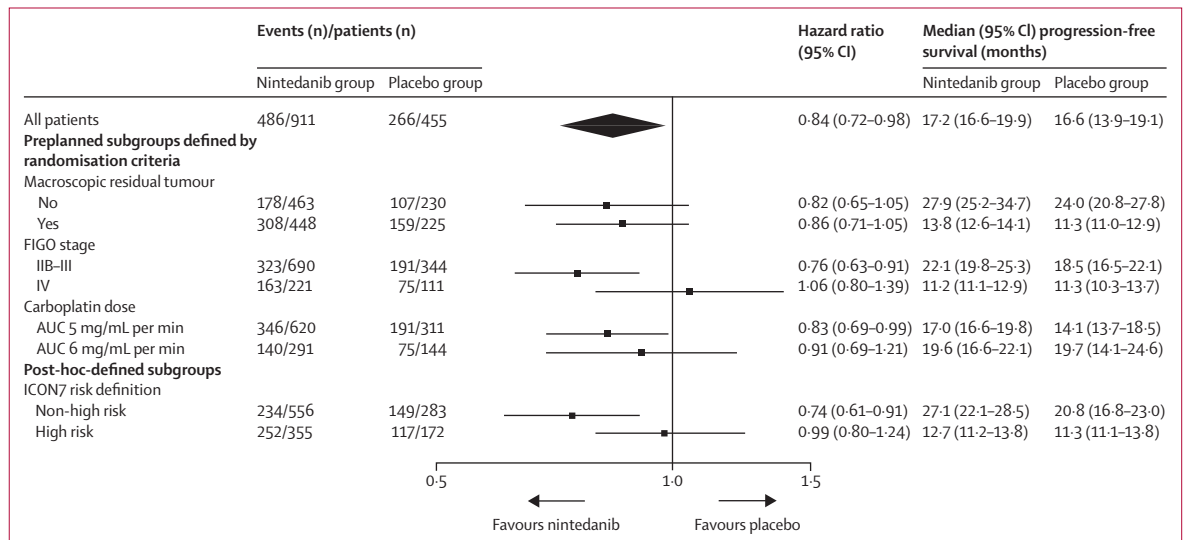


Figure 3: Preplanned and post-hoc subgroup analyses of progression-free survival
 Overall investigator-assessed analysis was stratified by (1) macroscopic residual postoperative tumour (yes vs no); (2) FIGO stage (IIB–III vs IV); and (3) carboplatin concentration (AUC 5 mg/mL per min vs 6 mg/mL per min). Subgroup analyses were stratified by the same factors minus the respective subgrouping factor. Hazard ratios and 95% CIs were calculated using the stratified Cox regression model. FIGO=International Federation of Gynecology and Obstetrics.

treatment at a lower dose after recovery. Gastrointestinal adverse events of grade 3 or worse other than diarrhoea occurred in less than 5% of patients and incidences were comparable between treatment groups. Among nintedanib-treated patients, 55 (28%) of 197 with bowel anastomoses experienced high-grade diarrhoea compared

with 140 (20%) of 705 without bowel anastomoses. In the placebo group, the proportion of patients with high-grade diarrhoea was higher in those with bowel anastomoses than in those without (five [5%] of 95 vs four [1%] of 355). Haematological adverse events (anaemia, neutropenia, and thrombocytopenia) were frequent in

	Nintedanib group (n=902)				Placebo group (n=450)			
	Grades 1 or 2	Grade 3	Grade 4	Grade 5	Grades 1 or 2	Grade 3	Grade 4	Grade 5
Anaemia	269 (30%)	108 (12%)	13 (1%)	1 (<1%)	124 (28%)	26 (6%)	5 (1%)	0
Thrombocytopenia	203 (23%)	105 (12%)	55 (6%)	0	74 (16%)	21 (5%)	8 (2%)	0
Leucopenia	120 (13%)	66 (7%)	15 (2%)	0	70 (16%)	23 (5%)	2 (<1%)	0
Neutropenia	118 (13%)	180 (20%)	200 (22%)	0	64 (14%)	90 (20%)	72 (16%)	0
Febrile neutropenia	1 (<1%)	17 (2%)	10 (1%)	0	0	7 (2%)	3 (1%)	0
Diarrhoea	504 (56%)	191 (21%)	3 (<1%)	1 (<1%)	107 (24%)	9 (2%)	0	0
Constipation	247 (27%)	21 (2%)	3 (<1%)	0	151 (34%)	9 (2%)	2 (<1%)	0
Ileus*	1 (<1%)	14 (2%)	1 (<1%)	1 (<1%)	1 (<1%)	4 (1%)	1 (<1%)	2 (<1%)
Abdominal discomfort	366 (41%)	49 (5%)	1 (<1%)	0	166 (37%)	13 (3%)	0	0
Vomiting	378 (42%)	27 (3%)	1 (<1%)	0	115 (26%)	11 (2%)	0	0
Nausea	550 (61%)	36 (4%)	0	0	222 (49%)	13 (3%)	1 (<1%)	0
Decreased appetite*	162 (18%)	9 (1%)	0	0	62 (14%)	0	0	0
Dysgeusia*	124 (14%)	1 (<1%)	0	0	37 (8%)	0	0	0
Myalgia or arthralgia	320 (35%)	20 (2%)	0	0	175 (39%)	12 (3%)	0	0
Pain	131 (15%)	7 (1%)	1 (<1%)	0	85 (19%)	8 (2%)	1 (<1%)	0
Pain in legs or arms*	92 (10%)	3 (<1%)	0	0	56 (12%)	2 (<1%)	0	0
Headache*	132 (15%)	7 (1%)	1 (<1%)	0	53 (12%)	1 (<1%)	0	0
Hypertension	87 (10%)	39 (4%)	3 (<1%)	0	23 (5%)	2 (<1%)	0	0
Liver-related investigation	147 (16%)	150 (17%)	8 (1%)	0	53 (12%)	21 (5%)	3 (1%)	1 (<1%)
ALT increased*	125 (14%)	133 (15%)	1 (<1%)	0	40 (9%)	8 (2%)	1 (<1%)	0
AST increased*	154 (17%)	65 (7%)	1 (<1%)	0	36 (8%)	4 (1%)	1 (<1%)	0
GGT increased*	22 (2%)	20 (2%)	4 (<1%)	0	8 (2%)	2 (<1%)	1 (<1%)	0
Alopecia*	520 (58%)	0	0	0	278 (62%)	0	0	0
Fatigue	469 (52%)	65 (7%)	0	0	250 (56%)	13 (3%)	0	0
Insomnia*	101 (11%)	2 (<1%)	0	0	56 (12%)	1 (<1%)	0	0
Peripheral neuropathies	494 (55%)	32 (4%)	0	0	260 (58%)	21 (5%)	1 (<1%)	0
Urinary tract infection*	127 (14%)	11 (1%)	0	0	46 (10%)	4 (1%)	0	0
Dyspnoea*	108 (12%)	6 (1%)	2 (<1%)	0	51 (11%)	6 (1%)	0	0
Rash	160 (18%)	13 (1%)	0	0	84 (19%)	2 (<1%)	0	0
Hypomagnesaemia*	86 (10%)	5 (1%)	2 (<1%)	0	22 (5%)	2 (<1%)	1 (<1%)	0
Hypokalaemia*	61 (7%)	27 (3%)	1 (<1%)	0	17 (4%)	7 (2%)	2 (<1%)	0
Drug hypersensitivity*	43 (5%)	23 (3%)	1 (<1%)	0	14 (3%)	10 (2%)	0	0
Dehydration	35 (4%)	10 (1%)	0	0	5 (1%)	4 (1%)	1 (<1%)	0
Syncope*	8 (1%)	13 (1%)	0	0	3 (1%)	2 (<1%)	0	0
Thromboembolic events	27 (3%)	27 (3%)	14 (2%)	2 (<1%)	10 (2%)	14 (3%)	5 (1%)	0
Arterial thromboembolism	2 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0
Venous thromboembolism	12 (1%)	12 (1%)	9 (1%)	0	6 (1%)	11 (2%)	5 (1%)	0
Pulmonary embolism*	0	2 (<1%)	9 (1%)	0	1 (<1%)	2 (<1%)	4 (1%)	0
Thrombosis*	5 (1%)	9 (1%)	0	0	1 (<1%)	1 (<1%)	0	0

Data are number of patients (%). Adverse events have been grouped by medical concept—ie, most categories cover several preferred terms of similar clinical conditions, except where indicated. A table with all grade 3–5 adverse events by preferred terms regardless of the number of patients in whom they occurred are shown in the appendix (p 22–34). ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=gamma-glutamyl transferase. *Individual preferred terms.

Table 2: Adverse events of grade 1–2 that occurred (regardless of grade) in at least 10% of patients or that occurred as grade 3 or worse in at least 1% of patients

both treatment groups (table 2). Thrombocytopenia of any grade occurred in 363 (40%) of 902 patients in the nintedanib group compared with 103 (23%) of 450 in the placebo group; anaemia also occurred in more patients in the nintedanib group (391 [43%]) than in the placebo group (155 [34%]). The incidence of haematological adverse events was higher in patients with carboplatin AUC 6 mg/mL per min than in those

with AUC 5 mg/mL per min, and the difference between groups seemed to be more pronounced in those with AUC 6 mg/mL per min compared with AUC 5 mg/mL per min (table 4).

Among adverse events associated with anti-angiogenic drugs defined by adverse event of special interest categories, higher incidences of the following events were reported in the nintedanib group compared

	Nintedanib group (n=902)	Placebo group (n=450)
Diarrhoea any grade	699 (77%)	117 (26%)
Onset of diarrhoea in initial 2 months of treatment	470 (52%)	69 (15%)
Diarrhoea resulting in dose reduction of oral investigational treatment	257 (28%)	7 (2%)
Diarrhoea resulting in discontinuation of oral investigational treatment	52 (6%)	1 (<1%)
Diarrhoea grade 2 or worse	486 (54%)	46 (10%)
Diarrhoea grade 3 or 4		
Any episode	195 (22%)*†	9 (2%)
One episode	147 (16%)	9 (2%)
Two episodes	35 (4%)	0
Three episodes	10 (1%)	0

Data are number (%). *66 patients had start or stop data missing for some periods. These periods were imputed with a 1-day duration (best-case imputation). A worst-case imputation using the whole episode duration led to similar results (with percentage differences <1%; data not shown). †Three patients had more than three episodes.

Table 3: Pattern and severity of diarrhoea

	AUC5 mg/mL per min		AUC6 mg/mL per min	
	Nintedanib group (n=613)	Placebo group (n=308)	Nintedanib group (n=289)	Placebo group (n=142)
Thrombocytopenia				
Any grade	205 (33%)	53 (17%)	158 (55%)	50 (35%)
Grade ≥3	74 (12%)	13 (4%)	86 (30%)	16 (11%)
Grade 4	23 (4%)	1 (<1%)	32 (11%)	7 (5%)
Anaemia				
Any grade	233 (38%)	91 (30%)	158 (55%)	64 (45%)
Grade ≥3	63 (10%)	14 (5%)	59 (20%)	17 (12%)
Neutropenia				
Any grade	299 (49%)	136 (44%)	199 (69%)	90 (63%)
Grade ≥3	224 (37%)	98 (32%)	156 (54%)	64 (45%)

Data are number of patients (%). Reported terms are grouped by medical concept.

Table 4: Haematological adverse events by planned AUC

with the placebo group: hypertension (any grade: 130 [14%] of 902 vs 25 [6%] of 450; grade ≥3: 42 [5%] vs two [<1%] of 450); gastrointestinal perforation (any grade: 20 [2%] vs three [1%]; grade ≥3: 17 [2%] vs two [<1%]); bleeding (any grade: 157 [17%] vs 55 [12%]; grade ≥3: eight [1%] vs four [1%]); there was no marked difference in the incidence of thromboembolic events between the two treatment groups (any grade: 70 [8%] vs 29 [6%]; grade ≥3: 43 [5%] vs 19 [4%]).

456 (51%) of 902 patients in the nintedanib group compared with 31 (7%) of 450 in the placebo group had an adverse event leading to dose reduction—primarily diarrhoea (255 in the nintedanib group vs seven in the placebo group) or raised liver aminotransferase concentrations (alanine aminotransferase: 155 vs three; aspartate aminotransferase: 73 vs two). 213 (24%) of 902 patients in the nintedanib group compared with 68 (15%) of 450 in the placebo group permanently discontinued nintedanib because of adverse events,

	Nintedanib group (n=902)	Placebo group (n=450)
Total with events*	213 (24%)	68 (15%)
Diarrhoea	50 (6%)	1 (<1%)
Vomiting	20 (2%)	2 (<1%)
Abdominal pain	19 (2%)	3 (1%)
Nausea	19 (2%)	2 (<1%)
Ascites	8 (1%)	5 (1%)
Thrombocytopenia	7 (1%)	0
Hypertension	6 (1%)	0
General deterioration in physical health	6 (1%)	0
Upper abdominal pain	5 (1%)	0
ALT increased	5 (1%)	3 (1%)
Asthenia	5 (1%)	0
Fatigue	5 (1%)	0
Ileus	5 (1%)	3 (1%)
Rash	5 (1%)	0
Malignant neoplasm progression	4 (<1%)	3 (1%)
Drug hypersensitivity	3 (<1%)	3 (1%)
AST increased	0	3 (1%)

ALT=alanine aminotransferase. AST=aspartate aminotransferase. *The total numbers and column sums differ because the total events includes all events even if they happened in fewer than 0.5% of patients in both groups.

Table 5: Adverse events leading to permanent drug discontinuation in at least 0.5% of patients in either treatment group

with gastrointestinal adverse events being the most common adverse events that led to discontinuation (table 5).

Serious adverse events were reported in 376 (42%) of 902 patients in the nintedanib group versus 155 (34%) of 450 patients in the placebo group. 29 (3%) of 902 patients in the nintedanib group and 16 (4%) of 450 in the placebo group had a serious adverse event associated with death, including 12 (1%) of 902 in the nintedanib group and six (1%) of 450 in the placebo group who had a malignant neoplasm progression classified as an adverse event by the treating investigator. Drug-related adverse events leading to death occurred in three patients in the nintedanib group (one without diagnosis of cause; one due to non-drug-related sepsis associated with drug-related diarrhoea and renal failure; and one due to peritonitis) and in one patient in the placebo group (cause unknown).

Quality-of-life data were available for 896 patients in the nintedanib group and 444 in the placebo group; those with no data (15 in the nintedanib group and 11 in the placebo group) were excluded from the analysis. Overall, quality of life was not adversely affected during treatment with nintedanib, despite the more frequent occurrence of gastrointestinal adverse events or symptoms in patients in the nintedanib group compared with those in the placebo group. The adjusted mean

global health status and quality-of-life score over the treatment period was 68.82 (SE 0.49; 95% CI 67.86–69.78) in the nintedanib group compared with 70.68 (0.65; 69.40–71.97) in the placebo group (difference in adjusted mean score –1.86, SE 0.76; 95% CI –3.35 to –0.36) on the scale normalised to 100, which is regarded as a clinically trivial change.²⁸ Further HRQoL data will be published separately. The appendix (p 20–21) includes a plot of the change in global health status and quality-of-life score over time.

Discussion

Addition of nintedanib to standard first-line carboplatin and paclitaxel chemotherapy significantly increased progression-free survival in women with advanced ovarian cancer compared with placebo. The efficacy of nintedanib seemed to be particularly notable in patients with low postsurgical disease burden, as defined by FIGO stage IIB–III and 1 cm or smaller residual postoperative tumour.

The efficacy of nintedanib—which targets VEGFRs 1–3, FGFRs 1–3, and PDGFRs α and β —in women with low disease burden is in line with findings for pazopanib, an inhibitor of VEGFRs 1–3 and PDGFRs α and β with anti-angiogenic activity.²⁹ In a phase 3 study (AGO-OVAR 16) of pazopanib as maintenance treatment after first-line chemotherapy,²² treatment with pazopanib extended progression-free survival by 5.6 months compared with placebo (HR 0.77, 95% CI 0.64–0.91; $p=0.0021$). Because of the inclusion criteria, most of the randomly assigned patients in the AGO-OVAR 16 trial²² had a low postsurgical tumour burden, defined in the same way as reported here. However, unlike our trial, these patients had had previous chemotherapy, although they had to be progression free after at least five cycles of platinum and taxane chemotherapy before receiving pazopanib as maintenance treatment. These findings seem to differ from the outcome of trials of the anti-angiogenic monoclonal antibody bevacizumab, which targets VEGF, in the same subgroup of patients.^{19,20} Data from ICON7^{19,20} suggested efficacy of bevacizumab in patients with high-risk features or high postsurgical tumour burden, with evidence of both a progression-free survival (HR 0.73, 95% CI 0.61–0.88; $p=0.001$) and overall survival benefit for this subgroup (0.78, 0.63–0.97), but not for patients without high-risk features. In GOG 218,³⁰ which included only patients with residual disease or FIGO stage IV, a significant improvement in progression-free survival was noted when bevacizumab was added as concomitant and maintenance therapy compared with chemotherapy only (HR 0.72, 95% CI 0.63–0.82; $p<0.001$), but no significant difference was noted for overall survival in the overall population. Thus, cross-trial comparison is difficult due to the different inclusion criteria between these four trials; inclusion criteria were most similar between AGO-OVAR 12 and ICON7.^{19,20}

Comparisons of subgroups defined mostly by tumour burden at baseline, although based on identical formal subgroup definitions, might be affected by the continued improvement of surgical goals and standards, which might affect the—primarily postsurgical—remaining tumour burden in different ways between trials done at different times. Therefore, patients with similar tumour biology might previously have retained characteristics of a high risk for disease progression because of a high volume of residual tumour at baseline, but could now be more likely to achieve non-high-risk tumour burden because of the up-to-date understanding that complete macroscopic debulking affords the best prognosis.⁴

Nonetheless, in view of the outcome for high-risk patients—in particular the outcome for patients with FIGO stage IV disease, which cannot be easily reconciled across trials—the differences in the outcomes of these studies raise the possibility that patterns of efficacy differ between anti-angiogenic tyrosine-kinase inhibitors (nintedanib and pazopanib) and antibodies (bevacizumab). However, this hypothesis needs further assessment.

The most common adverse events associated with nintedanib were primarily gastrointestinal and reversible increases in liver enzymes, in line with findings from previous clinical studies.^{24–26,31} However, the incidence of grade 3 diarrhoea in the nintedanib group was more than twice as high as reported in a second-line lung cancer trial³¹ in which docetaxel was combined with nintedanib. This difference might be related to the longer treatment duration, female sex, a combination backbone chemotherapy, and the different pre-treatment, such as debulking surgery, of the patients in the present study. The lower incidence of diarrhoea in the phase 2 study of nintedanib maintenance therapy in patients with relapsed ovarian cancer²⁶ seems to suggest that the frequency of gastrointestinal side-effects is not explained by the disease alone. Possibly, debulking surgery, particularly if including bowel resection, might have contributed to the higher proportion of patients who experienced gastrointestinal adverse events in this trial compared with these other trials.^{26,31} The early onset of diarrhoea soon after the preceding debulking surgery and the substantial proportion of patients in the control group who experienced at least low-grade diarrhoea in the AGO-OVAR 12 trial seems to support this notion. Diarrhoea was the main reason for nintedanib dose reductions or treatment discontinuation; proper management of this side-effect is therefore important to optimise treatment with nintedanib.

Treatment with nintedanib also led to a small increase in the incidence of haematological adverse events associated with carboplatin and paclitaxel chemotherapy, particularly thrombocytopenia in patients receiving carboplatin AUC 6 mg/mL per min. Thrombocytopenia has not been reported previously for nintedanib

monotherapy or other chemotherapy combinations. Because a pharmacokinetic interaction of nintedanib with carboplatin or paclitaxel has not been reported in phase 1 trials,²⁵ we speculate that a pharmacodynamic interaction, perhaps one interfering with the platelet-sparing effect of paclitaxel in the combination with carboplatin, is the reason for the increased incidence of thrombocytopenia. The relevance of this effect on study outcomes is unknown because dose changes of nintedanib were only rarely needed, and overall dosing of chemotherapy seemed to be largely unaffected.

A potential limitation of this study is that unmasking due to the occurrence of side-effects cannot be excluded. Although the follow-up duration was planned on the basis of earlier trials in this indication, it was too short to gain mature overall survival data within the estimated period. This problem may result in the need to prolong follow-up. The preplanned analyses of subgroups by tumour burden were based on the assumption that benefit from anti-angiogenic treatment might depend on the same cutoff for tumour burden that is considered the most relevant prognostic criterion regarding surgical outcome (0 cm vs >0 cm residual tumour), yet the trial outcome suggests that other criteria may be more relevant. Finally, a limitation shared with other anti-angiogenesis trials is the absence of a biomarker that is predictive of treatment activity for individual patients. Associated translational research programmes to elucidate this aspect are planned.

Pending the overall survival results, further studies are needed to prospectively assess the clinical value of nintedanib in patients with advanced ovarian cancer and especially in cohorts with lower tumour burden.

Contributors

AdB was study chair and contributed to all parts of this study and to this manuscript. GK, IR-C, SP, IV, JMdC, and PO were members of the steering committee and were involved in patient enrolment, data collection, data interpretation, and final review of the manuscript. AR was involved in study design, data analysis, data interpretation, and writing and final review of the manuscript. NC, NdG, JP, FH, MRM, and WM were involved in patient enrolment, data collection, data interpretation, and final review of the manuscript. UD, MH, TM, ES, MB, SM, GS, MON, LB, and AL were involved in patient enrolment, data collection, and final review of the manuscript. MOS was involved in study design, data analysis, data interpretation, and final review of the manuscript. MM was involved in study design, data analysis, data interpretation, and writing and final review of the manuscript. PH was involved in study design, the steering committee, patient enrolment, data collection, data interpretation, and writing and final review of the manuscript. All authors approved the final submitted version of the manuscript.

Declaration of interests

AdB has received personal fees for advisory boards and honoraria for lectures from Roche, MSD, AstraZeneca, Pharmamar, and Amgen. AR has received grants from AGO Research and non-financial support from Boehringer Ingelheim. SP, PO, MB, and JP have received grants from Boehringer Ingelheim. NC has received personal fees from Roche, Pharmamar, Clovis, AstraZeneca, and Amgen. MOS and MM are employees of Boehringer Ingelheim Pharma. PH has received honoraria for lectures from Boehringer Ingelheim, AstraZeneca, Roche, Takeda, and Novartis. All other authors declare no competing interests.

Acknowledgments

We thank all the patients and their families who participated in this study; all investigators and supporters at the study sites; the central study

offices of the study groups; the data manager Behnaz Aminossadati of the Coordinating Center for Clinical Trials, Philipps-University of Marburg (Marburg, Germany); and all involved staff at Boehringer Ingelheim. Michael Bookman (chair), Martin Gore, Michael Friedlander, Gavin Stewart, and Emmanuel Lesaffre (biostatistician) were the members of the data monitoring committee. The following cooperative academic study groups performed the trial (in alphabetical order): AGO Study Group (leading group) and AGO Austria, BGOG Belgium and Luxembourg, DGOG Netherlands, GEICO Spain, GINECO France, MaNGO Italy, MITO Italy, and NSGO Scandinavia. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Aurora O'Brate of inVentiv Medical Communications during the preparation of this manuscript. Financial support for this study was provided by Boehringer Ingelheim, Ingelheim, Germany.

References

- 1 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; **49**: 1374–403.
- 2 De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *Lancet Oncol* 2014; **15**: 23–34.
- 3 Oberaigner W, Minicozzi P, Bielska-Lasota M, et al. Survival for ovarian cancer in Europe: the across-country variation did not shrink in the past decade. *Acta Oncol* 2012; **51**: 441–53.
- 4 du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer* 2009; **115**: 1234–44.
- 5 Stuart GC, Kitchener H, Bacon M, et al. 2010 Gynecologic Cancer InterGroup (GIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. *Int J Gynecol Cancer* 2011; **21**: 750–55.
- 6 du Bois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003; **95**: 1320–29.
- 7 Neijt JP, Engelholm SA, Tuxen MK, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol* 2000; **18**: 3084–92.
- 8 Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003; **21**: 3194–200.
- 9 Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a phase III trial of the Gynecologic Cancer Intergroup. *J Clin Oncol* 2009; **27**: 1419–25.
- 10 Chan J, Brady M, Penson R, et al. Phase III trial of every-3-weeks paclitaxel vs. dose dense weekly paclitaxel with carboplatin +/- bevacizumab in epithelial ovarian, peritoneal, fallopian tube cancer: GOG 262 (NCT01167712). *Int J Gynecol Cancer* 2013; **23** (8 suppl 1): 9–10 (abstr).
- 11 du Bois A, Weber B, Rochon J, et al. Addition of epirubicin as a third drug to carboplatin–paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. *J Clin Oncol* 2006; **24**: 1127–35.
- 12 du Bois A, Herrstedt J, Hardy-Bessard AC, et al. Phase III trial of carboplatin plus paclitaxel with or without gemcitabine in first-line treatment of epithelial ovarian cancer. *J Clin Oncol* 2010; **28**: 4162–69.
- 13 Hoskins P, Vergote I, Cervantes A, et al. Advanced ovarian cancer: phase III randomized study of sequential cisplatin–topotecan and carboplatin–paclitaxel vs carboplatin–paclitaxel. *J Natl Cancer Inst* 2010; **102**: 1547–56.
- 14 Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** (suppl 6): vi24–32.

- 15 Pfisterer J, Weber B, Reuss A, et al. Randomized phase III trial of topotecan following carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a gynecologic cancer intergroup trial of the AGO-OVAR and GINECO. *J Natl Cancer Inst* 2006; **98**: 1036–45.
- 16 Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2014; **15**: 396–405.
- 17 Zand B, Coleman RL, Sood AK. Targeting angiogenesis in gynecologic cancers. *Hematol Oncol Clin North Am* 2012; **26**: 543–63, viii.
- 18 Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011; **365**: 2473–83.
- 19 Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011; **365**: 2484–96.
- 20 Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015; **16**: 928–36.
- 21 Heitz F, Harter P, Barinoff J, et al. Bevacizumab in the treatment of ovarian cancer. *Adv Ther* 2012; **29**: 723–35.
- 22 du Bois A, Floquet A, Kim JW, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. *J Clin Oncol* 2014; **32**: 3374–82.
- 23 Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res* 2008; **68**: 4774–82.
- 24 Doebele RC, Conkling P, Traynor AM, et al. A phase I, open-label dose-escalation study of continuous treatment with BIBF 1120 in combination with paclitaxel and carboplatin as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2012; **23**: 2094–102.
- 25 du Bois A, Huober J, Stopfer P, et al. A phase I open-label dose-escalation study of oral BIBF 1120 combined with standard paclitaxel and carboplatin in patients with advanced gynecological malignancies. *Ann Oncol* 2010; **21**: 370–75.
- 26 Ledermann JA, Hackshaw A, Kaye S, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. *J Clin Oncol* 2011; **29**: 3798–804.
- 27 Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997; **53**: 983–97.
- 28 Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol* 2011; **29**: 89–96.
- 29 Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther* 2007; **6**: 2012–21.
- 30 Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011; **365**: 2473–83.
- 31 Reck M, Kaiser R, Mellemegaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014; **15**: 143–55.