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Final results from GCIG/ENGOT/AGO-OVAR 12, a randomised placebo-controlled phase III trial of nintedanib combined with chemotherapy for newly diagnosed advanced ovarian cancer

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Additional Supporting Information may be found in the online version of this article.

Key words: antiangiogenic, nintedanib, ovarian cancer, overall survival, tyrosine kinase inhibitor

Abbreviations: AUC: area under the curve; CI: confidence interval; ENGOT: European Network of Gynaecological Oncological Trial; FIGO: International Federation of Gynecology and Obstetrics; GCIG: Gynecologic Cancer InterGroup; HR: hazard ratio; MRC: Medical Research Council; OS: overall survival; PARP: polyADP ribose polymerase; PFS: progression-free survival; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor

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AGO-OVAR 12 investigated the effect of adding the oral triple angiokinase inhibitor nintedanib to standard front-line chemotherapy for advanced ovarian cancer. At the primary analysis, nintedanib demonstrated significantly improved progression-free survival (PFS; primary endpoint) compared with placebo. We report final results, including overall survival (OS). Patients with primary debulked International Federation of Gynaecology and Obstetrics (FIGO) stage IIB–IV newly diagnosed ovarian cancer were randomised 2:1 to receive carboplatin (area under the curve 5 or 6) plus paclitaxel (175 mg/m^2) on day 1 every 3 weeks for six cycles combined with either nintedanib 200 mg or placebo twice daily on days 2–21 every 3 weeks for up to 120 weeks. Between December 2009 and July 2011, 1,366 patients were randomised (911 to nintedanib, 455 to placebo). Disease was considered as high risk (FIGO stage III with >1 cm residuum, or any stage IV) in 39%. At the final analysis, 605 patients (44%) had died. There was no difference in OS (hazard ratio 0.99, 95% confidence interval [CI] 0.83–1.17, $p = 0.86$; median 62.0 months with nintedanib *vs.* 62.8 months with placebo). Subgroup analyses according to stratification factors, clinical characteristics and risk status showed no OS difference between treatments. The previously reported PFS improvement seen with nintedanib did not translate into an OS benefit in the nonhigh-risk subgroup. Updated PFS results were consistent with the primary analysis (hazard ratio 0.86, 95% CI 0.75–0.98; $p = 0.029$) favouring nintedanib. The safety profile was consistent with previous reports.

What's new?

Primary results from the randomised phase III AGO-OVAR 12 trial comparing nintedanib (a triple angiokinase inhibitor) with placebo given in combination with chemotherapy and then continued as maintenance therapy in patients with newly diagnosed advanced ovarian carcinoma demonstrated a significant improvement in progression-free survival with nintedanib. However, as reported in this paper, final overall survival (OS) results showed that the addition of nintedanib had no impact on OS. These results do not, therefore, support use of nintedanib in ovarian cancer.

Introduction

Ovarian cancer is the sixth most common cause of cancer-related deaths among women in Europe[1] and the eighth most common in women worldwide.[2] For many years, surgery and chemotherapy have been the mainstay of treatment for advanced disease. More recently, there has been extensive clinical evaluation of targeted strategies, including antiangiogenic agents and polyADP ribose polymerase (PARP) inhibitors. Among the antiangiogenic therapies, bevacizumab—a monoclonal antibody targeting vascular endothelial growth factor (VEGF)—is the most broadly studied and is an approved therapy across the ovarian cancer treatment spectrum, based on results of phase III trials in the front-line, platinum-sensitive recurrent and platinum-resistant recurrent settings.[3–7] Other antiangiogenic approaches explored in ovarian cancer include tyrosine kinase inhibitors (TKIs), such as pazopanib[8] and nintedanib, a triple angiokinase inhibitor that targets VEGF receptors 1–3, platelet-derived growth factor receptor α and β, and fibroblast growth factor receptors 1–3.[9] Nintedanib demonstrated efficacy as maintenance therapy in a small randomised phase II trial ($n = 83$) in patients who had completed chemotherapy but remained at high risk of early recurrence.[10] These results led to phase III evaluation.

AGO-OVAR 12, a Gynecologic Cancer InterGroup (GCIG)/European Network of Gynaecological Oncological Trial groups (ENGOT) randomised phase III trial in patients with newly diagnosed advanced ovarian carcinoma, compared nintedanib *vs.* placebo given in combination with carboplatin and paclitaxel for six cycles and then continued as single-agent monotherapy for up to 120 weeks. At the primary analysis (data cut-off 29 April 2013, median observation period of 22.4 months), the addition of nintedanib to standard front-line chemotherapy demonstrated a statistically significant improvement in progression-free survival (PFS; primary endpoint).[11] The hazard ratio (HR) was 0.84 (95% confidence interval [CI] 0.72–0.98; $p = 0.024$), with median PFS of 17.2 months with nintedanib *vs.* 16.6 months with placebo. Interestingly, in *post hoc* subgroup analyses exploring outcomes in the population of patients defined as high-risk (International Federation of Gynecology and Obstetrics [FIGO] stage III with

residual disease >1 cm, or any stage IV) in the International Collaboration on Ovarian Neoplasms (ICON)7 trial of bevacizumab,[4] nintedanib was shown to have a diminished effect. In contrast, in nonhigh-risk patients (stage III with residual disease ≤1 cm, or any stage II), the effect of nintedanib on PFS was more pronounced (HR 0.74, 95% CI 0.61–0.91), with median PFS of 27.1 months with nintedanib *vs.* 20.8 months with placebo. The more favourable effect was consistent with findings from the AGO-OVAR 16 trial evaluating another tyrosine kinase inhibitor, pazopanib, given as maintenance therapy in a population characterised by low postsurgical disease burden,[8] but contrasted with findings from an exploratory analysis of the Medical Research Council (MRC) ICON7 trial, in which high-risk rather than nonhigh-risk patients derived the greatest benefit from bevacizumab, including an overall survival (OS) benefit.[4,12] The reason for these diverging observations is unclear. They may be chance findings with a drug showing only modest efficacy in epithelial ovarian cancer. Alternatively, the different mechanisms of action between the monoclonal antibody bevacizumab (which targets VEGF) and the TKIs pazopanib and nintedanib (which target multiple receptors) may contribute. Translational research into the microenvironment is ongoing to explore this question.

Here we report the final analysis of the AGO-OVAR 12 trial, including the key secondary endpoint of OS.

Patients and Methods

AGO-OVAR 12 (ClinicalTrials.gov NCT01015118) was a GCIG/ENGOT double-blind placebo-controlled randomised phase III trial conducted in 22 countries across Europe, North America and Australia/New Zealand. The trial conformed with the Declaration of Helsinki, Good Clinical Practice guidelines and applicable regulatory requirements, and was approved by

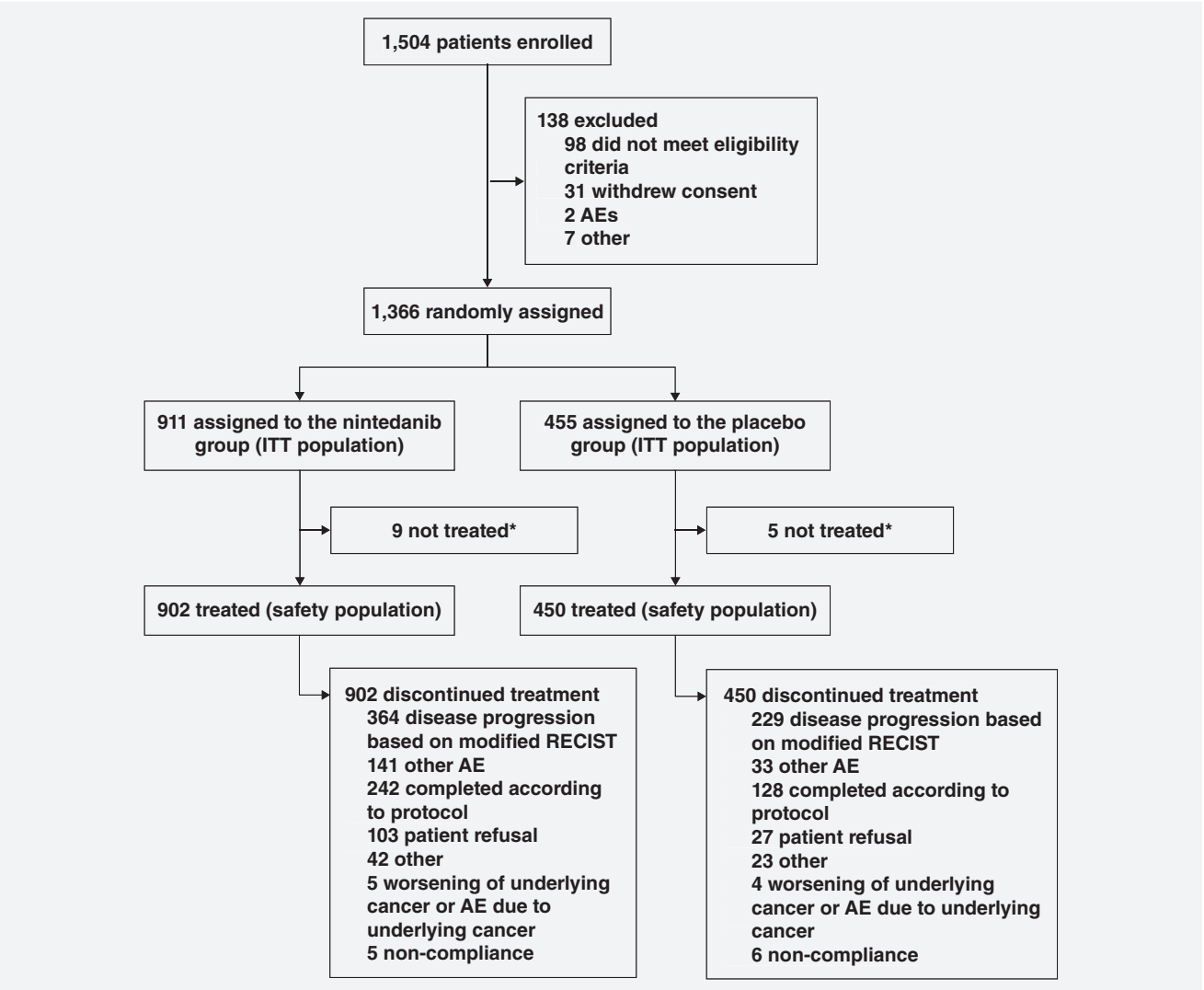

Figure 1. Patient flow. *Reasons for the 14 patients not treated were worsening of underlying cancer or AE due to underlying cancer in two, other AE in one, noncompliance with protocol in four, patient refusal in six and other reason in one. Abbreviations: AE, adverse event; ITT, intention-to-treat; RECIST, Response Evaluation Criteria in Solid Tumours.

the ethics committee at each participating centre. All patients provided written informed consent before undergoing any study-related procedure. An independent data safety monitoring board reviewed safety results during the study.

The design of the trial has been described comprehensively in the primary publication.[11] In brief, eligible patients had newly diagnosed advanced (FIGO stage IIB–IV) epithelial ovarian, fallopian tube or primary peritoneal cancer and had undergone initial debulking surgery (or if debulking surgery was not considered appropriate, had histologically confirmed disease and no planned surgery before progression). Patients were stratified by the presence of macroscopic residual postoperative tumour (yes *vs*. no), FIGO stage (IIB/III *vs*. IV) and selected carboplatin dose (area under the curve [AUC] 5 *vs*. 6 mg/ml per min). They were randomised 2:1 to either oral nintedanib 200 mg or placebo twice daily on days 2–21 every 21 days in combination with paclitaxel 175 mg/m^2 and carboplatin AUC 5 or 6 mg/ml per min administered on day 1 every 21 days for six cycles. Thereafter, nintedanib/placebo was continued as monotherapy for up to 120 weeks, or until disease progression, unacceptable toxicity or withdrawal of consent, whichever occurred earliest. Chemotherapy was to be initiated after wound healing and within 10 weeks after surgery. Nintedanib was omitted from cycle 1 in patients starting chemotherapy within 4 weeks of surgery.

The primary endpoint was investigator-assessed PFS, defined according to modified Response Evaluation Criteria in Solid Tumours (version 1.1) and cancer antigen-125 level in conjunction with clinical malignant bowel obstruction criteria. OS was a secondary endpoint, defined as the interval between randomisation and date of death from any cause and analysed using a stratified log-rank test including the stratification factors used at randomisation at a two-sided α level of 0.05.

Efficacy was analysed in the intention-to-treat population, which included all randomised patients. Treatment exposure and adverse events were analysed in the safety population, which included all patients who received at least one dose of study treatment. Each patient was to be followed for approximately 5 years for OS. Postprogression therapy and surgical interventions were recorded until the end of follow-up. Adverse events were monitored continuously until 28 days after the last treatment day (or longer if unresolved or considered drug related); adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Data availability

Currently, no mechanism is in place to allow sharing of individual deidentified patient data. Requests sent to AGO Research GmbH, AGO Study Group, Kaiser-Friedrich-Ring 71, 65185 Wiesbaden, Germany, office-wiesbaden@ago-ovar.de, will be considered on a case-by-case basis.

Results

Patient population

Between 9 December 2009 and 27 July 2011, 1,366 patients were randomised to nintedanib (n = 911) or placebo (n = 455; Fig. 1). In addition to the 14 patients who received no study

Table 1. Baseline characteristics

Characteristic	Nintedanib (n = 911)	Placebo (n = 455)
Median age, years (range)	58 (23–84)	58 (21–79)
ECOG performance status, *n* (%)		
0	542 (59)	293 (64)
1	334 (37)	149 (33)
2	25 (3)	12 (3)
Missing	10 (1)	1 (‹1)
Geographical region, *n* (%)		
Europe	751 (82)	388 (85)
North America	148 (16)	66 (15)
Australia/New Zealand	12 (1)	1 (‹1)
Primary tumour type, *n* (%)		
Epithelial ovarian	781 (86)	403 (89)
Primary peritoneal	72 (8)	29 (6)
Fallopian tube	55 (6)	22 (5)
Missing	3 (1)	1 (‹1)
Tumour histology, *n* (%)		
Serous	659 (72)	320 (70)
Mucinous	25 (3)	12 (3)
Clear cell	22 (2)	12 (3)
Other	205 (23)	111 (24)
Differentiation, *n* (%)		
Well differentiated	70 (8)	33 (7)
Moderately differentiated	157 (17)	96 (21)
Poorly differentiated/undifferentiated	576 (63)	267 (59)
Not reported	108 (12)	59 (13)
Macroscopic residual postoperative tumour, *n* (%)[1]		
No	463 (51)	230 (51)
Yes	448 (49)	225 (49)
FIGO stage, *n* (%)[1]		
IIB–III	690 (76)	344 (76)
IV	221 (24)	111 (24)
Carboplatin dose, *n* (%)[1]		
AUC 5 mg/ml per min	620 (68)	311 (68)
AUC 6 mg/ml per min	291 (32)	144 (32)
Risk status per ICON7 definition, *n* (%)		
High[2]	355 (39)	172 (38)
Nonhigh	556 (61)	283 (62)

[1]Stratification factor, as recorded in the case report form at baseline.
[2]High risk defined as FIGO stage III with ›1 cm residuum, or any FIGO stage IV.
Abbreviations: AUC, area under the curve; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; ICON, International Collaboration on Ovarian Neoplasms.

treatment (reasons provided in Fig. 1), analysed for efficacy according to the intention-to-treat approach, 12 patients in the nintedanib arm and five in the placebo arm received chemotherapy without nintedanib/placebo. These 17 patients were analysed for safety in their assigned randomised treatment arms in accordance with the protocol-specified analysis plan. Most patients (1,139, 83%) were from Europe (Table 1). Importantly, in both treatment arms, approximately half of the patients had macroscopic residual postoperative disease, one-quarter had stage IV disease and approximately 60% had nonhigh-risk disease according to MRC ICON7 criteria (Table 1).

Overall survival

At the data cut-off for the final analysis (26 September 2016), 62 months after the last patient had entered the trial, the median duration of follow-up was 60.9 (interquartile range: 60.5–61.3) months. At this date, 44% of patients had died (402 [44%] in the nintedanib arm and 203 [45%] in the placebo arm). The OS HR was 0.99 (95% CI 0.83–1.17; stratified log-rank $p = 0.86$). Median OS was 62.0 (95% CI 58.3–not estimable) months with nintedanib and 62.8 (95% CI 55.4–not estimable) months in the placebo arm (Fig. 2*a*). Five-year OS rates were 52% in the nintedanib arm and 51% in the placebo arm.

Subgroup analyses of OS according to stratification factors and other clinically relevant factors showed no difference between treatment arms (Fig. 3). In *post hoc* analyses of the previously defined subgroup of patients with nonhigh-risk disease (FIGO stage III with residual disease ≤1 cm, or FIGO stage II), OS was more favourable with nintedanib (HR 0.89, 95% CI 0.70–1.13), although the 95% CI for the HR crossed 1 (Fig. 2*b*). Median OS was not reached in either treatment arm. Conversely, OS in the high-risk subgroup (FIGO stage III with residual disease >1 cm, or FIGO stage IV) favoured the placebo arm (HR 1.14, 95% CI 0.89–1.45), again without reaching statistical significance (Fig. 2*c*). Median OS was 40.4 (95% CI 36.2–46.5) months with nintedanib *vs.* 42.7 (95% CI 33.0–52.9) months in the placebo arm. Further subgroup analyses within the nonhigh-risk population suggested an enhanced effect of nintedanib in patients with peritoneal disease or ascites (HR 0.73, 95% CI 0.53–1.00). Median OS was 60.6 (95% CI 52.6–not estimable) months with nintedanib *vs.* 50.0 (95% CI 40.4–56.2) months with placebo (Fig. 2*d*).

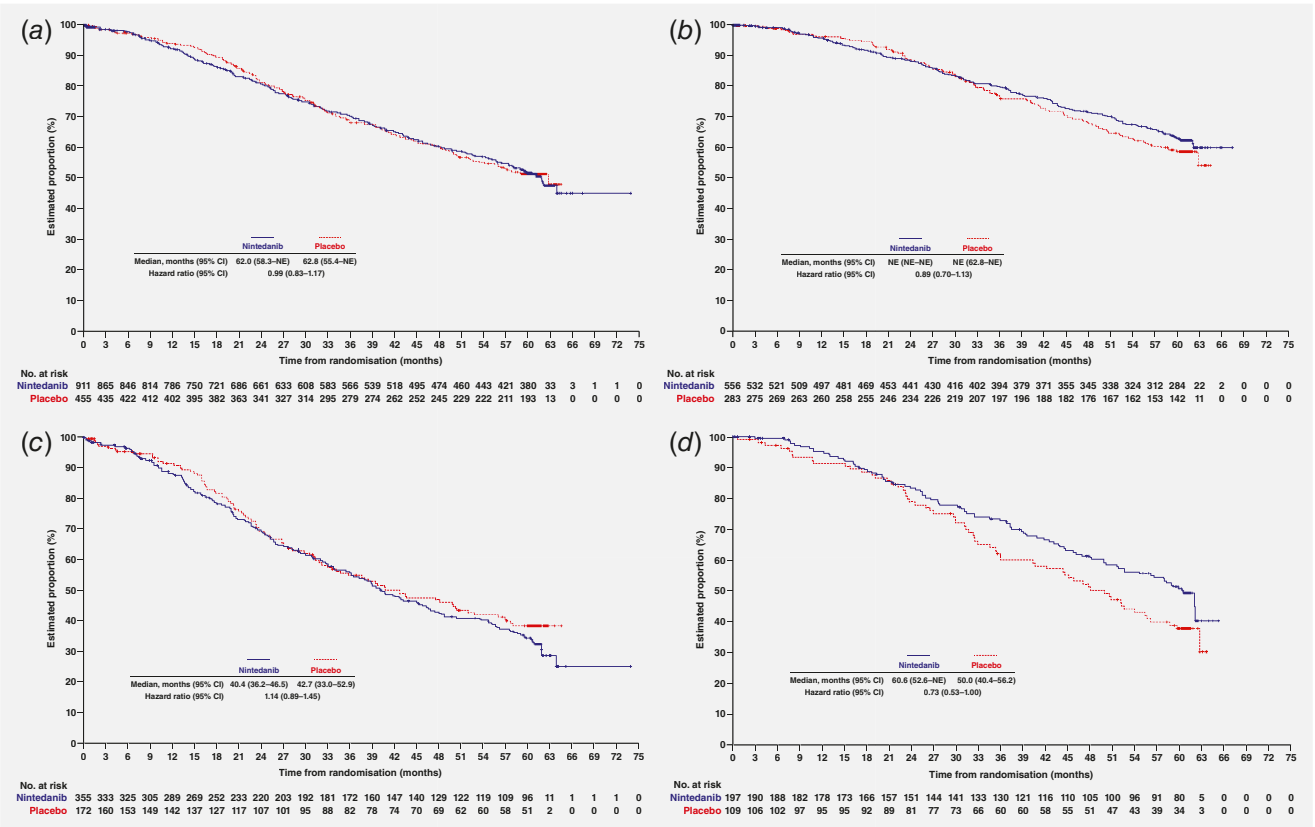

Figure 2. Final overall survival: (*a*) intent-to-treat population; (*b*) nonhigh-risk subgroup (FIGO stage III with residual disease ≤1 cm, or FIGO stage II); (*c*) high-risk subgroup (FIGO stage III with residual disease ›1 cm, or any FIGO stage IV); (*d*) nonhigh-risk subgroup but with peritoneal disease and/or ascites. Abbreviations: CI, confidence interval; FIGO, International Federation of Gynaecology and Obstetrics; NE, not estimable. [Color figure can be viewed at wileyonlinelibrary.com]

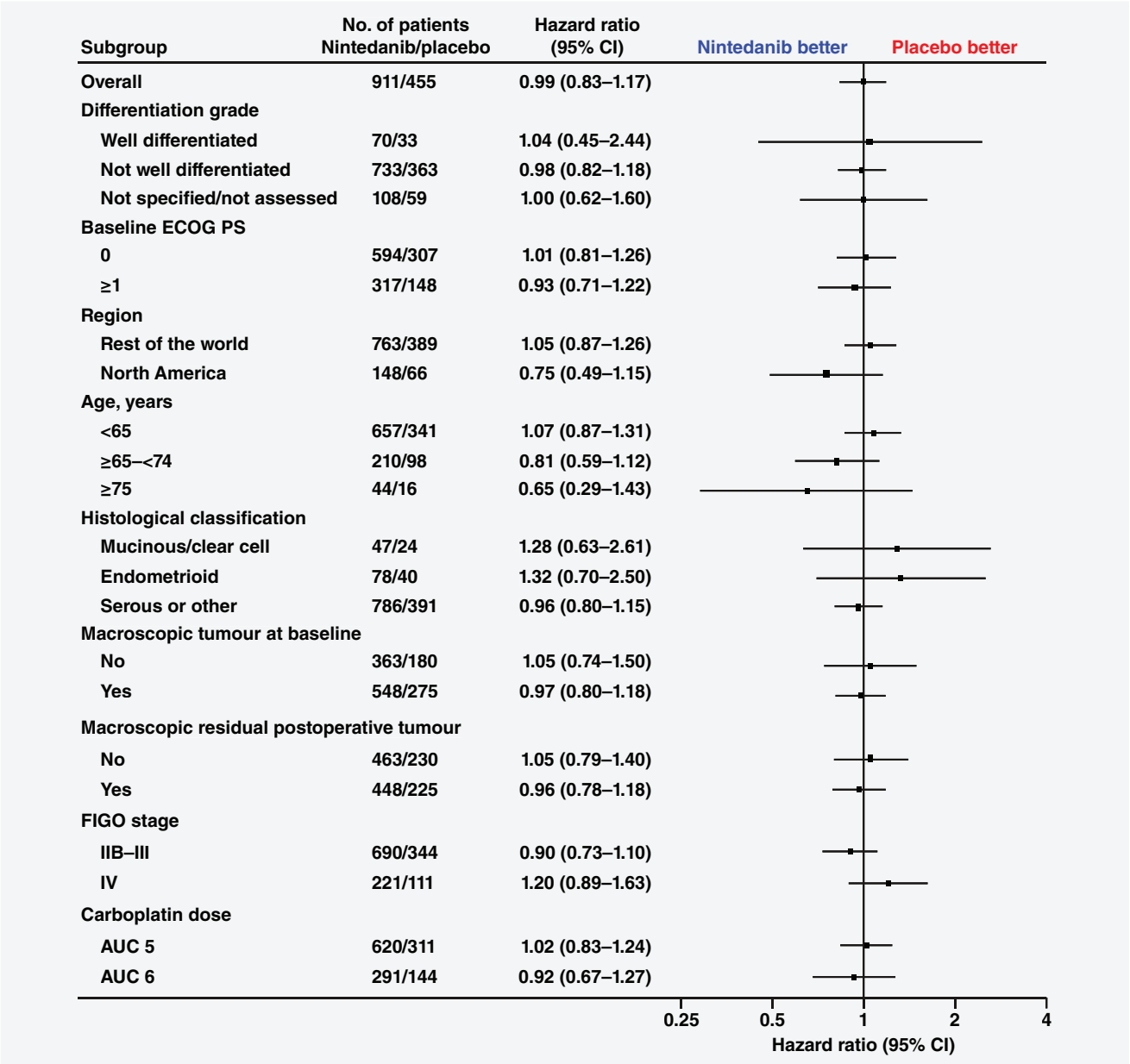

Figure 3. Subgroup analysis of final overall survival. Abbreviations: AUC, area under the curve; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynaecology and Obstetrics. [Color figure can be viewed at wileyonlinelibrary.com]

Updated PFS

At the final analysis, 595 patients (65%) in the nintedanib arm and 319 (70%) in the placebo arm had experienced disease progression or died. The PFS HR was 0.86 (95% CI 0.75–0.98; $p = 0.029$) favouring nintedanib (Fig. 4). Median PFS was 17.6 (95% CI 16.6–20.7) months with nintedanib *vs.* 16.6 (95% CI 13.9–19.7) months with placebo. Consistent with the primary analysis, the effect of nintedanib was more pronounced in patients with nonhigh-risk disease (HR 0.77, 95% CI 0.64–0.93; median PFS 27.7 months with nintedanib *vs.* 21.7 months with placebo), whereas no difference in PFS was detected in patients with high-risk disease (HR 1.03, 95% CI 0.84–1.27; Supporting Information Fig. S1).

Treatment exposure and postprogression therapy

The safety population included 1,352 patients (902 in the nintedanib arm and 450 in the placebo arm). At the data cut-off, all patients in both treatment arms had completed or discontinued treatment. Slightly fewer patients in the nintedanib

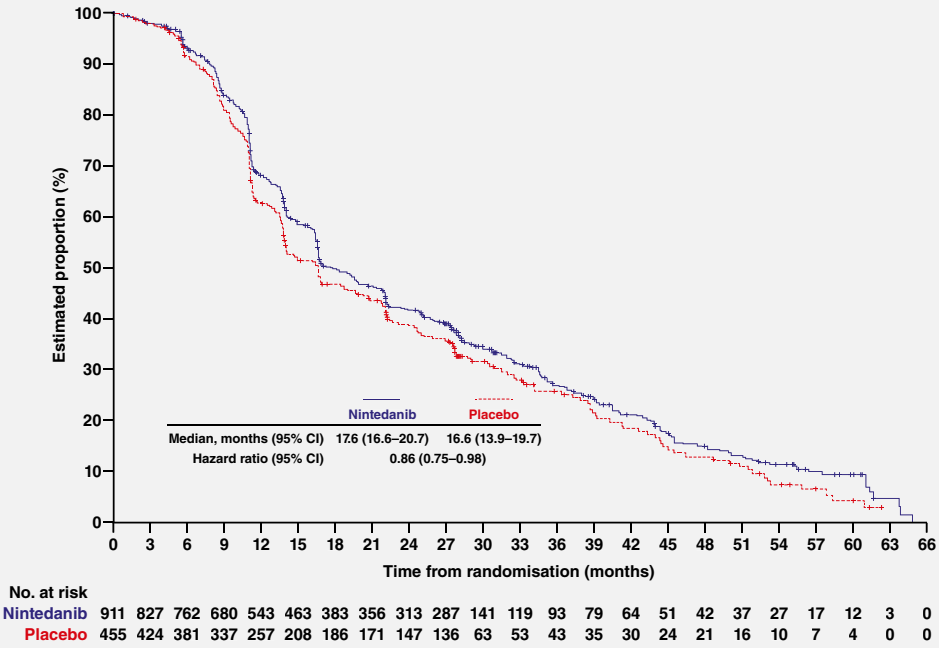

Figure 4. Updated progression-free survival. Abbreviation: CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

than the placebo arm completed six cycles of chemotherapy (86% *vs*. 92%, respectively). After completing chemotherapy, 82% of patients in the nintedanib arm and 86% in the placebo arm continued to single-agent maintenance treatment. The median duration of nintedanib treatment was 12.5 months and the median duration of placebo was 13.5 months (range 0–29 months in both arms). The proportion of patients undergoing nintedanib/placebo dose reduction was substantially higher in the nintedanib than the placebo arm (52% *vs*. 9%, respectively); corresponding figures for chemotherapy dose reductions were 21% *vs*. 11%. Permanent treatment discontinuation of nintedanib/placebo due to adverse events was also more common in the nintedanib arm (24% *vs*. 15%, respectively).

Approximately two-thirds of all patients received further anticancer therapy during study follow-up (62% in the nintedanib arm *vs*. 66% in the placebo arm). Approximately one-third of patients in each treatment group received at least one line of antiangiogenic therapy (18% *vs*. 20%, respectively) and 29% of patients in both treatment arms received fourth- or later-line therapy (Supporting Information Table S1).

Safety

The most common adverse events were diarrhoea (78% with nintedanib *vs*. 26% with placebo), nausea (65% *vs*. 53%) and alopecia (58% *vs*. 62%; Table 2). Diarrhoea, nausea, vomiting, thrombocytopenia and liver enzyme abnormalities were more common with nintedanib. Grade ≥3 adverse events were reported in 81% of nintedanib-treated *vs*. 67% of placebo-treated patients. Nintedanib was associated with more grade ≥3 diarrhoea (22% *vs*. 2% with placebo), thrombocytopenia (15% *vs*. 6%) and liver enzyme abnormalities (alanine aminotransferase increase 15% *vs*. 2%). Grade ≥3 gastrointestinal perforation was reported in 18 patients (2%) in the nintedanib arm and two patients (<1%) in the placebo arm. Three additional patients in the nintedanib arm and one in the placebo arm experienced grade 1/2 gastrointestinal perforation. Fatal adverse events were reported in 30 nintedanib-treated patients (3%) and 16 placebo-treated patients (4%), although many (21 [2%] *vs*. 10 [2%], respectively) were attributed to disease progression.

Safety was also analysed separately for the combination chemotherapy treatment phase *vs*. the maintenance phase. During the combination chemotherapy treatment phase, adverse events led to nintedanib dose reduction or discontinuation in 425 (47%) of 902 patients and placebo dose reduction or discontinuation in 51 (11%) of 450 patients. Corresponding proportions during the maintenance period were 36% (266 of 736 patients) *vs*. 12% (47 of 389 patients). In the combination chemotherapy phase, serious adverse events occurred in 286 (32%) of 902 nintedanib-treated patients *vs*. 94 (21%) of 450 placebo-treated patients (fatal in 12 patients [1%] *vs*. 10 patients [2%]). During maintenance therapy, serious adverse events occurred in 148 of 736 patients (20%) receiving maintenance nintedanib *vs*. 85 of 389 patients (22%) receiving maintenance placebo, including fatal events in 18 patients (2%) *vs*. six patients (2%), respectively.

Discussion

In the AGO-OVAR 12 trial, combining nintedanib with front-line chemotherapy and continuing as single-agent maintenance

Table 2. Summary of safety: adverse events in ≥10% of patients (any grade)

	Nintedanib (n = 902)		Placebo (n = 450)	
Adverse event, no. of patients (%)	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Diarrhoea	703 (78)	195 (22)	117 (26)	9 (2)
Nausea	589 (65)	36 (4)	237 (53)	14 (3)
Alopecia	519 (58)	17 (2)	278 (62)	12 (3)
Neutropenia	428 (47)	336 (37)	206 (46)	151 (34)
Vomiting	406 (45)	28 (3)	126 (28)	11 (2)
Fatigue	396 (44)	38 (4)	203 (45)	7 (2)
Anaemia	342 (38)	108 (12)	136 (30)	25 (6)
Thrombocytopenia	310 (34)	137 (15)	88 (20)	25 (6)
Abdominal pain	301 (33)	37 (4)	116 (26)	12 (3)
ALT increased	260 (29)	136 (15)	49 (11)	9 (2)
Constipation	260 (29)	10 (1)	158 (35)	5 (1)
Arthralgia	242 (27)	13 (1)	138 (31)	10 (2)
AST increased	220 (24)	64 (7)	41 (9)	5 (1)
Peripheral sensory neuropathy	214 (24)	11 (1)	114 (25)	7 (2)
Myalgia	202 (22)	10 (1)	109 (24)	3 (1)
Peripheral neuropathy	173 (19)	7 (1)	86 (19)	8 (2)
Asthenia	171 (19)	26 (3)	67 (15)	6 (1)
Decreased appetite	171 (19)	9 (1)	63 (14)	0
Leucopenia	168 (19)	67 (7)	78 (17)	18 (4)
Headache	143 (16)	8 (1)	53 (12)	1 (<1)
Urinary tract infection	139 (15)	11 (1)	50 (11)	4 (1)
Abdominal pain upper	132 (15)	9 (1)	58 (13)	3 (1)
Dysgeusia	126 (14)	1 (<1)	37 (8)	0
Hypertension	123 (14)	39 (4)	23 (5)	3 (1)
Dyspnoea	117 (13)	8 (1)	58 (13)	6 (1)
Insomnia	105 (12)	2 (<1)	57 (13)	1 (<1)
Paraesthesia	101 (11)	2 (<1)	64 (14)	2 (<1)
Rash	96 (11)	9 (1)	50 (11)	0
Pain in extremity	95 (11)	3 (<1)	57 (13)	1 (<1)
Hypomagnesaemia	93 (10)	7 (1)	25 (6)	3 (1)
Hypokalaemia	91 (10)	28 (3)	26 (6)	9 (2)
Back pain	84 (9)	4 (<1)	55 (12)	2 (<1)
Pyrexia	81 (9)	4 (<1)	53 (12)	2 (<1)
Hot flush	73 (8)	1 (<1)	45 (10)	1 (<1)
Peripheral oedema	49 (5)	0	48 (11)	2 (<1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

therapy did not improve OS, either in the overall population or in subgroups defined by stratification factors. Results of the updated PFS analysis including an additional 162 events were almost identical to the primary analysis, showing a statistically significant benefit but of limited clinical relevance with nintedanib. The HR was 0.86 (95% CI 0.75–0.98) favouring nintedanib; median PFS was 17.6 months with nintedanib *vs.* 16.6 months with placebo. The previously reported PFS benefit from nintedanib in patients with nonhigh-risk disease did not translate into a significant OS improvement. The only subgroup with a suggested hint of OS improvement was the population of patients with nonhigh-risk disease but with peritoneal disease/ascites. It is plausible that M1 polarised macrophages in the tumour microenvironment in ovarian cancer may relate to ascites formation and better prognosis, and may potentially affect the mechanisms of neoangiogenesis.[13,14] However, the exploratory *post hoc* nature of the analysis in a small subset limits the conclusions that can be drawn. Despite extensive research efforts, particularly with bevacizumab, no predictive biomarker for antiangiogenic therapies has been identified to date.

At the time of the primary analysis, maintenance treatment was ongoing in 135 patients (15%) in the nintedanib arm and

73 patients (16%) in the placebo arm.[11] At the final analysis reported here, all patients had completed treatment but the median duration of nintedanib/placebo exposure was unchanged. Consistent with previous experience,[10,11] nintedanib was associated with increased incidences of gastrointestinal effects compared with chemotherapy alone. However, nintedanib was not associated with detrimental effects on quality of life.[11] No new safety signals were observed in this updated analysis.

Although the previously reported primary results[11] and the final results reported here do not support a role for nintedanib in ovarian cancer, median OS exceeded 5 years in both treatment arms, representing meaningful progress in the management of ovarian cancer in the past decade. In the mid-2000s, AGO-OVAR trials in the front-line setting reported median OS of approximately 40–45 months[15,16] with combination chemotherapy regimens, increasing to approximately 50 months in AGO-OVAR 9,[17] compared with >60 months in the AGO-OVAR 12 trial reported here. This observation may reflect the increased proportion of patients receiving better surgical resection (50% of patients in AGO-OVAR 12 had no residual disease after upfront surgery) and the expanding treatment options available for recurrent disease, including maintenance PARP inhibitors and nonplatinum combination regimens, such as trabectedin and pegylated liposomal doxorubicin, or rechallenge with antiangiogenic therapy.[18–22] This progress continues with the remarkable activity seen in the recent phase III trial of olaparib as maintenance therapy after front-line chemotherapy in patients with *BRCA*-mutated advanced ovarian cancer.[23] Ongoing trials should inform whether the benefit of PARP inhibitors extends beyond *BRCA*-mutated disease to broader patient populations. Furthermore, the suggested OS benefit in certain subgroups treated with antiangiogenic agents supports further exploration of this strategy in combination with PARP inhibition, as in the PAOLA-1 trial (NCT02477644), with the goal of improving outcomes further.

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