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Safety and efficacy of single-agent bevacizumab-containing therapy in elderly patients with platinum-resistant recurrent ovarian cancer: Subgroup analysis of the randomised phase III AURELIA trial

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HIGHLIGHTS

- The PFS and response rate benefit from bevacizumab were similar regardless of age.
- Grade ≥ 3 hypertension was more common with bevacizumab in older vs younger patients.
- Thromboembolic events were not increased with bevacizumab in patients ≥65 vs <65 years.
- In older patients, no PRO benefit was seen with bevacizumab versus chemotherapy alone.

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ABSTRACT

Background. The AURELIA trial demonstrated significantly improved progression-free survival (PFS) with bevacizumab added to chemotherapy for platinum-resistant ovarian cancer (PROC).

Methods. Patients with PROC were randomised to receive investigator-selected single-agent chemotherapy alone or with bevacizumab. Post-hoc exploratory analyses assessed efficacy, safety and patient-reported outcomes according to age <65 versus ≥65 years.

Results. In the 133 patients (37%) aged ≥65 years, baseline hypertension was more frequent and ascites was less common than in patients <65 years. The magnitude of PFS benefit from bevacizumab was similar in patients ≥65 versus <65 years (hazard ratio 0.44 [95% CI, 0.31–0.64] versus 0.49 [95% CI, 0.37–0.64], respectively, treatment–age interaction $p = 0.58$), with similar improvements in response rates. Grade ≥ 3 hypertension was more common with bevacizumab than chemotherapy alone in both subgroups, and more common in older than younger patients irrespective of treatment. However, there was no excess of other adverse events of specific interest for bevacizumab, including venous thromboembolic events, in older patients. More patients receiving

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bevacizumab in the younger but not the older subgroup showed improved gastrointestinal/abdominal symptoms.

Conclusion. In exploratory analyses, PFS and response rate improvement with bevacizumab were consistent in older and younger patients. Grade ≥ 3 hypertension was more common in elderly bevacizumab-treated patients; careful monitoring is recommended. Overall, bevacizumab-containing therapy was well tolerated in a selected population aged ≥65 years, suggesting a favourable benefit:risk profile. However, geriatric assessments are needed to improve selection of elderly patients potentially gaining symptom and quality of life improvements from bevacizumab-containing therapy.

Clinical trials registration. ClinicalTrials.gov NCT00976911.

1. Introduction

The incidence of ovarian cancer (OC) diagnosis increases with age, peaking at 80–84 years [1]. More than half of all patients diagnosed with OC are aged ≥65 years; with increasing life expectancy and an ageing population, this proportion is likely to increase [2]. Nevertheless, prospective data for OC therapy in elderly populations are scarce [3,4]. Older patients are often under-represented or excluded from large prospective clinical trials because of upper age limits or strict eligibility requirements regarding performance status, comorbidities or concomitant medications, or because older patients choose not to participate in clinical trials [5,6]. Consequently, evidence in older patients is typically limited to small single-arm studies sometimes evaluating unconventional regimens, retrospective analyses or subgroup analyses of large clinical trials [7–10]. These generally suggest similar efficacy in older and younger patients [11]. However, some analyses and epidemiological studies have suggested that increased age is a negative prognostic factor [5,10,12]. Under-treatment may contribute to shorter survival expectations in older patients [13–17]. Some older patients may decline more intensive therapy, valuing quality of life over duration [14,17]; however, suboptimal regimens, less complete surgery and/or fear of toxicity with more effective therapies may also lead to under-treatment [18]. Worse tolerability may be expected in older patients because of the increased likelihood of poor performance status and comorbidities. In a recent meta-analysis, comorbid cardiovascular disease correlated significantly with increased risk of haematological, non-haematological, pulmonary and renal grade 3/4 toxicities [19]. Therefore it is important to understand whether toxicity is increased in older patients or if other factors may predict toxicity more accurately, and how tolerability can be improved without denying older patients effective therapy.

In platinum-resistant OC (PROC), single-agent chemotherapy has traditionally been considered the standard of care. The choice of regimen typically depends on patient-related and disease characteristics, including age, performance status and comorbidities. More recently, bevacizumab combined with chemotherapy has become an important treatment option in this setting. European and US regulatory approval of bevacizumab for PROC was based on results of the randomised phase III AURELIA trial [20], which demonstrated significantly improved progression-free survival (PFS) and overall response rate (ORR) with bevacizumab added to chemotherapy. Furthermore, patient-reported outcomes (PROs) demonstrated a significant benefit from bevacizumab for abdominal/gastrointestinal symptoms [21]. We performed exploratory post hoc subgroup analyses to assess the impact of bevacizumab on safety, efficacy and PROs in elderly patients treated in AURELIA.

2. Patients and methods

AURELIA (NCT00976911) was an open-label, two-arm, multinational phase III trial evaluating bevacizumab added to chemotherapy for PROC. Eligible patients had received no more than two prior chemotherapy regimens and had epithelial ovarian, primary peritoneal or fallopian tube cancer that had progressed within 6 months of receiving at least 4 cycles of platinum-based chemotherapy. Before randomisation, investigators selected chemotherapy for each patient (weekly paclitaxel, topotecan or pegylated liposomal doxorubicin [PLD]). Patients were randomised to receive this chemotherapy either alone or with bevacizumab 15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks, depending on the chemotherapy regimen chosen. Stratification factors were selected chemotherapy, prior anti-angiogenic therapy and platinum-free interval (PFI; <3 versus 3–6 months).

The primary end-point was PFS according to Response Evaluation Criteria in Solid Tumours (RECIST; version 1.0). Secondary end-points included ORR (best overall response by RECIST version 1.0), overall survival (OS), safety (adverse events [AEs] graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0), tolerability and PROs. The trial was not designed to formally compare OS between treatment arms, as crossover from chemotherapy alone to bevacizumab was permitted.

The primary PFS analysis was planned after PFS events in 290 patients in the intent-to-treat (ITT) population. Final OS analysis was performed after 70% of patients had died. For both end-points, hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using an unstratified Cox proportional hazards model. Median values in each group were estimated using Kaplan–Meier methodology.

For the primary PRO analyses, responder analyses compared the proportion of patients in each treatment arm achieving ≥15% improvement in an abdominal/gastrointestinal symptom subscale of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire ovarian cancer-specific module (EORTC QLQ-OV28). Details of compliance calculations and PRO analyses in AURELIA (including EORTC Core Module [QLQ-C30] and Functional Assessment of Cancer Therapy–Ovarian cancer Symptom Index [FOSI]) have been described previously [21].

In the present analyses, we focused on the primary and secondary PRO end-points. Proportions were calculated including all patients with baseline questionnaires and counting those patients with missing questionnaires at week 8/9 as not improved. No statistical adjustment for multiplicity was implemented for these exploratory post hoc analyses. Efficacy analyses included all randomised patients. Safety analyses included all patients who received at least one dose of study therapy. All reported data are based on the final OS data cutoff (January 25, 2013).

3. Results

The AURELIA trial included 133 patients aged ≥65 years (37% of the ITT population) and 228 aged <65 years. The most notable differences between these subgroups were the higher proportion of patients with comorbidities at baseline and the lower proportion with ascites at baseline, non-measurable disease or a PFI <3 months in elderly versus younger patients (Table 1). Within the elderly subgroup, baseline characteristics were generally evenly distributed between the treatment arms, the main exceptions being the higher proportion of patients in the chemotherapy-alone arm with two prior chemotherapy regimens or dyslipidaemia, and the lower proportion with a PFI <3 months or

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Table 1
Baseline characteristics according to age and treatment arm.

Characteristic, *n* (%)	Subgroup aged <65 years		Subgroup aged ≥65 years	
	Chemotherapy alone (*n* = 119)	Bevacizumab + chemotherapy (*n* = 109)	Chemotherapy alone (*n* = 63)	Bevacizumab + chemotherapy (*n* = 70)
Median age, years (range)	56 (25–64)	56 (25–64)	70 (65–84)	69 (65–80)
Histology at diagnosis				
Serous and adenocarcinoma	95 (80)	94 (86)	57 (90)	62 (89)
Mucinous	5 (4)	3 (3)	0	0
Endometrioid	7 (6)	7 (6)	2 (3)	1 (1)
Clear cell	11 (9)	3 (3)	1 (2)	1 (1)
Other	5 (4)	4 (4)	4 (6)	9 (13)
Two prior chemotherapy regimens	46 (39)	46 (42)	32 (51)	26 (37)
Platinum-free interval < 3 months	34 (29)	33 (30)	12 (19)	17 (24)
ECOG PS				
0	69 (58)	60 (55)	30 (48)	47 (67)
1	42 (35)	40 (37)	27 (43)	18 (26)
2	6 (5)	8 (7)	5 (8)	4 (6)
Missing	2 (2)	1 (1)	1 (2)	1 (1)
Disease measurability				
Non-measurable (0–<1 cm)	30 (25)	25 (23)	8 (13)	11 (16)
SLD 1–<5 cm	32 (27)	38 (35)	28 (44)	28 (40)
SLD ≥5 cm	57 (48)	46 (42)	27 (43)	31 (44)
Ascites at baseline	36 (30)	41 (38)	18 (29)	18 (26)
Comorbidities				
Hypertension	30 (25)	14 (13)	30 (48)	32 (46)
Dyslipidaemia	2 (2)	3 (3)	13 (21)	4 (6)
Abdominal pain[a]	11 (9)	16 (15)	6 (10)	7 (10)
Concomitant medications at baseline				
Antihypertensive	2 (2)	0	4 (6)	9 (13)
Anticoagulant	3 (3)	2 (2)	3 (5)	3 (4)

ECOG PS = Eastern Cooperative Oncology Group performance status; SLD = sum of the largest diameters.
[a] Includes the preferred terms abdominal pain, abdominal pain upper, abdominal distension and abdominal pain lower.

ongoing antihypertensive therapy. Among patients aged ≥65 years, the most frequently selected chemotherapy was topotecan in the chemotherapy-alone arm and PLD in the bevacizumab arm.

The median duration of chemotherapy was slightly longer in the bevacizumab than the chemotherapy-alone arm (Table 2). Almost half of the bevacizumab-treated patients completed ≥24 weeks of treatment, irrespective of age. Bevacizumab discontinuation because of AEs was marginally more common in elderly than younger patients.

The incidence of grade ≥3 AEs was 55% in both treatment arms in patients aged <65 years, of which 2% in the bevacizumab arm and 3% in the chemotherapy-alone arm were fatal. In the older subgroup, grade ≥3 AEs occurred in 64% of bevacizumab-treated patients versus 51% of those receiving chemotherapy alone. These included four treatment-related deaths in bevacizumab-treated patients (6%; one case each of: gastrointestinal haemorrhage, cardiac arrest, gastrointestinal perforation and general physical health deterioration) versus one death (2%) in the chemotherapy-alone arm (infectious peritonitis). Compared with their younger counterparts, older bevacizumab-treated patients experienced more grade ≥2 and grade ≥3 hypertension and slightly more grade ≥2 proteinuria (Table 3). Further analyses of hypertension in bevacizumab-treated patients aged ≥65 years revealed that the appearance of grade ≥2 hypertension during study therapy was at least as common in patients without hypertension at baseline (15 of 38 patients; 39%) as in those with pre-existing hypertension (7 of 32 patients; 22%). Corresponding proportions for grade ≥3 hypertension were 18% and 9%, respectively. There was no excess of thromboembolic events in older versus younger bevacizumab-treated patients. Subgroup analyses using a cut-off of 70 years showed similar effects to the main analysis (Appendix Table A1).

Efficacy findings were generally consistent with results in the ITT population and showed no differences according to age. PFS was significantly improved with bevacizumab-containing therapy in both elderly (HR 0.44 [95% CI, 0.31–0.64]; $p < 0.001$) and younger (HR 0.49 [95% CI, 0.37–0.64]; $p < 0.001$) patients but there was no significant difference in treatment effect in the two age subgroups (treatment–age interaction $p = 0.58$) (Fig. 1). Similarly, in the evaluable population of 286 patients, the RECIST ORR was higher with bevacizumab-containing therapy than chemotherapy alone in both the elderly subgroup (31.3% versus 16.4%,

Table 2
Summary of treatment exposure.

Characteristic	Subgroup aged <65 years		Subgroup aged ≥65 years	
	Chemotherapy alone (*n* = 118[a])	Bevacizumab + chemotherapy (*n* = 109)	Chemotherapy alone (*n* = 63)	Bevacizumab + chemotherapy (*n* = 70)
Median duration of study therapy (IQR), months	2.2 (1.4–4.1)	5.3 (3.3–7.9)	3.3 (1.4–4.8)	5.1 (2.5–9.7)
Chemotherapy	2.2 (1.4–4.1)	4.6 (2.8–6.2)	3.3 (1.4–4.8)	4.4 (1.9–5.8)
Bevacizumab	–	5.1 (2.3–7.8)	–	5.1 (1.8–9.7)
Patients completing >24 weeks of therapy, *n* (%)	13 (11)	52 (48)	11 (17)	32 (46)
Chemotherapy	13 (11)	36 (33)	11 (17)	22 (31)
Bevacizumab	–	48 (44)	–	31 (44)
Bevacizumab discontinuation due to adverse event, *n* (%)[b]	–	28 (24)	–	21 (30)
Chemotherapy discontinuation due to adverse event, *n* (%)[b]	8 (7)	28 (26)	3 (5)	23 (33)

IQR = interquartile range.
[a] One patient randomly assigned to chemotherapy also received bevacizumab and was therefore included in the bevacizumab + chemotherapy safety population. One patient randomly assigned to bevacizumab + chemotherapy received no study drug so was excluded from the safety population.
[b] Includes unacceptable toxicity.

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Table 3
Summary of safety.

Grade ≥ 3 adverse events of special interest[a], *n* (%)	Subgroup aged <65 years		Subgroup aged ≥65 years	
	Chemotherapy alone ($n = 118$[b])	Bevacizumab + chemotherapy ($n = 109$)	Chemotherapy alone ($n = 63$)	Bevacizumab + chemotherapy ($n = 70$)
Hypertension	0	4 (3.7)	2 (3.2)	10 (14.3)
Grade ≥ 2	3 (2.5)	14 (12.8)	9 (14.3)	22 (31.4)
Proteinuria	0	1 (0.9)	0	3 (4.3)
Grade ≥ 2	0	11 (10.1)	1 (1.6)	12 (17.1)
Gastrointestinal perforation	0	2 (1.8)	0	1 (1.4)
Grade ≥ 2	0	3 (2.8)	0	1 (1.4)
Fistula/abscess	0	1 (0.9)	0	1 (1.4)
Grade ≥ 2	0	3 (2.8)	0	1 (1.4)
Bleeding	2 (1.7)	0	0	2 (2.9)
Thromboembolic event	8 (6.8)	7 (6.4)	0	2 (2.9)
Arterial	1 (0.8)	1 (0.9)	0	2 (2.9)
Venous	7 (5.9)	6 (5.5)	0	0
Wound-healing complication	0	1 (0.9)	0	0
RPLS	0	0	0	1 (1.4)
Congestive heart failure	1 (0.8)	1 (0.9)	0	0

RPLS = reversible posterior leucoencephalopathy syndrome.
[a] Adverse-event group according to Roche bevacizumab baskets (Medical Dictionary for Regulatory Activities version 14.1).
[b] One patient randomly assigned to chemotherapy also received bevacizumab and was therefore included in the bevacizumab + chemotherapy safety population. One patient randomly assigned to bevacizumab + chemotherapy received no study drug so was excluded from the safety population.

respectively; $p = 0.03$) and the younger subgroup (25.0% versus 10.1%, respectively; $p = 0.01$) (treatment–age interaction $p = 0.88$). As in the ITT population, there was no OS difference between treatment arms in either age subgroup. The HR for OS was 0.82 (95% CI, 0.61–1.10; $p = 0.19$) in patients aged <65 years (median OS: 14.7 months with bevacizumab-containing therapy versus 12.9 months with chemotherapy alone; 1-year OS rates: 65% and 55%, respectively). In the older subgroup, the OS HR was 0.95 (95% CI, 0.62–1.46; $p = 0.83$). Median OS was 18.3 months with bevacizumab-containing therapy versus 16.7 months with chemotherapy alone; 1-year OS rates were 61% versus 63%, respectively (treatment–age interaction $p = 0.60$).

In the chemotherapy-alone group, 49 patients (41%) aged <65 years and 23 patients (37%) aged ≥65 years crossed over to single-agent bevacizumab after progression.

Compliance with questionnaire completion was broadly similar irrespective of age at all assessment points (84–96% at baseline, 65–92% at week 8/9 and 68–91% at week 16/18). The primary PRO end-point analysis showed a significant benefit favouring bevacizumab in younger patients. The proportion with ≥15% improvement in gastrointestinal/abdominal symptoms was 29% with bevacizumab versus 9% with chemotherapy alone ($p < 0.001$). However, in older patients, no difference between treatment arms was seen (11% in both arms; $p = 0.92$) (treatment–age interaction $p = 0.05$). In older patients, sensitivity analyses using a 10% threshold or excluding all missing questionnaires showed a small difference between treatments but there was no treatment–age interaction for either sensitivity analysis ($p = 0.30$ and $p = 0.05$, respectively).

For the secondary PRO end-point, a ≥ 15% improvement in FOSI score at week 8/9 was achieved in significantly more patients receiving bevacizumab than chemotherapy alone within the younger subgroup (18% versus 2%; $p < 0.001$) but not in the elderly subgroup (3% versus 5%, respectively; $p = 0.56$) (treatment–age interaction $p = 0.01$). Finally, QLQ-C30 analyses showed a benefit in physical, role and social functional subscales and global health status (although not emotional function) in younger patients, whereas no difference was seen for any of the subscales in older patients, although there was no treatment–age interaction for any subscale ($p > 0.05$).

4. Discussion

These post hoc exploratory analyses of AURELIA data suggest that the PFS and ORR benefits from combining bevacizumab with chemotherapy for PROC are similar in older and younger patients. The PFS HR of 0.44 (95% CI, 0.31–0.64) in patients aged ≥65 years and the more than doubling of median PFS are clinically meaningful. Importantly, this improvement was achieved without substantially increasing toxicity, except hypertension. Hypertension was more common with bevacizumab than chemotherapy alone, and in older than younger patients in both treatment arms. Age is a well-known risk factor for hypertension. Furthermore, the older subgroup in this study included a higher proportion of patients with ongoing hypertension and/or antihypertensive therapy at baseline compared with their younger counterparts.

The observed higher incidence of hypertension in older than younger bevacizumab-treated patients is consistent with reports in colorectal and breast cancers [22,23]. More recent data in older patients receiving front-line bevacizumab for OC in the German non-interventional OTILIA study suggested a similar incidence of hypertension in patients aged ≥70 and <70 years (18% versus 17%, respectively) [24], whereas in the ROSiA study, also evaluating bevacizumab in the front-line setting but for an extended duration, grade ≥3 hypertension was more common in patients ≥70 years than in their younger counterparts (41% versus 22%, respectively) [25]. In a retrospective analysis of 86 patients receiving bevacizumab-containing therapy, predominantly for PROC, grade ≥ 3 hypertension was significantly more common in elderly than younger patients, both at baseline and during bevacizumab-containing therapy [26]. The authors reported that baseline hypertension was associated with an increased risk of developing grade 3/4 hypertension during bevacizumab therapy, and recommended multidisciplinary cardiovascular assessment before starting anti-angiogenic therapy in older patients. Interestingly, these results differ from our observations: we found no correlation between pre-treatment and on-treatment hypertension. However, analyses from both studies are limited by their exploratory nature and small patient numbers. In a much larger cohort of patients receiving first-line bevacizumab-containing therapy for metastatic breast cancer in the single-arm ATHENA study, hypertension was more common in patients with versus without pre-existing hypertension, but in-depth analyses revealed no relationship between the presence or severity of baseline hypertension and severity of hypertension during bevacizumab exposure [23]. Nevertheless, the possibility that pre-existing hypertension may increase the risk of hypertension during bevacizumab therapy for OC, particularly in the elderly, cannot be excluded and underlines the importance of monitoring patients carefully and managing hypertension promptly and effectively to avoid escalation to more severe hypertension.

Reassuringly, we observed no increase in the incidence of thromboembolic events in older versus younger patients. This finding is

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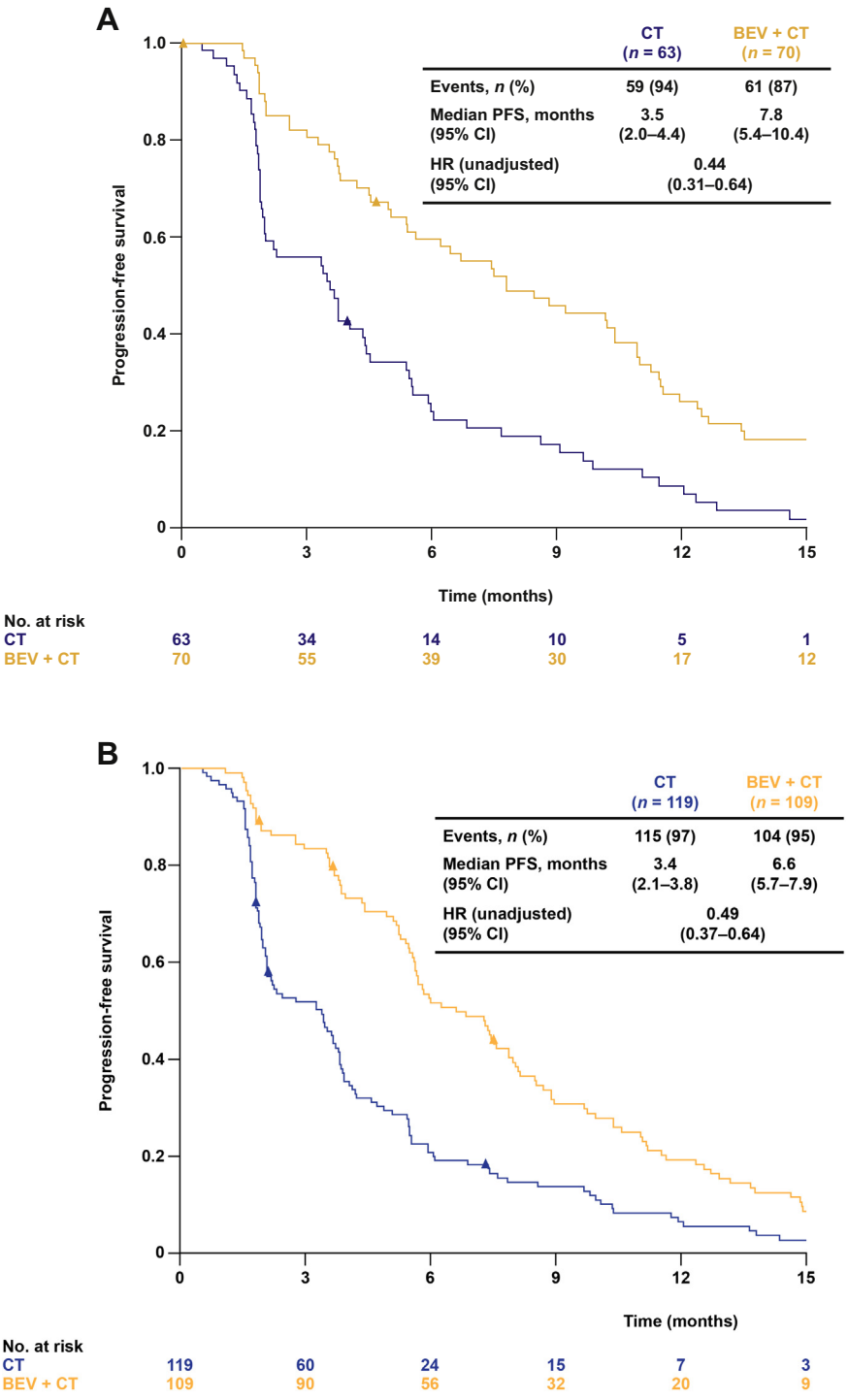

Fig. 1. PFS in the subgroups of patients aged: (A) ≥65 years (median duration of follow-up: 22.9 months [range <0.1–31.5 months]; and (B) <65 years (median duration of follow-up: 27.0 months [range 0.6–35.6 months]. BEV = bevacizumab; CI = confidence interval; CT = chemotherapy; HR = hazard ratio; PFS = progression-free survival.

noteworthy because thromboembolic events may be a particular concern in elderly patients. Specifically among bevacizumab-treated patients, an increased incidence of arterial thromboembolic events has been reported in older versus younger patients in some analyses in colorectal, breast and lung cancers [27–29] but not in others [23,30]. In the OTILIA study in OC [24], venous and arterial thromboembolic events were no more common in patients aged ≥70 versus <70 years, whereas in the ROSiA study, thromboembolic events were slightly more common in older patients [25].

The improvement in gastrointestinal/abdominal symptoms in the overall population and the subgroup of younger patients was not observed in the older subgroup, perhaps because older patients were less symptomatic and therefore less able to show a meaningful improvement in symptoms. Of note, the proportion of elderly bevacizumab-treated patients achieving a ≥15% improvement in gastrointestinal/abdominal symptoms was similar to that in the control arm of both age subgroups, and substantially lower than that seen in the younger subgroup of bevacizumab-treated patients. A similar pattern was seen for FOSI.

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The main limitation of our exploratory analyses, besides lack of adjustment for multiplicity, is that patients in AURELIA were carefully selected to reduce the risk of severe AEs, and therefore the elderly subgroup is probably not representative of a general population of elderly patients. Therefore our findings should not be extrapolated to all elderly patients without consideration of risk factors for severe AEs. Furthermore, a 65-year cut-off to define 'elderly' is perhaps too low and does not take into account the biological age of patients, considering factors such as comorbidities, functional and cognitive status, and performance status. Unfortunately, the subgroup of 67 patients aged ≥70 years is too small for meaningful interpretation. Ideally elderly patients should undergo careful geriatric assessment to inform about functional status during treatment selection. Factors such as performance status have long been recognised as important aspects influencing outcome [14,31] and should be considered. Geriatric assessment helps in predicting survival outcomes and the risk of severe toxicity from chemotherapy [4,32]. A dedicated ongoing trial programme in elderly women with OC (EWOC) by the French Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) includes evaluation of geriatric assessment. Results of the EWOC1 trial showed that depression at baseline, functional dependence and Eastern Cooperative Oncology Group performance status ≥2 were prognostic for toxicity [33]. Prognostic factors for OS were depression, International Federation of Gynecology and Obstetrics (FIGO) stage IV and more than six medications per day. The AURELIA trial included PRO assessments but the number of elderly patients is too small to enable interpretation of subgroup analyses within this population according to baseline depression. Nevertheless, this analysis may be of interest in the broader AURELIA population, irrespective of age.

It would be interesting to try to determine whether one chemotherapy partner for bevacizumab is more appropriate than another in elderly patients, based on both tolerability and efficacy. However, the AURELIA trial design does not enable conclusions to be drawn about specific chemotherapies, as investigators selected each individual's chemotherapy, probably influenced by patient characteristics. Within the elderly subgroup, the numbers of patients in each chemotherapy cohort are very small and baseline characteristics show substantial imbalances.

Overall, bevacizumab-containing therapy was well tolerated in a selected population of patients aged ≥65 years, suggesting a favourable benefit:risk profile. Age alone should not be a reason to withhold active therapy. However, geriatric assessment is needed to enable better selection of elderly patients who could benefit from bevacizumab-containing therapy in terms of symptoms and quality of life.

Conflict of interest statement

F Hilpert has received honoraria from Roche for advisory boards and presentations, from Johnson and Johnson for advisory boards and presentations and from GlaxoSmithKline for advisory boards and presentations. Y Garcia García has served on advisory boards for Roche, AstraZeneca and Boehringer Ingelheim and has received travel grants from Roche, Bristol-Myers Squibb, AstraZeneca and PharmaMar. H-J Lück has served on the speakers' bureau for Novartis, Celgene, AstraZeneca and Eisai and has participated in advisory boards for Roche, Eisai, AstraZeneca and Celgene. A González-Martín has served on advisory boards and the speakers' bureau for Roche, AstraZeneca and PharmaMar, and has received travel grants from Roche and PharmaMar. The clinical research association of which C-B Levaché is president has received a grant from Roche France. E Pujade-Lauraine has received honoraria and travel/accommodation for consultancy/advisory boards from Roche, AstraZeneca and Pfizer. R Sorio, C Bécuwe, E Gibbs, J Kaern, M Huizing, P Witteveen, F Zagouri, D Coeffic, G Kristensen, C Khoon Lee and V Gebski report conflicts of interest: none.

Role of the funding source

F Hoffmann-La Roche Ltd. sponsored and funded the trial. The trial was designed by the trial steering committee in collaboration with the sponsor. Statistical analyses for this paper were performed by Parexel and the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Australia. The sponsor had the opportunity to review the content, but the final decision to submit the manuscript for publication was the responsibility of the authors.

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Appendix Table A1
Adverse events of special interest in patients aged <70 versus ≥70 years.

Grade ≥ 3 adverse events of special interest[a], *n* (%)	Subgroup aged <70 years		Subgroup aged ≥70 years	
	Chemotherapy alone (*n* = 147)	Bevacizumab + chemotherapy (*n* = 146)	Chemotherapy alone (*n* = 34)	Bevacizumab + chemotherapy (*n* = 33)
Hypertension	1 (0.7)	7 (4.8)	1 (2.9)	7 (21.2)
Grade ≥2	7 (4.8)	23 (15.8)	5 (14.7)	13 (39.4)
Proteinuria	0	1 (0.7)	0	3 (9.1)
Grade ≥2	0	16 (11.0)	1 (2.9)	7 (21.2)
Gastrointestinal perforation	0	2 (1.4)	0	1 (3.0)
Grade ≥2	0	3 (2.1)	0	1 (3.0)
Fistula/abscess	0	1 (0.7)	0	1 (3.0)
Grade ≥2	0	3 (2.1)	0	1 (3.0)
Bleeding	2 (1.4)	2 (1.4)	0	0
Thromboembolic event	8 (5.4)	7 (4.8)	0	2 (6.1)
Arterial	1 (0.7)	1 (0.7)	0	2 (6.1)
Venous	7 (4.8)	6 (4.1)	0	0
Wound-healing complication	0	1 (0.7)	0	0
RPLS	0	0	0	1 (3.0)
Congestive heart failure	1 (0.7)	1 (0.7)	0	0

RPLS = reversible posterior leucoencephalopathy syndrome.
[a] Adverse-event group according to Roche bevacizumab baskets (Medical Dictionary for Regulatory Activities version 14.1).

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