Safety and efficacy of extended bevacizumab therapy in elderly (≥70 years) patients treated for newly diagnosed ovarian cancer in the international ROSiA study

ROSiA

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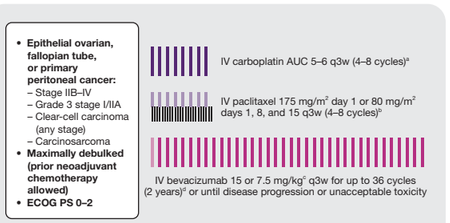
Background

- The efficacy and safety of bevacizumab combined with carboplatin and paclitaxel and then continued as a single agent for up to 15 months have been established in two randomized phase III trials, GOG-0218 and ICON7.[1,2]
- Numerous exploratory and prespecified subgroup analyses of efficacy have been reported from these two trials.[1–6] However, there is limited information on the safety and efficacy of bevacizumab-containing therapy in elderly patients with ovarian cancer.
- The single-arm ROSiA safety study explored an extended duration of bevacizumab-containing therapy (up to 24 months) as front-line therapy for ovarian cancer.[7]
  - We report exploratory analyses of safety and efficacy according to age.

Patients and methods

- The study design is shown in Figure 1.
- The primary endpoint was safety (adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03).
- Secondary endpoints included progression-free survival (PFS; defined by Response Evaluation Criteria in Solid Tumors [RECIST] version 1.0 or symptomatic deterioration) and overall response rate (ORR; according to RECIST version 1.0).
- Exploratory analyses according to age <70 vs ≥70 years were predefined in the statistical analysis plan.

Figure 1. Study design



[a]Cisplatin permitted in patients with hypersensitivity to carboplatin. [b]A change from one paclitaxel regimen to the alternative during the study was not permitted. [c]Bevacizumab 15 mg/kg was recommended but investigators could choose a dose of 7.5 mg/kg. [d]Patients without progression at cycle 36 could continue therapy after discussion with the Steering Committee.
AUC = area under the curve; ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous; q3w = every 3 weeks.

Results

Patient population

- Of the 1021 patients treated in ROSiA:
  - 258 (25%) were aged ≥65 years
  - 121 (12%) were aged ≥70 years
  - 44 (4%) were aged ≥75 years.
- Baseline characteristics and comorbidities according to age are summarized in Tables 1 and 2. Compared with patients aged <70 years, the elderly subgroup included more patients with:
  - ECOG performance status ≥1 (39% vs 29%)
  - Stage IIIB–IV disease (84% vs 76%)
  - Hypertension at baseline (70% vs 28%, respectively).

Table 1. Baseline characteristics by age

Characteristic, n (%)	Age <70 years (n=900)	Age ≥70 years (n=121)
ECOG performance status[a]		
0	632 (70.2)	74 (61.2)
1	242 (26.9)	40 (33.1)
2	18 (2.0)	7 (5.8)
Origin of cancer[b]		
Ovary	826 (91.8)	104 (86.0)
Fallopian tube	37 (4.1)	4 (3.3)
Primary peritoneal	35 (3.9)	13 (10.7)
Grade[c]		
1	64 (7.1)	11 (9.1)
2	167 (18.6)	26 (21.5)
3	629 (69.9)	74 (61.2)
Measurable disease	366 (40.7)	55 (45.5)
Histology[d]		
Serous	663 (73.7)	87 (71.9)
Endometrioid	83 (9.2)	7 (5.8)
Clear cell	60 (6.7)	8 (6.6)
Mucinous	23 (2.6)	0
Mixed	59 (6.6)	6 (5.0)
Adenocarcinoma NOS	74 (8.2)	14 (11.6)
Other	38 (4.2)	10 (8.3)
FIGO stage		
I/II	154 (17.1)	13 (10.7)
III (not further classified)	27 (3.0)	2 (1.7)
IIIA	36 (4.0)	4 (3.3)
IIIB	53 (5.9)	7 (5.8)
IIIC	428 (47.6)	57 (47.1)
IV	202 (22.4)	38 (31.4)
High risk (MRC ICON7 definition)[e]	404 (44.9)	64 (52.9)

[a]Missing in 8 patients (0.9%; all aged <70 years). [b]Other in 2 patients (0.2%) aged <70 years. [c]Missing in 40 patients (4.4%) aged <70 years and 10 patients (8.3%) aged ≥70 years. [d]Multiple entries possible. [e]FIGO stage III with residual disease >1 cm, or any stage IV, or no debulking surgery. FIGO = International Federation of Gynecology and Obstetrics; MRC = Medical Research Council; NOS = not otherwise specified.

Table 2. Previous/ongoing medical conditions at baseline

Previous/ongoing medical condition, n (%)	Age <70 years (n=900)	Age ≥70 years (n=121)
Active hypertension	251 (27.9)	85 (70.2)
Active proteinuria	14 (1.6)	5 (4.1)
Potential risk factors for VTE		
Deep vein thrombosis	5 (0.6)	4 (3.3)
Venous thrombosis limb	3 (0.3)	0
Thrombosis	2 (0.2)	0
Venous thrombosis	2 (0.2)	0
Embolism	1 (0.1)	0
Potential risk factors for ATE		
Arteriosclerosis	1 (0.1)	2 (1.7)
Myocardial ischemia	5 (0.6)	3 (2.5)
Arteriosclerosis coronary artery	4 (0.4)	0
Coronary artery disease	1 (0.1)	1 (0.8)
Myocardial infarction	1 (0.1)	1 (0.8)
Angina pectoris	0	2 (1.7)
Acute coronary syndrome	0	1 (0.8)
Embolism arterial	1 (0.1)	0
Carotid endarterectomy	0	1 (0.8)
Vascular operation	1 (0.1)	0
Potential risk factors for GI perforation		
Ileostomy	0	1 (0.8)
Colitis	2 (0.2)	2 (1.7)
Colitis ulcerative	1 (0.1)	0
Crohn's disease	1 (0.1)	0
Subileus	0	1 (0.8)
Upper GI hemorrhage	1 (0.1)	0

ATE = arterial thromboembolic event; GI = gastrointestinal; VTE = venous thromboembolic event.

Treatment exposure

- A bevacizumab dose of 15 mg/kg was chosen in 83% of patients aged ≥70 years versus 90% of patients aged <70 years
  - The proportion electing for weekly paclitaxel was similarly small in both subgroups (9% vs 7%, respectively).
- The median duration of bevacizumab therapy was 14.6 months in older patients versus 15.9 months in younger patients (Table 3).
- Bevacizumab was continued for:
  - >15 months in 49% of older vs 53% of younger patients
  - >24 months in 21% vs 30%, respectively.
- Bevacizumab was discontinued for reasons other than disease progression in 53% of older vs 41% of younger patients
  - 22% vs 17%, respectively, discontinued bevacizumab because of unacceptable toxicity
  - Median time to discontinuation for toxicity was 7.1 vs 11.5 months, respectively.

Table 3. Extent of treatment exposure by age

Treatment	Age <70 years (n=900)	Age ≥70 years (n=121)
Bevacizumab		
Median No. of cycles (range)	23 (1–61)	21 (1–52)
Median duration, months (range)	15.9 (<0.1–43.2)	14.6 (<0.1–36.8)
Duration, n (%)		
>12 months	566 (62.9)	66 (54.5)
>15 months	478 (53.1)	59 (48.8)
>24 months	273 (30.3)	25 (20.7)
Delay/modification for adverse events, n (%)	527 (58.6)	70 (57.9)
Discontinuation for unacceptable toxicity, n (%)	149 (16.6)	27 (22.3)
Paclitaxel		
Median No. of cycles (range)	6 (1–8)	6 (1–8)
Median duration, months (range)	3.5 (<0.1–28.1[a])	3.5 (<0.1–6.7)
Weekly schedule	3.9 (0.5–5.6)	4.2 (0.7–5.1)
q3w schedule	3.5 (<0.1–28.1[a])	3.5 (<0.1–6.7)
Carboplatin		
Median No. of cycles (range)	6 (1–8)	6 (1–8)
Median duration, months (range)	3.5 (<0.1–28.1)	3.6 (<0.1–6.7)

[a]Assumed to be a data entry error.

Efficacy

- There was no striking difference in efficacy between older and younger patients (Table 4).
- Age was not a significant prognostic factor for overall response in univariate (odds ratio 1.63 [95% confidence interval (CI) 0.90–2.96]) or multivariate (odds ratio 1.39 [95% CI 0.73–2.64]) analyses.
- Overall survival results are immature with events in only 27% vs 22% of patients, respectively.

Table 4. Efficacy according to age

Outcome	Age <70 years (n=900)	Age ≥70 years (n=121)
PFS		
No. of events (%)	488 (54.2)	70 (57.9)
Median PFS, months (95% CI)	25.6 (23.7–28.4)	23.7 (18.6–27.9)
1-year PFS rate, % (95% CI)	83.2 (80.5–85.6)	77.6 (68.7–84.3)
Overall response rate	(n=366)	(n=55)
Response, n (%)	271 (74.0)	35 (63.6)
(95% CI)	(69.2–78.5)	(49.6–76.2)

Safety

- The most common all-grade adverse events, irrespective of age, were hypertension, neutropenia, and alopecia (Figure 2).
  - Anemia, diarrhea, and asthenia were more common in older than younger patients.
- Grade ≥3 adverse events were more common in older than younger patients (80% vs 65%, respectively).
  - This difference was driven by a higher incidence of hypertension in older patients (41% vs 22%, respectively; Figure 3).
- Adverse events considered to be of special interest for bevacizumab are shown in Figure 4 and Table 5.
  - The only grade ≥3 adverse events of special interest for bevacizumab that were observed more frequently in older than younger patients were hypertension and thromboembolic events (Table 5).
- Twelve patients experienced grade 5 adverse events, six of which were considered related to bevacizumab:
  - Age <70 years: five events in six patients (peritoneal abscess [during the concurrent chemotherapy phase]; one case each of myocardial infarction and unexplained death in the maintenance bevacizumab phase; one case each of cerebral hemorrhage and septic shock in the post-study phase)
  - Age ≥70 years: one event in six patients (venous embolism during the concurrent chemotherapy phase).

Figure 2. Most common (>20% of patients) adverse events of any grade by age

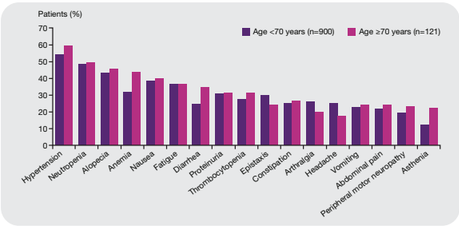


Figure 3. Most common (≥2% of patients) grade ≥3 adverse events by age

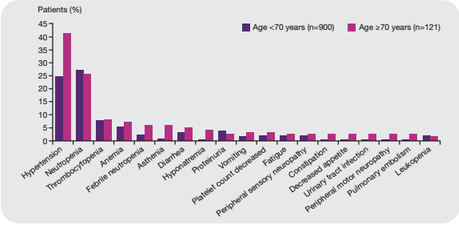
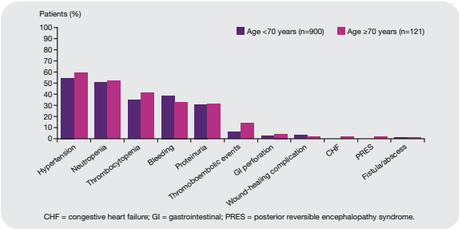


Figure 4. Adverse events of special interest for bevacizumab (all grades, grouped terms) by age



CHF = congestive heart failure; GI = gastrointestinal; PRES = posterior reversible encephalopathy syndrome.

Table 5. Summary of grade ≥3 adverse events of special interest by age

Patients, %	Age <70 years (n=900)			Age ≥70 years (n=121)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Any adverse event of special interest	**37.9**	**13.7**	**0.3**	**52.1**	**13.2**	**2.5**
Hypertension	22.0	0.4	0	39.7	1.7	0
Neutropenia	18.2	11.1	0	18.2	9.9	0.8
Thrombocytopenia	8.0	1.7	0	9.1	1.7	0
Thromboembolic events	1.4	0.8	0.1	5.0	0.8	1.7[a]
Proteinuria	4.0	0	0	2.5	0	0
Gastrointestinal perforation	0.8	0.2	0.1	1.7	1.7	0
Bleeding	0.4	0.1	0.1	0.8	0	0.8[b]
Congestive heart failure	0	0.1	0	0	0	0.8[c]
Fistula/abscess	0.2	0.1	0	0.8	0	0
PRES	0	0	0	0	0.8	0
Wound-healing complication	0.4	0	0	0	0	0

[a]Venous embolism (n=1), disseminated intravascular coagulation (n=1). [b]Disseminated intravascular coagulation. [c]Congestive cardiac failure. PRES = posterior reversible encephalopathy syndrome.

Conclusions

- **In bevacizumab-treated ovarian cancer patients aged ≥70 years, the incidences of low-grade diarrhea and grade ≥3 hypertension, thromboembolic events, and asthenia were higher than those in patients aged <70 years**
  - **There were no other relevant increases in toxicity.**
- **Median PFS of ~2 years in patients aged ≥70 years is similar to that observed in younger patients treated in ROSiA despite the worse prognosis in older patients.**
  - **This finding is consistent with a recently presented interim analysis of ~200 patients aged ≥70 years treated in OTILIA, a German non-interventional study of front-line bevacizumab therapy.[8]**
- **Given the higher background prevalence of hypertension, elderly patients should be monitored more closely while receiving bevacizumab.**
- **However, older age should not preclude use of bevacizumab for ovarian cancer in carefully selected patients aged ≥70 years.**

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