

# Horizon Scanning in Oncology

Bevacizumab (Avastin<sup>®</sup>) for  
platinum-resistant recurrent  
epithelial ovarian, fallopian  
tube or primary peritoneal  
cancer



Ludwig Boltzmann Institut  
Health Technology Assessment

DSD: Horizon Scanning in Oncology Nr. 48  
ISSN online 2076-5940



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Vienna, September 2014

Institute for Health Technology Assessment  
Ludwig Boltzmann Gesellschaft

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External reviewer: This report was reviewed by an external expert in the field of gynaecological tumours. The reviewer refrained from being named in accordance with processes applicable to peer-reviewed journals.

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This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

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Ludwig Boltzmann Gesellschaft GmbH  
Nußdorferstr. 64, 6 Stock, A-1090 Vienna  
<http://www.lbg.ac.at/de/lbg/impressum>

##### **Responsible for Contents:**

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DSD: Horizon Scanning in Oncology Nr.48  
ISSN-online: 2076-5940

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# 1 Drug description

## Generic/Brand name/ATC code:

Bevacizumab / Avastin® / L01XC07

## Developer/Company:

Roche Registration Ltd.

## Description:

Bevacizumab (Avastin®) is a recombinant monoclonal antibody targeting the vascular endothelial growth factor receptor (VEGFR). By inhibiting the binding of VEGF which is responsible for the growth of blood vessels, it prevents the development of the blood supply of cancer cells and thus inhibits tumour angiogenesis [1].

Bevacizumab (Avastin®) is administered as an infusion (drip into a vein). The dosage ranges from 5 mg/kg of body weight to 15 mg/kg of body weight depending on the type of cancer [1]. The recommended dose of bevacizumab (Avastin®) in combination with paclitaxel or pegylated liposomal doxorubicin for the treatment of recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer is 10 mg/kg of body weight given once every two weeks. In combination with topotecan, the recommended dose of Avastin® is 15 mg/kg of body weight once every three weeks. It should be administered as an intravenous infusion [1].

Bevacizumab (Avastin®), in addition to carboplatin and paclitaxel as a front-line treatment for epithelial ovarian, fallopian tube and primary peritoneal cancer, is given for up to six cycles of treatment followed by continued use of bevacizumab (Avastin®) as single agent. Treatment can be continued either until disease progression, for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier [1].

Side effects commonly observed are hypertension, fatigue, diarrhoea, abdominal pain, as well as asthenia. Gastrointestinal perforation, haemorrhage and arterial thromboembolism are the most severe side effects of Avastin® [1, 2]. People who are allergic to bevacizumab, recombinant antibodies or any other ingredients must not receive Avastin®. It must also not be used for pregnant women [1].

**bevacizumab prevents the growth of blood vessels**

**the dosage varies from 5 mg/kg to 15 mg/kg of bodyweight depending on cancer type**

**administration is given until disease progression, unacceptable toxicity or max. 15 months**

**most frequent side effect is hypertension**

# 2 Indication

Bevacizumab (Avastin®) is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

**Avastin® is indicated for platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer**

### 3 Current regulatory status

**EMA approved  
bevacizumab for  
platinum-resistant  
epithelial ovarian cancer  
in July 2014**

The EMA extended the licensed indication of bevacizumab on the 31<sup>st</sup> of July 2014 to

- ✧ bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

The EMA has also approved Avastin<sup>®</sup> for the following indications [1]:

- ✧ Front-line treatment of adult patients with advanced (FIGO [Fédération Internationale de Gynécologie et d'Obstétrique]) stages III B, IIIC, IV) epithelial ovarian, fallopian tube or primary peritoneal cancer (in combination with carboplatin and paclitaxel).
- ✧ Adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (in combination with carboplatin or gemcitabine).
- ✧ First-line treatment of adult patients with metastatic breast cancer (combination with paclitaxel).
- ✧ First-line treatment of adult patients with metastatic breast cancer in combination with capecitabine (when other chemotherapy options including taxanes or anthracyclines are not considered appropriate).
- ✧ Adult patients with unresectable, advanced, metastatic or recurrent non-small cell lung cancer (in addition to platinum-based chemotherapy).
- ✧ In combination with fluoropyrimidine-based chemotherapy it is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.
- ✧ First-line treatment of adult patients with advanced and/or metastatic renal cancer (in combination with interferon alfa-2a).

**indication not yet  
approved by the FDA**

In the U.S., the FDA has not yet approved Avastin<sup>®</sup> for the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. However, it is licensed for [3]:

- ✧ Patients with metastatic colorectal cancer, combined with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment.
- ✧ The second-line treatment in combination with fluoropyrimidine-, irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for patients with metastatic colorectal cancer who have progressed on a first-line Avastin<sup>®</sup>-containing regimen [3].
- ✧ Non-squamous non-small cell lung cancer (in combination with carboplatin and paclitaxel, for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease).

- ✿ Glioblastoma in adult patients with progressive disease following prior therapy (used as single agent).
- ✿ Patients with metastatic renal cell carcinoma in combination with interferon alfa [3].

## 4 Burden of disease

Epithelial ovarian cancer, fallopian tube and primary peritoneal cancer show similar clinical characteristics and behaviour. Therefore, they are often considered collectively [4].

Ovarian cancer forms in tissues of the ovary [5]. 95% of ovarian malignancies are derived from epithelial cells [6]. Epithelial ovarian cancer remains the fourth most frequent cause of cancer death in European women. Additionally, it is the most lethal gynaecological tumour in Western Countries [7, 8]. 21,980 new cases are expected in the US in 2014 [9] and in Austria, 646 women were newly diagnosed with ovarian cancer in 2011 [10]. Overall, the annual age-adjusted death rate per year of patients suffering from ovarian cancer was 7.5 per 100,000 women in the US and 5.3 per 100,000 women in Austria in 2011, respectively [9].

Therefore, ovarian cancer is the eighth most frequent cancer and it represents approximately 4% of all tumours in Austrian women. However, according to Statistik Austria, the incidence of ovarian cancer and disease-related death rate continuously declined over the past decades (e.g., reduction of disease-related death rate of 11% over the last ten years) [10, 11].

The median age at diagnosis of ovarian cancer is 63 years (out of these women 12% are < 45 years, 41.2% are between 45 and 64 years, and 44.5% are ≥ 65 years at time of diagnosis) [12]. Since the incidence of epithelial ovarian cancer increases with age, the prevalence (57/100,000 women) is highest in the eighth decade of life [13].

Different systems are available to classify cancer stages. The most commonly used for staging ovarian cancer are the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) and the TNM (tumour, node, metastasis) staging system. The five general stages of the FIGO system are:

- ✿ **Stage 0:** “Pre-cancer” or carcinoma in situ.
- ✿ **Stage I:** Tumour limited to ovaries.
- ✿ **Stage II:** Tumour involves one or both ovaries with pelvic extension and/or implants
- ✿ **Stage III:** Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis.
- ✿ **Stage IV:** Patient shows distant metastasis [14].

Signs and symptoms of ovarian cancer occur very late; therefore, over 75% of ovarian cancer patients suffer from advanced stage III or stage IV disease at the time of diagnosis [15, 16].

After cytoreductive surgery and platinum-based adjuvant chemotherapy in combination with paclitaxel, several factors (disease stage, age, etc.) play an

**epithelial ovarian, fallopian tube and primary peritoneal cancer often considered together**

**in the US 100,000 women diagnosed with ovarian cancer per year**

**63 years median age of diagnosis of epithelial ovarian cancer**

**ovarian classification systems: FIGO and TNM**

**diagnosis at late stage of disease (75%)  
1st-line therapy:  
cytoreductive surgery + platinum-based chemotherapy**

**risk factors: age, stage of disease, nulliparous, family history regarding cancer, time of menopause and menarche**

essential role in disease relapse. Patients with stage I/II disease show a relapse rate of 10-20%, whereas patients at advanced stage III-IV ovarian cancer have relapses in 60-85% of cases [4].

Age is also considered as a risk factor for relapse and survival. Whilst women under 40 years have a five-year survival rate of 65%, only 20% of ovarian cancer patients older than 40 years are alive five years after diagnosis [4].

Besides age and null parity, risk factors for developing the disease are early age of menarche, late age of menopause and family history of ovarian, breast or endometrial (uterine) cancer [17]. An identifiable genetic predisposition (e.g. BRCA1/BRCA2) is present in only 10% to 15% of patients [18].

Depending on the response to therapy, epithelial ovarian cancer can be divided into:

- ✿ platinum-refractory: patients progressing during therapy or within four weeks after the last dose;
- ✿ platinum-resistant: patients progressing within six months of platinum-based therapy;
- ✿ platinum-sensitive: patients progressing with an interval of more than 12 months
- ✿ partially platinum-sensitive: patients progressing between six and 12 months [19, 20].

Women with platinum-resistant or platinum-refractory disease usually have a poor prognosis (i.e., expected overall survival < 12 months) [19].

## 5 Current treatment

**surgery and chemotherapy are the current treatments**

Since about 80% of patients with ovarian cancer will relapse after first-line platinum-based and taxane-based chemotherapy, the choice of second-line therapy does not primarily depend on risk factors such as age or stage of disease, but rather on the progression-free interval from the last chemotherapeutic regimen [4, 15, 19, 21]. Recommended second-line treatment options for platinum-recurrent/resistant ovarian cancer patients are:

- ✿ paclitaxel,
- ✿ pegylated liposomal doxorubicin,
- ✿ topotecan,
- ✿ or gemcitabine [15, 19, 22].

Due to the poor prognosis, treatment should focus on improving the quality of life and on alleviating symptoms [19].

**several active agents in ovarian cancer 2nd-line therapy for platinum-resistant refractory/relapsed ovarian cancer**

Although combination regimens with non-cross-resistant agents are associated with higher objective response rates and a two- to three-month improvement in progression-free survival (PFS), they were also more toxic in clinical trials. Therefore, single-agent therapy is the standard of care for platinum-resistant/refractory ovarian cancer patients [4]. Rarely, re-treatment with platinum drugs may also be used as a treatment option.



## 6 Evidence

A systematic literature search was conducted in Embase, Ovid Medline, the CRD Database and the Cochrane Library on the 28<sup>th</sup> of July 2014. 660 references were identified. Additionally, the manufacturer was contacted, and submitted seven [23-29] abstracts and one full-text publication [30] which had already been identified by our systematic search.

**one phase III trial and five phase II trials included**

Articles were excluded when results for platinum-resistant and platinum-sensitive were not provided separately, and if patients had received more than a mean of two prior lines of therapy.

Therefore, only trials with the following criteria were included:

- ✿ Platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer.
- ✿ No previous bevacizumab therapy.
- ✿ Mean  $\leq 2$  prior treatment lines.

Ultimately, one phase III trial [30] and five phase II trials [31-35] were included in this report.

### 6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

<b>Study title</b>		Bevacizumab Combined with Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial [30, 36, 37]
<b>Study identifier</b>	AURELIA trial, NCT00976911 (ClinicalTrials.gov Identifier), MO22224 (Protocol number), 2009-011400-33 (EUDRACT-number)	
<b>Design</b>	Phase III, randomised, open-label, multicentre	
	Duration	<i>Enrolment:</i> October 2009–April 2011 <i>Median follow-up:</i> 13.9 months in the control group, 13.0 months in the intervention group <i>Cut-off date for primary analysis:</i> November 2011 <i>Cut-off date for final OS analysis:</i> January 2013
<b>Hypothesis</b>	Superiority sample size of $\geq 360$ patients was calculated to provide 80% power with a one-sided log-rank test at 0.05, assuming a hazard ratio (HR) of 0.72, corresponding to median PFS of 4.0 months with chemotherapy versus 5.56 months with bevacizumab-chemotherapy	
<b>Funding</b>	Hoffmann-La Roche	
<b>Treatment groups</b>	Patients allocated	Overall: 361
	Intervention (n=179)	Bevacizumab: 10 mg/kg IV every two weeks or 15 mg/kg IV every three weeks (for patient receiving topotecan)  plus Paclitaxel: 80 mg/m <sup>2</sup> IV on days 1, 8, 15 and 22 of each 4-week cycle

		Topotecan: 4 mg/m <sup>2</sup> IV on days 1, 8 and 15 of each 4-week cycle, or 1.25 mg/m <sup>2</sup> on days 1-5 of each 3-week cycle Pegylated liposomal doxorubicin: 40 mg/m <sup>2</sup> IV every four weeks	
	Control (n=182)	Single-agent chemotherapy at the investigators' discretion: Paclitaxel: 80 mg/m <sup>2</sup> IV on days 1, 8, 15 and 22 of each 4-week cycle Topotecan: 4 mg/m <sup>2</sup> IV on days 1, 8 and 15 of each 4-week cycle, or 1.25 mg/m <sup>2</sup> on days 1-5 of each 3-week cycle Pegylated liposomal doxorubicin: 40 mg/m <sup>2</sup> IV every four weeks	
<b>Endpoints and definitions</b>	Progression-free survival (primary outcome)	PFS	Investigator-assessed PFS by RECIST criteria, defined as interval between random assignment and first radiologically documented progression of disease or death, whichever occurs first
	Objective response rate	ORR	Objective response rate according to RECIST and/or GCIg CA-125 criteria
	Overall survival	OS	Time from date of randomisation to the date of death from any cause.
	Quality of life	QoL	Assessed by using questionnaires such as EORTC, HADS, FOSI, which measure quality of life at weeks 8, 16, 24 or 8, 18 and 27
<b>Results and analysis</b>			
<b>Analysis description</b>	Intention-to-treat By using an unstratified, two-sided log-rank test, the PFS of the intervention and control group was compared. Additionally, a post-hoc analysis was performed by using an unstratified, two-sided log-rank test. After the death of 70% of patients, a final OS analysis was done.		
<b>Analysis population</b>	Inclusion	<ul style="list-style-type: none"> <li>✱ Patients ≥ 18 years of age</li> <li>✱ Histologically confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer (measurable by RECIST or GCIg CA-125)</li> <li>✱ Platinum-resistant disease (progression within &lt; 6 months of completing ≥ 4 cycles of platinum-based therapy)</li> <li>✱ ECOG performance status 0-2</li> </ul>	
	Exclusion	<ul style="list-style-type: none"> <li>✱ Previous treatment with &gt; 2 prior anticancer regimens</li> <li>✱ Platinum-refractory disease</li> <li>✱ Non-epithelial tumours</li> <li>✱ Ovarian tumours with low malignant potential</li> <li>✱ Prior radiotherapy to the pelvis or abdomen</li> <li>✱ Surgery (incl. open biopsy) within four weeks before starting study medication</li> <li>✱ Anticipated need for major surgery during study treatment</li> <li>✱ Treatment with another investigational drug within 30 days prior to first study dose</li> <li>✱ Untreated CNS or symptomatic CNS metastasis</li> <li>✱ Thrombotic or haemorrhagic disorders within six months before first study dose</li> <li>✱ Uncontrolled hypertension</li> <li>✱ Active clinically significant cardiovascular disease</li> <li>✱ Non-healing wound, ulcer or bone fracture</li> </ul>	
	Characteristics	Median age, years (range): C 61 (25–84), I 62 (25–80) Histological grade at diagnosis, number (%): 1: C 9 (5), I 10 (6) 2: C 48 (26), I 53 (30) 3: C 105 (58), I 94 (53)	

		Missing: C 20 (11), I 22 (12) Prior anti-angiogenic therapy, number (%): C 14 (8), I 12 (7) Two prior CT regimens, number (%): C 78 (43), I 72 (40) ECOG Performance Status, number (%): 0: C 99 (54), I 107 (60) 1: C 69 (38), I 58 (32) 2: C 11 (6), I 12 (7) Missing: C 3 (2), I 2 (1) Measurable disease, number (%): C 144 (79), I 143 (80) Ascites, number (%): C 54 (30), I 59 (33)	
<b>Descriptive statistics and estimated variability</b>	Treatment group	Chemotherapy only	Bevacizumab + chemotherapy
	Number of subjects	N = 182	N = 179
	Median PFS, months (95% CI)	3.4 (2.2 to 3.7)	6.7 (5.7 to 7.9)
	Median OS, months (95% CI)	13.3 (11.9 to 16.4)	16.6 (13.7 to 19.0)
	ORR (measurable by RECIST), % [n = 287]	11.8 (p = .001)	27.3 (p = .001)
	PRO (measurable by QLQ-OV28) ≥ 15% improvement in abdominal/GI symptoms n (%) at week 8/9	15 (9.3)	34 (21.9)
<b>Effect estimate per comparison</b>	<i>Comparison groups</i>		<i>Bevacizumab + chemotherapy vs Chemotherapy only</i>
	Median PFS	HR	0.48
		95% CI	0.38 to 0.60
		P value	< .001
	OS	HR	0.85
		95% CI	0.66 to 1.08
		P value	< .174
	ORR (measurable by RECIST and/or GCIG CA-125)	Percentage point difference	18.3
		95% CI	9.6 to 27.0
		P value	< .001
	≥ 15% improvement in abdominal/GI symptoms measurable by QLQ-OV28	Percentage point difference	12.7
		95% CI	4.4 to 20.9
P value		0.002	

Abbreviations: NCT = National Clinical Trial; IV = intravenous; PFS = progression-free survival; OS = overall survival; ORR = objective response rate; PRO = patient-reported outcome; ST = safety and toxicity; RECIST = Response Evaluation Criteria in Solid Tumours; GCIG CA-125 = Gynaecological Cancer Intergroup Cancer Antigen 125; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Cancer Module C30; EORTC QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Ovarian Cancer Module 28; FOSI = Functional Assessment of Cancer Therapy-Ovarian Cancer Symptoms Index; AEs = adverse events; ECOG = Eastern Cooperative Oncology Group; CNS = central nerve system; CI = confidence interval

Table 2: Summary of grade  $\geq 3$  adverse events of special interest

Study ID: NCT00976911			
Grade (according to CTC version 3.0)	Outcome, n (%)	Control (n=181)	Intervention (n=179)
Grade $\geq 3$	Hypertension	2 (1)	13 (7)
	Proteinuria	0 (0)	3 (2)
	Gastrointestinal (GI) perforation	0 (0)	3 (2)
	Fistula/abscess	0 (0)	2 (1)
	Bleeding	2 (1)	2 (1)
	Wound healing complications	0 (0)	0 (0)
	Thromboembolic event arterial	0 (0)	4 (2)
	Thromboembolic event venous	8 (4)	5 (3)
	Congestive heart failure	1 (1)	1 (1)
Cardiac disorders	0 (0)	0 (0)	
Others	Deaths, not considered due to primary progressive disease	5 (2.8)	5 (2.8)

**361 patients were enrolled comparing bevacizumab + chemotherapy to chemotherapy platinum-refractory disease, no more than 2 prior therapies**

In this open-label, randomised phase III trial, 361 patients were enrolled and randomised either to a single-agent chemotherapy or to a chemotherapy in combination with bevacizumab (Avastin<sup>®</sup>) [30]. The choice of chemotherapeutic regimen (i.e., topotecan, pegylated liposomal doxorubicin or paclitaxel) was at the investigator's discretion. Eligible patients had an epithelial ovarian, fallopian tube or primary peritoneal cancer (measurable by RECIST or by Gynecologic Cancer Intergroup CA 125 Response Definition) that had progressed within < 6 months after completing  $\geq 4$  cycles of platinum-based therapy. Patients with platinum-refractory disease, with more than two prior chemotherapy regimens and those with a bowel obstruction related to an underlying disease were excluded [30, 36]. Only patients with ECOG performance status 0–2 were included. Most of the enrolled patients showed a histological grade 3 tumour at diagnosis; only about 7% had received prior antiangiogenic therapy [30].

**significant improvement of PFS (3.4 vs. 6.7 months)**

The AURELIA trial demonstrated a statistically significant improvement in investigator-assessed PFS, the primary outcome, for platinum-resistant ovarian cancer patients treated with bevacizumab and a chemotherapy regimen. The median PFS in the group treated with single-agent chemotherapy was 3.4 months (95% CI 2.2 to 3.7). In comparison, the median PFS was 6.7 months (95% CI 5.7 to 7.9) for the combination group, yielding a hazard ratio of 0.48. The PFS was consistent in subgroups according to age, measurable disease and ascites. For patients younger than 65 years, the hazard ratio was 0.49 and for elderly patients ( $\geq 65$  years) 0.47 respectively. Patients with ascites had a hazard ratio of 0.40, whereas patients without ascites yielded a hazard ratio of 0.48. In the subgroup analyses, the hazard ratio ranged from 0.40 to 0.53 [30].

**no statistically significant difference of OS**

With a median overall survival (OS) of 13.3 months (95% CI 11.9 to 16.4) in the control group and 16.6 months (95% CI 13.7 to 19.0) in patients additionally treated with bevacizumab, there was no statistically significant difference between the two treatment options. However, these results may be influenced by the fact that upon evidence of disease progression patients were allowed to cross-over to the combination arm; consequently about 40% of patient in the chemotherapy arm crossed over to bevacizumab and chemotherapy [30].

During the study period, five deaths (2.8% of patients) in each group which were not primarily caused by disease progression were reported. Infection with neutropenia, cardiac failure, septic shock, peritonitis and gastrointestinal (GI) haemorrhage were the causes of death in the control group. Patients in the bevacizumab and chemotherapy group died due to infection with neutropenia, GI haemorrhage, GI perforation, cardiac arrest and shock [30].

**5 deaths in each study group during the trial not primarily caused by disease progression**

Regarding side effects, the AURELIA trial showed similar results as previous studies with bevacizumab in ovarian cancer. Hypertension and proteinuria  $\geq$  grade 2 were more common in the treatment arm with bevacizumab. 20% of patients treated with this regimen showed a hypertension and 2% showed a proteinuria. Grade 3 adverse events such as GI perforation, proteinuria, fistula/abscess and reversible posterior leukoencephalopathy syndrome only occurred in the treatment arm with bevacizumab. Bleeding, thromboembolic event, wound-healing complication and congestive heart failure ( $\geq$  grade 3) occurred in both groups [30].

**GI perforation, proteinuria, fistula/abscess and reversible posterior leukoencephalopathy only in bevacizumab treatment arm**

43.6% of patients in the intervention group experienced grade 2–5 adverse events and therefore discontinued study treatment, in comparison to 8.8% in the single-agent chemotherapy group. The median time to withdrawal from study treatment in the combination therapy group was 5.2 months, compared to 2.4 months in the chemotherapy only group. Regarding the subgroup of patients older than 65 years, the rates of discontinuation due to adverse events were 8.8% (chemotherapy arm) versus 50.0% (combination with bevacizumab) [2, 30].

For the analysis of patient-reported outcomes (PROs), the primary hypothesis was that more patients treated with bevacizumab would experience  $\geq$  15% improvement in abdominal/GI symptoms at week 8/9 measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC), Ovarian Cancer Module 28. From the overall 361 patients allocated to AURELIA, 317 (88%) completed the baseline questionnaire, 206 (57%) filled in the questionnaires at week 8/9 and 129 (36%) at week 16/18. Fewer results are available for the chemotherapy group, where only 24% completed the 16-/18-week follow-up in comparison with 48% in the bevacizumab and chemotherapy group. At week 8/9, 34 (21.9%) of patients allocated to bevacizumab and chemotherapy showed the above mentioned improvement in comparison to 15 (9.3%) patients in the single-agent chemotherapy. The difference, therefore, was 12.7% favouring bevacizumab (95% CI 4.4 to 20.9%;  $p = .002$ ). Also at week 16/18, significantly more patients dedicated to bevacizumab showed a  $\geq$  15% improvement in abdominal/GI symptoms, i.e. 15.5% in the bevacizumab group and 5.6% in the chemotherapy group. This yielded a difference of 9.9% (95% CI 2.9 to 17.0%;  $p = .005$ ). A mixed-model repeated-measures analysis for the abdominal/GI subscale of the EORTC was performed to summarise the effects of the two treatment arms. It demonstrates a 6.4-point difference (CI 95% 1.3 to 11.6;  $p=.015$ ) favouring the group treated with bevacizumab and chemotherapy [37].

**analysis of PROs showed positive influence of bevacizumab and chemotherapy on improvement of abdominal/GI symptoms**

**57% questionnaires completed at week 8/9 follow-up and 36% at week 16/18**

## 6.2 Efficacy and safety – further studies

### Bevacizumab + topotecan

<p>phase II trial with bevacizumab + topotecan</p>	<p>40 patients (mean age 58.6 years) were enrolled in this phase II trial [38]. Inclusion criterion was primary or secondary platinum-resistant disease. Patients were treated, in median, with eight cycles of bevacizumab 10 mg/kg on days 1 and 15. In addition, they received topotecan 4 mg/m<sup>2</sup> on days 1, 8 and 15 of a 4-week cycle until the progression of disease or excessive toxicity occurred. 21 (53%) patients had one prior treatment regimen, whereas 19 (47%) had already received two prior therapies. The median PFS (RECIST criteria) was 7.8 months (95% CI 3.0 to 9.4) and the OS was 16.6 months (95% CI 12.8 to 22.9) in all patients. Ten patients (25%) had partial response (PR), 14 patients (35%) had stable disease (SD) and 16 patients (40%) had a progressive disease (PD). 55% of patients were progression-free for more than six months. Most of the toxicities were classified as mild or moderate.</p>
<p>PFS 7.8 months and OS 16.6 months</p>	
<p>most toxicities mild or moderate</p>	<p>The most common adverse events ≥ grade 3 were hypertension (20%), neutropenia (18%), gastrointestinal toxicity (18%), metabolic toxicity (16%) or pain (13%) [32].</p>

### Bevacizumab + paclitaxel

<p>phase II trial investigated bevacizumab + paclitaxel</p>	<p>Another phase II study by Tillmanns et al. [33] investigated bevacizumab with albumin-bound paclitaxel in patients with recurrent, platinum-resistant epithelial ovarian or primary peritoneal cancer. The 48 patients enrolled (mean age 61.0 years) received ab-paclitaxel 100 mg/m<sup>2</sup> IV on days 1, 8 and 15 with bevacizumab 10 mg/kg IV on days 1 and 15 every four weeks (28 days). The patients had received a mean of 1.8 (range 1.0–6.0) prior treatment lines. All patients were treated until disease progression.</p>
<p>median PFS was 8.1 and OS was 17.2 months</p>	<p>The median PFS measured by RECIST criteria was 8.08 months (95% CI 5.78 to 10.15) and the median OS was 17.15 months (95% CI 13.57 to 23.82). Four patients (8.3%) showed a complete response (CR) and 20 patients (41.7%) had a PR, yielding an overall response rate (ORR) of 50% (95% CI 34.8% to 65.1%). 14 patients (29.2%) had an SD, eight patients (16.7%) had a PD and two patients (4.2%) could not be evaluated.</p>
<p>nearly half of patients had at least one grade 3 toxicity</p>	<p>Nearly half of the patients (43.8%) had at least one grade 3 non-serious adverse event and four patients (8%) experienced a grade 4 event. The most frequent toxicities were gastrointestinal (16.7%), vascular disorders (6.3%), as well as infections and infestations (6.3%) [33].</p>

### Bevacizumab + pegylated liposomal doxorubicin (PLD)

<p>phase II trial with bevacizumab + PLD</p>	<p>46 patients (mean age 64 years) participated in the phase II study and they received a treatment regimen with bevacizumab 15 mg/kg (starting at cycle 2) and PLD 30 mg/m<sup>2</sup> every three weeks [34].</p>
<p>median PFS was 7.8 months</p>	<p>The median of prior treatment lines was 2.0 (range 1.0–3.0). The median PFS (by GCIC criteria) was 6.6 months (95% CI 5.5 to 8.7) and 7.8 months (95% CI 6.4 to 9.7) by RECIST criteria. 33.2 months (95% CI 18.8 to not applicable) was the OS. The ORR measured by RECIST criteria was 30%, four patients (9%) had CR, nine patients (21%) had PR and 24 patients (56%) had SD.</p>

Several adverse events occurred during this trial. Mucositis (64%), palmar-plantar erythrodysesthesia (PPE)/ulceration (52%), asthenia (52%) and rash/pruritus (50%) were the most common non-haematological toxicities. No treatment-related deaths were observed. The most frequent grade 3 toxicities were PPE/ulceration and hypertension. The most common adverse events related to the administration of bevacizumab were hypertension (46%), headaches (41%) and epistaxis (21%) [34].

**several adverse events occurred**

### **Bevacizumab + pemetrexed**

In the phase II study, 34 patients (mean age 61.5 years) were enrolled [31]. The administration of pemetrexed 500 mg/m<sup>2</sup> IV and bevacizumab 15 mg/kg IV was given every three weeks. 35% of the patients were platinum-resistant with a median PFS of 6.7 (95% CI 4.1 to 9.9) months and an OS of 16.7 months. 53% of all patients (platinum-resistant and platinum-sensitive) showed hematologic side effects (grade 3–4).

**investigation of bevacizumab + pemetrexed**

The most frequent grade 3–4 adverse events were neutropenia (47%), leukopenia (27%), metabolic toxicity (24%) and pain (21%). Fatigue occurred in nearly all patients (94%), but was mostly (76%) of grade 1-2. The treatment combination of bevacizumab and pemetrexed is an active combination for platinum-resistant and platinum-sensitive recurrent ovarian cancer [31].

**median PFS was 6.7 and OS was 16.7 months**

### **Bevacizumab + docetaxel**

This phase II trial investigated the safety and efficacy of bevacizumab (15 mg/kg) on day one of a 3-week cycle and docetaxel (40 mg/m<sup>2</sup>) on days 1 and 8 [35]. In this trial, 41 patients (mean age 58.2 years) with a platinum-free interval < 12 months were enrolled. The median PFS for the 19 patients with a platinum-free interval < 6 months was 6.2 months (95% CI 4.1 to 4.7).

**investigation of bevacizumab – docetaxel**

Regarding the response rates and the toxicities, no distinction between platinum-resistant and platinum-sensitive can be made. ORR was 56.4% with the majority, i.e., 55.3 being PR. Six patients (15.8%) had PD and ten patients (26.3%) had SD. 65.9% of the patients experienced grade 3–4 toxicity. The most frequent grade 3–4 adverse events were neutropenia (14.6%), fatigue (12.2%), leukopenia (12.2%) and metabolic/laboratory toxicity (12.2%) [35].

**median PFS was 6.2 months**

## **7 Estimated costs**

The recommended dosage for Avastin<sup>®</sup> in patients with recurrent platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer is 10 mg/kg bodyweight every two weeks or 15 mg/kg bodyweight every three weeks [30].

**recommended dosage: 10 mg/kg every two weeks or 15 mg/kg every three weeks**

Avastin<sup>®</sup> is available in vials of 4 ml (25 mg/ml) and in vials of 16 ml (25 mg/ml). The costs for Avastin<sup>®</sup> are €414 for the 4 ml vials, and €1,421 for the 16 ml vials [39]. The overall treatment costs for one cycle of Avastin<sup>®</sup> (assuming 10 mg/kg are administered every two weeks by using one 16 ml vial and two 4 ml vials) for a woman assuming a body weight of 60 kg would therefore be approximately €4,500. In the AURELIA trial, the median dura-

**€414 for 4 ml vial  
€1,421 for 16 ml vial**

**approximately €4,500 per month**

tion of bevacizumab was six cycles, leading to total costs of €27,000. In addition, the costs for the previous treatment regimens, prior surgery and the treatment of the side effects accrue.

## 8 Ongoing research

**no ongoing phase III trials**

In August 2014 no on-going phase III trials investigating bevacizumab (Avastin®) for patients with recurrent platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer were found at ClinicalTrials.gov and clinicaltrialsregister.eu.

**two ongoing phase II trial investigating bevacizumab**

Two ongoing phase II trials are registered:

- ✳ **NCT01936974:** This study investigates platinum-gemcitabine-avastin (PGA) for platinum-resistant/refractory, paclitaxel-pretreated recurrent ovarian and peritoneal carcinoma. September 2014 is the estimated primary completion date.
- ✳ **NCT01652079:** A phase II, 2-stage trial of CRLX101 in combination with bevacizumab in recurrent platinum-resistant ovarian, tubal and peritoneal cancer. The estimated primary completion date is April 2016.

At the moment there are various ongoing phase III trials investigating bevacizumab for different types of cancer such as head and neck cancer, colorectal and breast cancer. In addition, several trials investigate bevacizumab for already approved indications like glioblastoma or advanced non-small cell lung cancer.

## 9 Commentary

**EMA has approved Avastin® for epithelial ovarian cancer impact of efficacy, safety and quality of life was investigated**

Since the end of July 2014, the EMA has approved bevacizumab (Avastin®) in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents [1, 2].

This decision was based on the findings of a randomised phase III trial (AURELIA) that investigated the combination of bevacizumab with chemotherapy in comparison to chemotherapy alone for platinum-resistant recurrent ovarian cancer. Only patients who had received < 2 prior anticancer regimen and no prior VEGF therapy were eligible [30].

**significant improvement of PFS in bevacizumab + chemotherapy**

This trial demonstrated a statistically significant improvement in PFS for platinum-resistant ovarian cancer patients treated with bevacizumab and chemotherapy in comparison to chemotherapy alone, a setting where only suboptimal treatment options are available. The administration of bevacizumab in combination with paclitaxel, topotecan or pegylated liposomal



doxorubicin resulted in an absolute gain in median PFS of 3.3 months and reduced the risk of progression or death by 52%. Noteworthy is the fact that the PFS was assessed by investigators and not by an independent review committee; the results, therefore, could have been influenced [30]. However, an independent review of data confirmed these findings [40]. Regarding OS, with 13.3 months in median OS for the control group and 16.6 months for the patients treated additionally with bevacizumab, there was no statistically significant difference between the two treatment options [30]. However, these results are compromised due to the fact that 40% of patients crossed-over from single-agent chemotherapy to bevacizumab in addition to a chemotherapy regimen [30, 41].

Regarding side effects, the AURELIA trial showed similar results as previous studies with bevacizumab in ovarian cancer. GI perforation, neutropenia and hypertension also occurred in several phase II trials investigating bevacizumab in combination with a chemotherapy regimen [31-35]. Grade 3 adverse events such as gastrointestinal (GI) perforation, proteinuria, fistula/abscess and reversible posterior leukoencephalopathy syndrome only occurred in the bevacizumab arm. Hypertension and proteinuria grade  $\geq 2$  were more common in the treatment arm with bevacizumab; 20% of patients treated with this regimen had hypertension and 2% had proteinuria [30] in comparison to 7% and 0% in the chemotherapy only arm.

Bevacizumab can be associated with serious adverse events and the toxicities can sometimes be life-threatening. Therefore, the improvement of quality and life, as well as alleviation of symptoms, plays an important role in the decision of the treatment regimen for patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer [41, 42]. Some indications for a positive impact on quality of life can be derived from patients included in the AURELIA trial. The main hypothesis, i.e., that more patients in the bevacizumab arm will experience a  $\geq 15\%$  improvement in abdominal/GI symptoms, showed a statistically significant difference favouring bevacizumab [37].

However, findings related to quality of life have to be put into perspective; due to the open-label design of this trial, results may be potentially biased in favour of the bevacizumab arm. Moreover, the permission of crossover could have an influence on this outcome [41, 42] and as mentioned by the authors themselves, a considerable number of patients overall and even more in the chemotherapy group did not complete the questionnaires at the follow-up mainly because patients with progressive disease were not assessed. Missing data was then rated as non-responders. How to deal with missing data in PRO analyses is still under discussion, but it may be the case that some patients with progressive disease did not experience aggravation of symptoms. The larger number of missing questionnaires in the chemotherapy only group, may have therefore contributed to a more favourable result for the bevacizumab and chemotherapy group. When missing data was excluded from the analysis, the result did not become statistically significant [41].

**GI perforation, proteinuria, fistula/abscess and reversible posterior leukoencephalopathy only in bevacizumab arm**

**symptom alleviation and improvement of quality of life important aim**

**statistically significant symptom improvement for bevacizumab and chemotherapy**

**but open-label design, cross-over, more missing data in chemotherapy only group potentially biasing results in favour of bevacizumab and chemotherapy**

**in which setting  
bevacizumab ideally?**

**efficacy in VEGF  
pretreated patients?**

**sequential  
administration of  
bevacizumab  
monotherapy followed  
by chemotherapy?**

**costs of prolonged  
administration of  
bevacizumab may not  
be underestimated**

Even though the AURELIA trial has found improved results in terms of PFS and response rate for bevacizumab in addition to chemotherapy, the question posed is when and in which setting bevacizumab can derive the greatest benefit. Bevacizumab in combination with chemotherapy is also licensed in the front-line setting, but only 7% of patients in the bevacizumab group were previously treated with VEGF therapy. Therefore, it remains unknown if patients previously treated with bevacizumab will have comparable results to those included in the phase III study [41]. Due to the lack of an arm assessing bevacizumab monotherapy only, outcomes for the sequential use of bevacizumab and chemotherapy rather than administration of combination therapy as initial regimen for platinum-resistant ovarian cancer cannot be derived [41]. Since monotherapy may be less toxic than combinations with cytotoxic regimens, this should be considered in further trials [30].

Cost considerations are also associated with questions on the optimal sequencing and setting of bevacizumab therapy. Several economic analyses did not prove cost-effectiveness generally, but rather for patients at high-risk [43, 44]. Biomarkers or factors predictive of response to bevacizumab in patients with ovarian cancer have thus been suggested for patient selection. However, no reliable biomarker has been defined yet and, therefore, further studies are required to confirm the clinical usefulness of markers [43].

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