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Bevacizumab (Avastin®) in addition to standard chemotherapy for the first-line treatment of ovarian cancer

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 56
ISSN online 2076-5940

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Vienna, January 2016

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

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The HTA Core Model ® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

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Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://hta.lbg.ac.at/page/imprint

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DSD: Horizon Scanning in Oncology No. 56
ISSN-online: 2076-5940

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in this assessment.

Element ID	Research question
Description of the technology	
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2 Drug description

Generic/Brand name/ATC code:
Bevacizumab/Avastin®/L01XC07

B0001: What is bevacizumab?

bevacizumab inhibits growth and maintenance of tumour blood vessels

Bevacizumab (Avastin®) is a recombinant monoclonal antibody that binds to the vascular endothelial growth factor (VEGF). By inhibiting VEGF receptor binding, bevacizumab prevents the growth and maintenance of tumour blood vessels [2].

intravenous administration

For the front-line treatment of patients with advanced epithelial ovarian, fallopian tube and primary peritoneal cancer, the recommended dose of bevacizumab is 15 mg/kg of body weight given intravenously (IV) once every three weeks. It is administered in addition to carboplatin and paclitaxel for up to six cycles of treatment followed by continued use as a single agent. If the initial dose of bevacizumab, which should be delivered over 90 minutes IV, is well tolerated, the second infusion can be administered over 60 minutes, followed by 30-minute infusions for all subsequent infusions. Treatment should be continued until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier [3].

most serious/most frequent adverse reactions

The most serious adverse reactions with bevacizumab observed in safety analysis (including patients with various malignancies) were gastrointestinal perforations, haemorrhage and arterial thromboembolism. The most frequent adverse reactions with bevacizumab occurring in patients across clinical trials were hypertension, fatigue, asthenia, diarrhoea and abdominal pain. The occurrence of hypertension and proteinuria are likely to be dose-dependent [3].

A0022: Who manufactures bevacizumab?

Genentech, Inc./Roche

3 Indication

A0007: What is the target population in this assessment?

indicated as first-line treatment of advanced ovarian cancer

Bevacizumab (Avastin®), combined with carboplatin and paclitaxel, is indicated for the front-line treatment of adult patients with advanced (FIGO[1] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer [3].

[1] FIGO = International Federation of Gynecology and Obstetrics

4 Current regulatory status

A0020: For which indications has bevacizumab received marketing authorisation?

approved by the EMA for first-line treatment of ovarian cancer

Bevacizumab was approved by the EMA in December 2011 for the front-line treatment of adults with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer (in combination with carboplatin and paclitaxel) [3]. Bevacizumab is also licensed for the treatment of 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 and gemcitabine) and for the treatment of adults 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 (in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin).

bevacizumab is already approved by the EMA for several indications

Furthermore, the EMA granted marketing authorisation for bevacizumab for the following indications [3]:

- for the treatment of adult patients with metastatic carcinoma of the colon or rectum (in combination with fluoropyrimidine-based chemotherapy)
- for the first-line treatment of adults with metastatic breast cancer (combined with paclitaxel)
- for the first-line treatment (in combination with capecitabine) of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate
- for the first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer with other than predominantly squamous cell histology (in addition to platinum-based chemotherapy)
- for the first-line treatment (combined with interferon alfa-2a) of adults with advanced and/or metastatic renal cell cancer
- for the treatment of adult patients with persistent, recurrent or metastatic carcinoma of the cervix (in combination with paclitaxel and cisplatin, or, alternatively, paclitaxel and topotecan).

In December 2014, the EMA granted orphan designation for bevacizumab for the treatment of hereditary haemorrhagic telangiectasia [4].

not approved by the FDA for the first-line treatment of ovarian cancer

To date, bevacizumab is not approved for the first-line treatment of patients with ovarian cancer by the FDA. The FDA granted marketing authorisation for bevacizumab for the treatment of [5]:

- metastatic colorectal cancer, with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment
- metastatic colorectal cancer, with fluoropyrimidine-, irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen

several other indications are approved by the FDA

- non-squamous, non-small cell lung cancer, with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease
- glioblastoma, as a single agent for adults with progressive disease following prior therapy
- metastatic renal cell carcinoma with interferon alfa
- cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent or metastatic disease
- platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan.

5 Burden of disease

A0002: What is ovarian cancer?

A0004: What is the natural course of ovarian cancer?

approx. 90% are of epithelial origin

Ovarian cancer develops in the ovaries and is mostly of epithelial origin. Various subtypes (having prognostic importance) of epithelial ovarian cancer can be distinguished: serous, endometrioid, clear cell, mucinous, transitional cell (Brenner), mixed epithelial tumours, undifferentiated and unclassified subtypes [6]. In advanced ovarian cancers, invasive serous carcinomas are the most common histological type.

potentially metastatic disease

Ovarian cancer is a potentially metastatic disease that mainly spreads to the peritoneum, the omentum and to abdominal and pelvic organs. In advanced disease, ovarian cancer can disseminate to the lung and liver or, in rare cases, even to the brain or skin [7].

median age at diagnosis: 63 years

The median age at diagnosis of ovarian cancer is 63 years; the disease is most commonly diagnosed among women at the age of 55–64 years. 15% of ovarian cancer cases are diagnosed at local stage, 19% at regional stage and 60% at distant stage (6% of cases remain unstaged)[8].

45.6% of patients survive 5 years

The survival rate of patients with ovarian cancer depends on the stage of the disease. Overall, 45.6% of patients with ovarian cancer survive 5 years. 5-year survival rates are 92.1% in patients with localised disease, 73.2% in patients with regional disease (cancer has spread to regional lymph nodes), 28.3% in patients who have distant metastatic disease and 22.9% in patients with unstaged disease [8].

A0003: What are the known risk factors for ovarian cancer?

family history of breast/ovarian cancer is the most important risk factor

A strong family history of breast cancer or ovarian cancer is deemed to be the most important risk factor for the development of ovarian cancer. Studies indicate that preventive removal of the ovaries and fallopian tubes in women who have a history of breast cancer or who have tested positive for inherited

mutations in BRCA1 or BRCA2[2] may decrease their risk [9]. Patients with an inherited BRCA1 mutation have a 15–45% lifetime risk of developing ovarian cancer, a BRCA2 mutation increases the lifetime risk of ovarian cancer to 10–20% [6]. However, there is evidence showing that 44% of patients with high-grade serous ovarian cancer and a germline BRCA mutation had no reported family history of breast or ovarian cancer [6, 10].

Further risk factors are pelvic inflammatory disease, Lynch syndrome, the use of single-agent oestrogen as menopausal hormone therapy, tobacco smoking and heavier body weight. In contrast, pregnancy, the long-term use of oral contraceptives and tubal ligation, as well as hysterectomy and salpingectomy may reduce the risk for ovarian cancer [9].

A0005: What are the symptoms of ovarian cancer?

symptoms are rare in early stages of disease

Since ovarian cancer that is confined to the ovary causes few or no symptoms, the disease is difficult to detect in early stages [6]. However, there is evidence that some women experience persistent, non-specific symptoms (including bloating, pelvic or abdominal pain, difficulty eating, feeling full quickly or feeling urinary urgency or frequency) [9]. Symptoms of ovarian cancer of all stages are abdominal or pelvic pain, constipation, diarrhoea, urinary frequency, vaginal bleeding, abdominal distension and fatigue. Symptoms more often occur in advanced stages of the disease and include ascites and abdominal masses (leading to increased abdominal girth), bloating, nausea, anorexia, dyspepsia and early satiety. When the disease spreads to other parts of the body, patients may develop respiratory symptoms, or may recognise an abdominal or nodal mass in the inguinal region, axillae or the supraclavicular fossa [6].

A0024: How is ovarian cancer currently diagnosed according to published guidelines and in practice?

rare early-stage symptoms make the disease difficult to detect

Early ovarian cancer rarely causes symptoms when it is confined to the ovaries and is therefore difficult to detect [6]. Hence, 70% of epithelial ovarian cancers are not discovered until the disease has progressed to advanced stages and has spread to other parts of the body [11]. Currently, no sufficient screening test for the early detection of ovarian cancer in women with an average risk for the disease exists [9]. Although the measurement of serum cancer antigen (CA) 125 is used routinely to support diagnosis after conducting a full clinical assessment, its fitness for the purpose of detecting ovarian cancer in its early stages is questionable [6].

tests for diagnosis of ovarian cancer

The following tests (in addition to a physical examination) may be used for diagnosing ovarian cancer [11]:

- pelvic examination (including uterus, vagina, ovaries and rectum)
- transvaginal ultrasonography
- CA 125 assay
- imaging methods, including X-ray examination, computed tomography, positron emission tomography, lower gastrointestinal series and magnetic resonance imaging
- biopsy.

[2] BRCA1, BRCA2 = Breast Cancer Genes 1 and 2

Ovarian cancer is staged according to the FIGO classification which was updated in 2014 [12]:

Stage I: Tumour confined to ovaries	
IA	Tumour limited to 1 ovary, capsule intact, no tumour on surface, negative washing
IB	Tumour involves both ovaries, otherwise like IA
IC	Tumour limited to 1 or both ovaries
IC2	Capsule rupture before surgery or tumour on ovarian surface
IC3	Malignant cells in the ascites or peritoneal washings
Stage II: Tumour involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer	
IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal issues
Stage III: Tumour involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
IIIA	Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
IIIA1	Positive retroperitoneal lymph nodes only IIIA1(i): metastasis ≤ 10 mm IIIA1(ii): metastasis > 10 mm
IIIA2	Microscopic, extrapelvic (above the brim), peritoneal involvement ± positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes; includes extension to capsule of liver/spleen
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes; includes extension to capsule of liver/spleen
Stage IV: Distant metastasis excluding peritoneal metastasis	
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

A0006: What are the consequences of ovarian cancer for the society?

A0023: How many people belong to the target population?

incidence in Austria: 8.5/100,000 women per year

In Austria, the incidence of ovarian cancer is 8.5 per 100,000 women per year; 653 women were newly diagnosed with ovarian cancer in 2012 [13]. In Europe, the estimated incidence of ovarian cancer was 13.1 per 100,000 persons in 2012 with higher incidence rates in northern European countries (e.g. 18.9 per 100,000 persons in Latvia or 18.2 per 100,000 in Lithuania) [14]. Assuming that 60% of ovarian cancer cases are diagnosed at a distant stage of the disease [8], in Austria, 392 patients would qualify for bevacizumab therapy each year.

6 Current treatment

A0025: How is ovarian cancer currently managed according to published guidelines and in practice?

primary treatment: cytoreductive surgery and systemic chemotherapy

If ovarian cancer is assumed, appropriate surgical staging and cytoreduction, mostly followed by systemic chemotherapy, are conducted as part of the primary treatment [15]. As most ovarian cancer patients present with advanced disease, primary cytoreduction is not only performed to document the stage and extent of the disease but also to resect as much visible tumour mass as possible [16]. The initial surgery should be conducted as a comprehensive staging laparotomy and should include a total abdominal hysterectomy and a bilateral salpingo-oophorectomy. In women who wish to maintain fertility, a unilateral salpingo-oophorectomy may be appropriate for the treatment of tumour stages 1A, 1C and/or low-risk ovarian tumours. Optimal surgical cytoreduction is achieved when residual tumour nodules are less than 1 cm in maximum diameter or thickness. Minimally invasive procedures and techniques may be used in selected patients for surgical staging and in early-stage disease to achieve the surgical goals [15].

In primary advanced ovarian cancer, cytoreduction of all visible disease is required, including intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky para-aortic lymph nodes and splenectomy [6].

role of adjuvant chemotherapy

Although the therapeutic benefit of adjuvant chemotherapy is still controversial, it may be considered (followed by interval cytoreduction, which is administered after chemotherapy) in patients with bulky stage III to IV disease (assessed by a gynaecological oncologist) who are not appropriate for surgery [15]. The European Society for Medical Oncolgy (ESMO) strongly recommends offering adjuvant chemotherapy not only to suboptimally staged patients, but also to patients who are optimally staged at a higher risk of disease recurrence [6]. The European Organisation for Research and Treatment of Cancer – Gynaecological Oncology Group (EORTC-GOG) defined an optimal staging procedure for early ovarian cancer as [17]:

- inspection and palpation of all peritoneal surfaces
- biopsies of any suspected lesions
- peritoneal washings
- blind biopsies of the right diaphragm and right and left para-colic gutter, pelvic side-walls of the ovarian fossa and the bladder peritoneum
- sampling of iliac and para-aortic lymph nodes.

chemotherapy regimens

For all patients with FIGO stage II–IV disease, chemotherapy is recommended after surgery. ESMO [6] strongly recommends (IA[3]) standard chemotherapy, consisting of combined paclitaxel 175 mg/m^2 and carboplatin at an area under the curve (AUC) 6–5, both given IV every 3 weeks (usually for 6 cycles). For patients developing an allergy or patients who do not tolerate paclitaxel, a treatment with the combination of docetaxel and carboplatin or pegylated liposomal doxorubicin (PLD) and carboplatin can be considered. Alternative-

[3] Level/grade of recommendation IA = Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity; strong evidence for efficacy with a substantial clinical benefit, strongly recommended

ly, paclitaxel and platinum chemotherapy can be administered in alternative schedules, including intraperitoneal administration and dose-dense regimens. While these alternative ways of administration may provide an option (e.g. in the context of randomised trials), they are not considered standard of care [6]. According to the National Comprehensive Cancer Network (NCCN) [15], the administration of single-agent platinum agents may provide an appropriate option for patients with poor performance status, comorbidities, stage IV disease or elderly patients (< 65 years) who may not tolerate the recommended regimens.

bevacizumab: generally recommended by ESMO

ESMO generally recommends (IB[4]) the addition of bevacizumab to paclitaxel and carboplatin in the front-line treatment of patients with advanced ovarian cancer showing poor prognostic factors, including stage IV or suboptimal debulking, as defined in the ICON7 trial [6].

7 Evidence

386 references in total, 2 phase III trials included

A literature search was conducted on 3 November 2015 in four databases (The Cochrane Library, CRD Database, Embase, Medline). Search terms were "Bevacizumab", "Avastin", "Altuzan" "nsc 704865", "ovarian neoplasms", "ovary cancer", "newly diagnosed", "front line", "first line". Also, the manufacturer was contacted, and it submitted 13 additional references (9 of them had already been identified by systematic literature search) and further information.

Overall, 386 references were identified. Included in this report were only randomised controlled trials:

- 1 phase III trial, assessing the addition of bevacizumab to standard chemotherapy in the first-line treatment of ovarian cancer [18, 19]
- 1 phase III trial, evaluating the integration of bevacizumab into front-line ovarian cancer therapy [20].

[4] Level/grade of recommendation IB = Evidence from at least one large randomised, controlled trial of good methodological quality or meta-analyses of well-conducted randomised trials without heterogeneity; strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

7.1 Clinical efficacy and safety – phase III studies

The ICON7 trial

ICON7 trial

The ICON7 trial was conducted to assess the addition of bevacizumab to standard chemotherapy (carboplatin AUC 5 or 6 and paclitaxel 175 mg/m^2 of body surface area, given every 3 weeks for 6 cycles) in the first-line treatment of women with ovarian cancer; first results were published in 2011 [19]. In 2015, Oza et al. [18] presented the final analysis of mature overall survival (OS) data from ICON7, including detailed data about the effect of bevacizumab according to stage and extent of residual disease after primary debulking surgery.

phase III trial with 1,528 participating women

ICON7 was an international, multicentre, open-label, randomised phase III trial. A total of 1,528 women with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer (FIGO stage IIb–IV or high-risk stage I–IIa disease) who had undergone debulking cytoreductive surgery (or, in advanced disease, had a biopsy with no further surgery planned) were enrolled. The median age of patients was 57 (range 18–81) years in both groups; the majority of patients had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, epithelial ovarian (histologically serous) cancer and FIGO stage IIIC disease. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 5.

patients received carboplatin and paclitaxel ± bevacizumab

Patients were randomised in a 1:1 ratio and received either six 3-weekly cycles of IV carboplatin at an area under the curve (AUC) of 5 or 6 mg/ml per minute and paclitaxel (175 mg/m^2 of body surface area) or the same chemotherapy regimen with IV bevacizumab at a dose of 7.5 mg/kg of body weight, given concurrently, and continued for 12 further 3-weekly cycles. Bevacizumab was administered about 1 year or until disease progression. Median follow-up was 48.6 months in the standard chemotherapy group and 48.8 months in the bevacizumab group (shorter follow-up durations for high-risk patients).

PFS was primary outcome

The primary outcome of ICON7 was progression-free survival (PFS); secondary outcomes were OS and safety outcomes including adverse events (AEs), laboratory results and worsened ECOG performance status. Exploratory outcomes were quality of life (= QoL, assessed with the EORTC[5] QLQ-C30 and QLQ-OV28[6] questionnaires), health economic and translational research. Results of these endpoints have already been reported [19].

definition of high-risk patients

To enable comparison with the GOG-0218 study population (the EMA approval was based on the results of the GOG-0218 study), risk groups were defined: high risk of progression was defined as stage IV disease, inoperable stage III disease or suboptimally debulked (> 1 cm) stage III disease. Patients who did not meet the criteria for high-risk disease were defined as non-high-risk patients.

[5] EORTC = European Organisation for Research and Treatment of Cancer

[6] QLQ-C30 = quality of life questionnaire – core 30, QLQ-OV28 = quality of life questionnaire – ovarian cancer module

The GOG-0218 trial

GOG-0218 trial

phase III trial of standard chemotherapy ± bevacizumab in 1,873 women

The GOG-0218 trial [20] was an international, double-blind, placebo-controlled phase III trial. 1,873 women were enrolled and randomly assigned to 3 study regimens, each comprising 22 3-week cycles. Initially, all patients received standard chemotherapy for the first 6 cycles, consisting of carboplatin (AUC 6) and paclitaxel at a dose of 175 mg/m^2 of body surface. Patients of the control group received chemotherapy in addition to placebo from cycles 2 through 22. Patients of the bevacizumab-initiation group received chemotherapy, followed by bevacizumab (15 mg/kg) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Patients who were assigned to the bevacizumab-throughout group received chemotherapy with bevacizumab added in cycles 2 through 22. Treatment was discontinued in case of disease progression, the occurrence of unacceptable toxic effects, completion of all 22 cycles or withdrawal. Median follow-up at the time of the primary analysis was 17.4 months.

newly diagnosed ovarian cancer

Enrolled patients had previously untreated, incompletely resectable stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian tube cancer. The median age of patients was 60 years, with a wide range from 22 to 89 years. The majority of patients had a Gynecologic Oncology Group (GOG) performance status of 0 or 1 and presented with serous adenocarcinomas. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 6.

primary endpoint was changed during the trial

Initially, the primary endpoint of the GOG-0218 trial was OS. Since numerous investigators and patients contested the continued blinding of the treatment assignments after disease progression, the primary endpoint was changed to PFS. Further endpoints were safety and QoL, which were assessed by the use of the Trial Outcome Index of the Functional Assessment of Cancer Therapy – Ovary (FACT-O TOI).

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of bevacizumab on mortality?

ICON7

ICON7: no significant OS benefit of bevacizumab in either group

There was no significant difference in OS between the randomised groups, neither clinically nor statistically. Due to the evidence of non-proportionality, the restricted mean survival was estimated in each group. Restricted mean survival was 44.6 months (95% CI, 43.2 to 45.9) for patients receiving standard chemotherapy, compared to 45.5 months (44.2 to 46.7) in patients receiving additional bevacizumab. Restricted mean OS time in high-risk patients was 39.3 months (95% CI, 37.0 to 41.7) for patients of the bevacizumab group and 34.5 months (95% CI, 32.0 to 37.0) for patients of the chemotherapy group (log-rank p = 0.03). In non-high-risk patients, the restricted mean survival time did not differ significantly between the standard chemotherapy group (49.7 months, 95% CI, 48.3 to 51.1) and the bevacizumab group (48.4 months, 47.0 to 49.9, p = 0.20). During the study, 46% of standard chemotherapy-group patients and 47% of bevacizumab-group patients died.

benefit of +4.8 months in restricted mean OS in high-risk patients

benefit in patients with worsening prognostic factors

Analyses according to survival by stage, residual disease burden and risk of recurrence showed an increased benefit for the addition of bevacizumab to standard chemotherapy with worsening prognostic factors (e.g. in high-risk patients and patients with disease stage III, IV or inoperable disease).

There was no benefit reported from adding bevacizumab in other predefined poor-prognosis tumour types, including clear-cell tumours, low-stage high-grade tumour and low-grade serous tumours.

no benefit in poor-prognosis tumour types

GOG-0218

Median OS was 38.7 months in patients of the bevacizumab-initiation group, 39.7 months in patients of the bevacizumab-throughout group and 39.3 months in patients of the control group. Compared with the control group, the HR of death was 1.04 (95% CI, 0.83 to 1.29, p = 0.76) in the bevacizumab-initiation group and 0.92 (95% CI, 0.73 to 1.15, p = 0.45) in the bevacizumab-throughout group. There were no significant differences in OS among the three treatment groups.

GOG-0218: no significant differences in OS among treatment groups

At the time of primary analysis, 76.3% of study patients were alive.

D0006: How does bevacizumab affect progression of ovarian cancer?

ICON7

Perren et al. reported PFS results of ICON7 in 2011 [19]: at the time of the primary analysis, restricted mean PFS at 36 months was 20.0 months in patients receiving standard chemotherapy and 21.8 months in patients receiving standard chemotherapy with bevacizumab; HR for progression or death with bevacizumab added was 0.81 (95% CI, 0.70 to 0.94, p = 0.004 by log-rank test). At the time of the updated analysis, restricted mean PFS was 20.6 months (standard chemotherapy group) and 22.5 months (bevacizumab group) at 36 months and 22.4 months (standard chemotherapy group) compared to 24.1 months (bevacizumab group) at 42 months (HR for progression or death in the bevacizumab group was 0.87, 95% CI, 0.77 to 0.99, p = 0.04), which corresponds to a long-term improvement in PFS with bevacizumab compared to standard chemotherapy.

ICON7: bevacizumab improved restricted mean PFS (+ 1.8 months)

In 2015, Oza et al. presented an updated analysis of PFS [18], showing that the overall difference in PFS was no longer statistically significant between the randomised groups. In high-risk patients, a significant benefit of p = 0.001 remained (with strong evidence of non-proportional hazards of p < 0.0001 and longer mean restricted PFS in the bevacizumab group than in the chemotherapy group).

updated analysis: overall difference in PFS no longer statistically significant

GOG-0218

The median PFS was 11.2 months in patients of the bevacizumab-initiation group, 14.1 months in the bevacizumab-throughout group and 10.3 months in patients of the control group. HR (compared to the control group) for progression or death was lower (0.908, 95% CI, 0.795 to 1.040, p = 0.16) in the bevacizumab-initiation group and significantly lower (0.717, 95% CI, 0.625 to 0.824, p < 0.001) in the bevacizumab-throughout group. Compared with control treatment, the estimated treatment effect of bevacizumab-throughout on PFS was consistent across various prognostic factors including cancer stage, histologic tumour type and tumour grade, GOG performance status and age of patients.

GOG-0218: bevacizumab prolongs PFS when added to standard therapy (+ 0.9–3.8 months)

As required by regulatory agencies, an analysis of PFS with censored data of patients with increased CA-125 levels was performed: median PFS was 18.0 months in the bevacizumab-throughout group versus 12.0 months in the control group (HR = 0.645, 95% CI, 0.551 to 0.756, p < 0.001).

D0005: How does bevacizumab affect symptoms and findings (severity, frequency) of ovarian cancer?

ICON7

higher response rate in the bevacizumab group

Perren et al. assessed the best overall response: the rate of complete or partial remission was 48% in the standard chemotherapy group compared to 67% in the bevacizumab group (difference of 19 percentage points (95% CI, 11 to 28, $p < 0.001$).

GOG-0218

There was no response rate data available from the GOG-0218 trial.

D0011: What is the effect of bevacizumab on patients' body functions?

No evidence was found to answer this research question.

D0012: What is the effect of bevacizumab on generic health-related quality of life?

D0013: What is the effect of bevacizumab on disease-specific quality of life?

ICON7

In 2013, Stark et al. [21] presented QoL outcomes of the ICON7 trial, concluding that continuing bevacizumab in patients with ovarian cancer is apparently associated with a small but clinically significant decrement in QoL as compared to standard treatment.

ICON7: no difference in global QoL between the groups

Updated analysis of Oza et al. [18], including data up to week 76, showed that there was no difference in global QoL between patients receiving standard chemotherapy and patients receiving bevacizumab at week 76 ($p = 0.43$). Further exploratory analyses were conducted, showing a clinically small difference in patients of the non-high-risk bevacizumab group relative to patients not receiving bevacizumab (–5.1 points, 95% CI –9.4 to –0.7, $p = 0.02$), whereas a small and not significant benefit of +4.3 points (95% CI, –4.9 to 13.4, $p = 0.36$) relative to patients not receiving bevacizumab was recorded in high-risk patients.

GOG-0218

GOG-0218: no significant differences in QoL across the 3 treatment groups

Results of the FACT-O TOI showed no significant differences across the three treatment groups. Generally, the mean FACT-O TOI scores increased over the duration of the study. During the chemotherapy phase, mean scores were slightly lower in both bevacizumab groups as compared to the control group. After completion of the chemotherapy, there were no significant differences in the FACT-O TOI mean scores between the bevacizumab-throughout group and the control group [20, 22].

Table 1: Efficacy results of the ICON7 trial

Descriptive statistics and estimate variability		All patients		High-risk patients	
	Treatment group	Bevacizumab	Standard therapy	Bevacizumab	Standard therapy
	Number of subjects	n = 764	n = 764	n = 248	n = 254
	Median OS (95% CI), months	58.0 (52.4–66.9)	58.6 (53.5–67.5)	39.7 (36.0–44.2)	30.2 (27.0–34.3)
	Median PFS (95% CI), months	19.9 (19.1–22.0)	17.5 (15.7–18.7)	16.0 (14.2–17.8)	10.5 (9.3–12.0)
	QoL score, mean (sd) Baseline Week 76 Sensitivity analysis	54.7 (19.1) 72.6 (18.9) NR	57.0 (20.0) 75.9 (19.3) NR	51.5 (19.8) 76.7 (18.0) 63.5 (15.3)	54.1 (20.1) 72.4 (19.4) 61.4 (14.2)
		Bevacizumab n = 257		Standard therapy n = 263	
	Response (95% CI), % Responders (CR/PR) Non-responders (SD/PR) CR PR SD PD	 67 33 15.2 52.0 29.2 3.6		 48 52 4.8 42.9 45.7 6.5	
Effect estimate per comparison	Comparison groups			All patients Bevacizumab vs. Standard chemotherapy	High-risk patients Bevacizumab vs. Standard chemotherapy
	OS	HR		0.99	0.78
		95% CI		0.85–1.14	0.63–0.97
		Unstratified log-rank test p value [7]		0.85	0.03
		Non-proportionality p value [8]		0.02	0.01
	PFS	HR		0.93	0.73
		95% CI		0.83–1.05	0.61–0.88
		Log-rank test p value		0.25	0.001
		Non-proportionality p value		< 0.0001	< 0.0001
	QoL Week 76/Sensitivity analysis	HR		NR	NR
		P value		0.43/NR	0.36/0.36
	CR + PR (bevacizumab: n = 257, standard therapy: n = 263	Percentage points, difference		19	
		95% CI		11–28	
		P value		< 0.001	

Abbreviations: CI = confidence interval, CR = complete remission, HR = hazard ratio, n = number, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial remission, QoL = quality of life, sd = standard deviation, SD = stable disease

Sources: [18, 19]

[7] Primary analysis used an unstratified log-rank test to compare OS between the randomised groups

[8] Grambsch-Therneau test

Table 2: Efficacy results of the GOG-218 trial

Descriptive statistics and estimate variability	Treatment group	Bevacizumab initiation	Bevacizumab throughout	Control
	Number of subjects	n = 625	n = 623	n = 625
	Median PFS (95% CI), months	11.2	14.1	10.3
	Median OS (95% CI), months	38.7	39.7	39.3
	Quality of life	NR	NR	NR
Effect estimate per comparison	Comparison groups	Bevacizumab Initiation vs. Control	Bevacizumab Initiation vs. Control	Bevacizumab throughout vs. Control
	PFS	HR	0.908	0.717
		95% CI	0.795–1.040	0.625–0.824
		P value	0.16	< 0.001
	OS	HR	1.036	0.915
		95% CI	0.827–1.297	0.727–1.152
		P value	0.76	0.45
	QoL, mean FACT-O TOI scores (during chemotherapy phase)	Reduction of points	2.7	3.0
		98.3% CI	0.88–4.57	1.13–4.78
		P value	< 0.001	0.001
Notes	❁ 19% of patients completed the planned treatment ❁ 15% of patients were still receiving treatment at the time of database lock ❁ 66% of the study population discontinued the study treatment prematurely, mostly due to disease progression			

Abbreviations: CI = confidence interval, FACT-O TOI = Trial Outcome Index of the Functional Assessment of Cancer Therapy – Ovarian, HR = hazard ratio, n = number, NR = not reported, OS = overall survival, PFS = progression-free survival, QoL = quality of life

Source: [20]

7.1.2 Safety

C0008: How safe is bevacizumab in relation to the comparator(s)?

C0002: Are the harms related to dosage or frequency of applying bevacizumab?

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of bevacizumab?

ICON7

bleeding, hypertension, thromboembolic and gastrointestinal events were more common with bevacizumab

AEs of grade 3 or higher were reported in 66% of patients in the bevacizumab group compared to 56% of patients in the standard chemotherapy group. Bleeding (mainly grade 1 mucocutaneous bleeding), hypertension of grade 2 or higher, thromboembolic events of grade 3 or higher and gastrointestinal perforations occurred more frequently in the bevacizumab group than in the standard chemotherapy group. In total, 5 patients died due to treatment or due to treatment and disease: one death was reported from the standard chemotherapy group (caused by central nervous system ischaemia) and four patients died in the bevacizumab group (caused by gastrointestinal perforation, intracerebral haemorrhage, recurrent bowel perforation and ovarian cancer, and neutropenic sepsis and ovarian cancer). According to Oza et al. [18], the following AEs occurred during the extended follow-up: one treatment-related grade 3 event (gastrointestinal fistula/bevacizumab group), 3 grade 2 treatment-related AEs in the bevacizumab group (cardiac failure, sarcoidosis, foot fracture) and 1 grade 1 treatment-related AE (vaginal haemorrhage) in a patient treated with standard chemotherapy.

GOG-0218

hypertension was significantly more common with bevacizumab

Hypertension of grade 2 or higher was significantly ($p < 0.001$) more common in the bevacizumab-initiation group (16.5%) and in the bevacizumab-throughout group (22.9%) than in the control group (7.2%). Hence, 2.4% of the patients of the bevacizumab-throughout group discontinued study treatment.

Concerning other selected AEs, including gastrointestinal events (perforation, fistula, necrosis or anastomotic leak), proteinuria, of grade 3 or higher, neutropenia of grade 4 or higher, neutropenia, venous or arterial thrombosis and wound disruption, no significant differences among the 3 treatment groups were reported. Other AEs, including clinically relevant bleeding or central nervous system complications were rare.

fatal AEs more frequent with bevacizumab

Fatal AEs occurred in 1.6% of patients of the bevacizumab-initiation group, in 2.3% of patients of the bevacizumab-throughout group compared to 1.0% of patients of the control group.

Most AEs occurred during the chemotherapy phase, with the exception of hypertension, proteinuria and pain, which occurred more commonly during the extended-therapy phase in patients of the bevacizumab-throughout group.

Due to AEs, treatment was discontinued in 15% (bevacizumab-initiation group), 17% (bevacizumab-throughout group) and 12% (control group) of patients respectively. 76% of AEs leading to discontinuation of study treatment occurred during the chemotherapy phase.

Table 3: Most frequent adverse events of the ICON7 trial

Adverse event (according to CTCAE version 3.0)	**Bevacizumab** (n = 745)			**Standard chemotherapy** (n = 753)		
	None n (%)	Grade 1 or 2 n (%)	Grade 3 or 4	None n (%)	Grade 1 or 2 n (%)	Grade ≥ 3
Any event	0	254 (34)	483 (65)	3 (< 1)	331 (44)	410 (54)
Any event (grade 5)	8 (1)			9 (1)		
Any bleeding	450 (60)	286 (38)	9 (1)	666 (88)	85 (11)	2 (< 1)
Bleeding other than mucocutaneous, tumour-associated, or within CNS	688 (92)	55 (7)	2 (< 1)	712 (95)	39 (5)	2 (< 1)
Mucocutaneous bleeding	469 (63)	271 (36)	5 (1)	698 (93)	55 (7)	0
Tumour-associated bleeding	0	0	0	0	0	0
Bleeding within CNS	743 (99)	0	2 (< 1)	753 (100)	0	0
Abscess and fistula	732 (98)	7 (1)	6 (1)	743 (99)	3 (< 1)	7 (1)
Gastrointestinal perforation	735 (99)	0	10 (1)	750 (99)	0	3 (< 1)
Hypertension	552 (74)	57 (8)/90 (12)	46 (6)	706 (94)	45 (6)	2 (< 1)
Proteinuria	712 (96)	29 (4)	4 (1)	734 (97)	18 (2)	1 (< 1)
Any thromboembolic event	665 (89)	29 (4)	51 (7)	708 (94)	22 (3)	23 (3)
Venous thromboembolic event	695 (93)	18 (2)	32 (4)	722 (96)	18 (2)	13 (2)
Arterial thromboembolic event	718 (96)	7 (1)	20 (3)	742 (99)	1 (< 1)	10 (1)
Local thrombosis	740 (99)	5 (1)	0	750 (99)	3 (< 1)	0
Neutropenia	534 (72)	88 (12)	123 (17)	534 (71)	105 (14)	114 (5)
Febrile neutropenia	724 (97)	2 (< 1)	19 (3)	738 (98)	1 (< 1)	14 (2)
Thrombocytopenia	652 (88)	67 (9)	26 (3)	684 (91)	54 (7)	15 (2)

Adverse event (according to CTCAE version 3.0)	Bevacizumab (n = 745)			Standard chemotherapy (n = 753)		
	None n (%)	Grade 1 or 2 n (%)	Grade 3 or 4	None n (%)	Grade 1 or 2 n (%)	Grade ≥ 3
Reversible posterior leuko-encephalopathy syndrome	0	0	0	0	0	0
Congestive heart failure	742 (99)	1 (< 1)	2 (< 1)	750 (99)	0	3 (< 1)
Complication of wound healing	708 (95)	27 (4)	10 (1)	737 (98)	13 (2)	3 (< 1)
Hyperbilirubinaemia	742 (99)	2 (< 1)	0	753 (100)	0	0

Abbreviations: CNS = central nervous system, n = number

Sources: [18, 23, 24]

Table 4: Selected adverse events of the GOG-218 trial[9]

Adverse event (according to NCI-CTCAE version 3.0)	Bevacizumab initiation (n = 607)	Bevacizumab throughout (n = 608)	Control (n = 601)
	n (%)	n (%)	n (%)
Gastrointestinal events (grade ≥ 2)	17 (2.8)	16 (2.6)	7 (1.2)
Hypertension (grade ≥ 2)	100 (16.5)	139 (22.9)	43 (7.2)
Proteinuria (grade ≥ 3)	4 (0.7)	10 (1.6)	4 (0.7)
Pain (grade ≥ 2)	252 (41.5)	286 (47.0)	250 (41.6)
Neutropenia (grade ≥ 4)	384 (63.3)	385 (63.3)	347 (57.7)
Febrile neutropenia	30 (4.9)	26 (4.3)	21 (3.5)
Venous thromboembolism	32 (5.3)	41 (6.7)	35 (5.8)
Arterial thromboembolism	4 (0.7)	4 (0.7)	5 (0.8)
Wound disruption	22 (3.6)	18 (3.0)	17 (2.8)
CNS bleeding	0	2 (0.3)	0
Non-CNS bleeding (grade ≥ 3)	8 (1.3)	13 (2.1)	5 (0.8)
Reversible posterior leukoencephalopathy syndrome	1 (0.2)	1 (0.2)	0

Abbreviations: CNS = central nervous system, n = number, NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events

Source: [20]

8 Estimated costs

A0021: What is the reimbursement status of bevacizumab?

In Austria, bevacizumab (Avastin®) is available in vials of 4 ml (25 mg/ml) at € 414.05 and vials of 16 ml (25 mg/ml) at € 1,421.90 [25].

approved at a dosage of 15 mg/kg every 3 weeks

In patients with advanced epithelial ovarian, fallopian tube and primary peritoneal cancer, the recommended and EMA-approved dose is 15 mg/kg of body weight given IV once every 3 weeks [3]. According to this treatment regimen (assuming an average body weight of 70 kg), costs for one dose of bevacizumab are € 4,086 (2 x 16 ml vial + 3 x 4 ml vial); for one year of bevacizumab treatment, costs of € 70,824 would incur.

[9] Selected AEs with onset between cycle 2 and 30 days after the date of the last treatment

In the ICON7 trial, a different dosing regimen was used: bevacizumab was administered at a dose of 7.5 mg/kg of body weight every 3 weeks. Assuming an average body weight of 70 kg, one dose of bevacizumab costs € 2,250 (1 x 16 ml vial + 2 x 4 ml vials). Patients received 6 cycles of standard chemotherapy with or without bevacizumab, which was given concurrently and continued for 12 further 3-weekly cycles, with an overall duration of bevacizumab exposure of about one year (or until disease progression). For one year of bevacizumab, costs of € 39,000 would incur.

one dose of bevacizumab costs € 2,250

dose-dependent: € 39,000 to € 70,824 for 12 months

At any rate, the costs for bevacizumab incur in addition to the costs of standard chemotherapy.

9 Ongoing research

In December 2015, a search in www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. The following phase IV and phase III trials, evaluating the use of bevacizumab for the first-line treatment of ovarian cancer, were identified:

1 phase IV, 4 phase III and various phase II and observational studies are ongoing

- **NCT01706120:** A multicentre phase IV study in patients with stage III–IV epithelial ovarian cancer treated with carboplatin + paclitaxel with bevacizumab, assessing clinical and biological prognostic factors (MITO-16/MANGO2). Estimated study completion date is July 2016.
- **NCT01081262:** A multicentre, open-label phase III trial of carboplatin and paclitaxel with or without bevacizumab, compared with oxaliplatin and capecitabine with or without bevacizumab as first-line therapy in patients with mucinous epithelial ovarian or fallopian tube cancer (MEOC). Estimated primary completion date is July 2020.
- **NCT01462890:** A prospective, randomised phase III trial to evaluate the optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube or peritoneal cancer (BOOST). Estimated study completion date is November 2021.
- **NCT01167712:** A phase III trial of every-3-weeks paclitaxel vs. dose-dense weekly paclitaxel in combination with carboplatin with/without concurrent and consolidation bevacizumab in the treatment of primary stage II, III or IV epithelial ovarian, peritoneal or fallopian tube cancer and ACRIN 6695: perfusion CT imaging to evaluate treatment response in patients participating in GOG-0262. Estimated study completion date is December 2015.
- **NCT00951496:** A phase III trial of bevacizumab with IV versus IP chemotherapy in ovarian, fallopian tube and primary peritoneal carcinoma. Estimated primary completion date is March 2016.

Furthermore, bevacizumab for the first-line therapy in patients with ovarian cancer is evaluated in the following phase II studies, in different settings and combinations:

- NCT00511992: A phase II study of paclitaxel, cisplatin IP and bevacizumab IV followed by bevacizumab consolidation for advanced ovarian and peritoneal carcinoma or fallopian tube cancer.
- NCT01097746: A phase II trial of bevacizumab with carboplatin and weekly paclitaxel as first-line treatment in epithelial ovarian, primary peritoneal and fallopian tube carcinoma.
- NCT01010126: A phase II trial of temsirolimus and bevacizumab in patients with endometrial, ovarian, hepatocellular carcinoma, carcinoid or islet cell cancer.
- NCT01847677: A randomised, multicentre, open-label phase II trial to determine the efficacy and toxicity of preoperative chemotherapy with/without bevacizumab in patients with advanced ovarian cancer (NOVA).

Additionally, various observational studies were identified, assessing the use of bevacizumab for the front-line treatment of ovarian cancer (e.g. ENCOURAGE trial, BOVARI trial and OSCAR trial).

10 Discussion

indication approved by the EMA, but not by the FDA

Since 2011, bevacizumab (Avastin®), in combination with carboplatin and paclitaxel, has been approved by the EMA for the front-line treatment of women with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer [26]; the FDA has not granted marketing authorisation for this indication yet.

approval based on ICON7 and GOG-0218

The EMA approval was based on the efficacy and safety results of two phase III trials, evaluating the addition of bevacizumab to the front-line treatment with carboplatin and paclitaxel: the ICON7 trial and the GOG-0218 trial [3].

differences between phase III trials

The two trials differed significantly in their setting and study design [27]: ICON7 was an open-label, two-arm study; patients received bevacizumab for 12 months at a dosage of 2.5 mg/kg per week. In contrast, the GOG-0218 trial was double-blind, placebo-controlled and conducted as a 3-arm study; bevacizumab was administered for 15 months at a dose of 5 mg/kg per week. Furthermore, the patient populations differed: in the ICON7 trial, patients with stage I or IIA (up to 10 %) and with stages IIB to IV (all) participated; in the GOG-0218 trial, patients had stage III (suboptimal, optimal or visual/palpable) and stage IV disease. In contrast to the GOG-0218 trial, there was no independent review committee in the ICON7 trial [27]. The primary endpoint of the ICON7 trial was PFS, OS was defined as a secondary outcome [18]. In the GOG-0218 study, OS was initially defined as the primary endpoint which was then changed to PFS [20]. Since numerous investigators and patients contested the maintenance of blinding the treatment assignments after disease progression, the primary endpoint was changed, causing a major limitation of the GOG-0218 trial [20]. Safety and quality of life were endpoints of both trials. According to the National Institute for Health and Care Excellence (NICE)

major limitation of GOG-0218: change of endpoint

[28], the two trials are difficult to compare as they differ regarding inclusion criteria, administered bevacizumab dose, duration of treatment, definitions of progression and optimal debulking as well as in baseline factors.

modest overall benefit

Although both trials [18–20] initially showed an improvement of PFS when bevacizumab was added to standard chemotherapy, the overall benefit for the patients was modest. In the ICON7 trial, an updated analysis (results published in 2015 [18]) even showed no difference in PFS between the treatment groups. Regarding OS, there was no significant difference between the treatment groups in both trials: in the ICON7 trial, a gain of 0.9 months in restricted mean survival has been shown; patients of the GOG-0218 trial did not achieve any gain in OS by receiving study treatment. However, the benefits in OS and PFS were greater among patients who had a high risk for progression than in lower-risk patients. The benefit in restricted mean survival for high-risk patients of the ICON7 trial was 4.8 months when bevacizumab was added to standard chemotherapy. There were no significant differences in the quality of life of patients of both trials.

no significant OS benefit for non-high-risk patients

significant OS benefit in poor-prognosis patients of ICON7 trial

higher rate of AEs with bevacizumab

Generally, AEs were more frequent in patients who received additional bevacizumab compared to standard chemotherapy. In the ICON7 trial [18], AEs of grade 3 or higher occurred more frequently in patients of the bevacizumab group compared to chemotherapy-group patients (66% vs. 56% respectively). Bleeding, hypertension (≥ grade 2), thromboembolic events and gastrointestinal perforation were more common with bevacizumab. 5 Patients died due to treatment or to treatment and disease. In the GOG-0218 trial [20], hypertension (≥ grade 2) occurred significantly more frequent in patients receiving bevacizumab; fatal AEs were most frequent in the bevacizumab-throughout group, compared to the bevacizumab-initiation group and the control group (2.3% vs. 1.6% and 1.0% respectively). A meta-analysis [29] including 4 randomised controlled trials (ICON7, GOG-0218 and two trials evaluating bevacizumab for the treatment of platinum-resistant recurrent ovarian cancer and platinum-sensitive recurrent ovarian cancer respectively) showed a significantly increased risk of gastrointestinal events, hypertension, proteinuria and arterial thromboembolism with bevacizumab, whereas there was no evidence of a significant increased risk of venous thromboembolism. Results from a further meta-analysis [30] including the same 4 randomised controlled trials showed that the combination of bevacizumab with chemotherapy increases non-CNS bleeding, hypertension grade ≥2, arterial thromboembolism, gastrointestinal perforation and proteinuria grade ≥3.

meta-analyses showed increase of AEs in patients receiving bevacizumab

ICON7: unlicensed dose of bevacizumab was used

bevacizumab not used consistently in Europe

Important issues to discuss are the role and the applicability of the results of the ICON7 trial, considering that an unlicensed dose of bevacizumab has been used. According to ESMO, bevacizumab is not consistently used in Europe, as some clinicians restrict the use to „higher-risk" patients (as defined in the ICON7 trial), some use bevacizumab in its licensed dose and indication and others administer the drug to patients with recurrent ovarian cancer [6]. However, the EMA recommended the use of 15 mg/kg of bevacizumab every 3 weeks, which differs from the dose used in the ICON7 trial (7.5 mg/kg) and makes the results difficult to compare to phase III data from the GOG-0218 trial. More importantly, the use of a lower dose of bevacizumab than the approved dose would halve the treatment costs. More data concerning the optimal dose and duration of bevacizumab in the front-line setting is required. The results of the BOOST trial (NCT01462890), evaluating the optimal treatment duration of first-line bevacizumab, may help to resolve this issue. According to information from the manufacturer, results of the primary analysis of the BOOST trial are expected for the second half of 2016. First results from

the ROSiA trial (NCT01239732), a study evaluating the addition of bevacizumab to standard chemotherapy for the first-line treatment in patients with ovarian cancer with a median number of 23 (range 1–61, median exposure duration of 15.5 months) administered cycles, indicate that the longer duration of bevacizumab exposure may improve PFS but may also increase toxicity [31].

identification of biomarkers needed to determine appropriate patient population

Another unresolved issue is the selection of the most appropriate patient population for the addition of bevacizumab to standard chemotherapy. With respect to personalised medicine for affected patients, more research is needed to identify molecular markers [6]. The use of biomarkers that can predict the therapeutic effect of bevacizumab therapy would enable a more effective administration [32]. Since results of both phase III trials showed an improved efficacy in patients of the high-risk subgroups; further investigation is needed in this special group of patients.

ESMO, NCCN: different grades of recommendation

ESMO generally recommends the use of bevacizumab for patients with advanced ovarian cancer with poor prognostic features (e.g. stage IV or suboptimal debulking) [6]. Likewise, NCCN recommends the addition of bevacizumab to the upfront chemotherapy of ovarian cancer; however, the recommendation is classified as "category 3", based on any level of evidence and with major objections by NCCN on the grounds that the intervention is appropriate. The disagreement among panel members is caused by a lack of significant benefit in OS and QoL in phase III data from randomised trials. If bevacizumab is administered with first-line chemotherapy followed by bevacizumab maintenance, the panel recommends the (category 3) administration of regimens used in the GOG-0218 or ICON7 trials [15]. NICE [28] does not recommend bevacizumab given with paclitaxel and carboplatin for the first-line treatment of advanced ovarian cancer (only the results of GOG-0218 were accepted as key evidence and were supported by the ICON7 results).

NICE: additional treatment option for patients with limited options

However, NICE noted that, for patients with advanced ovarian cancer whose treatment options are limited, bevacizumab provides an additional option. Moreover it was concluded that compared with chemotherapy alone, the combination regimen did not lead to unacceptable toxicity, and occurring AEs were manageable. Furthermore, NICE stressed not to underestimate the impact of any PFS prolongation for the patients and their families [28]. Also, the impact of patient crossover from the control arm on the overall survival results was discussed. However, the addition of bevacizumab to standard chemotherapy for the first-line treatment of ovarian cancer was not recommended due to its lack of cost-effectiveness [28].

results not clinically significant, but impact on patient's life has to be considered

Generally, adding bevacizumab to standard chemotherapy in the front-line treatment of advanced ovarian cancer in the overall cancer population has not been considered cost-effective by several authors [33–35]. However, the combination regimen might become effective with biosimilar bevacizumab (which is currently in development in 7 companies) administered in patients with stage IV disease, ECOG performance status 1 and in patients at high risk of disease progression [34]. In the course of the expiration of the product patent on bevacizumab in July 2019 (in the US) and 2018 (in the EU) [34], the administration of biosimilar bevacizumab may become relevant.

administration of bevacizumab to all patients is not cost-effective

to date: no reliable effect of any anti-angiogenic agent on OS confirmed

However, no significant improvement in OS has been shown for the addition of bevacizumab to standard therapy among the entire (high-risk and non-high-risk patients) patient population of the ICON7 and GOG-0218 trials. This fact is supported by Mahner et al., who showed that no reliable effect of any anti-angiogenic agent on OS could be observed to date [36]. Additionally, no significant improvement in the quality of life of patients has been recorded.

treatment option for high-risk patients

In conclusion, the addition of bevacizumab to standard chemotherapy in patients with advanced ovarian cancer showed no survival benefit in the overall study population. However, high-risk patients with a poor prognosis achieved a benefit in OS, although it has to be considered that the increase is based on data of the ICON7 trial using an unlicensed dose of bevacizumab. Furthermore, the improvements in PFS are not statistically significant. Hence, high additional costs and increased AEs stand in contrast to modest improvements in efficacy. However, the impact of any prolongation of the patient's life might be relevant even if the addition of bevacizumab is not associated with an improved quality of life. Since the ICON7 trial was conducted with an unlicensed dose of bevacizumab, it is difficult to assess the applicability of the results and, not least, their impact on the treatment costs.

high additional costs vs. modest benefits

application in unselected patients questionable

Facing the recent results from the ICON7 trial and considering the high costs for modest improvements – importantly with no increase in the patient's quality of life – it is questionable if the broad administration of bevacizumab to an unselected patient population (including high-risk and non-high-patients) is still appropriate.

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12 Appendix

Table 5: Characteristics of the ICON7 trial

Title: **Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase III randomised trial [18, 19, 23, 37]**			
Study identifier	ISRCTN91273375, NCT00483782, EudraCT number 2005-003929-2, ICON-7		
Design	Phase III, randomised, international, multicentre, open-label trial		
	Duration of main phase:		Enrolment: 2006-12-18 to 2009-02-16 End of follow-up: 2013-03-31 Median follow-up: 48.9 months
Hypothesis	Superiority This study was designed and powered to detect differences in PFS and OS between the treatment groups. The analysis of OS needed 715 deaths to detect a 10-month improvement in median survival from 43 to 53 months (HR 0.81), with 80% power and a two-sided 5% significance level. The PFS analysis needed 684 disease progression events to show a 5-month PFS increase from 18 to 23 months, with 90% power and a two-sided 5% significance level.		
Funding	The National Institute for Health Research through the UK National Cancer Research Network, the Medical Research Council, and Roche		
Treatments groups	Bevacizumab (n = 764)		6 3-weekly cycles of IV carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m² of body surface area) plus IV bevacizumab (7.5 mg/kg of body weight) given concurrently and continued for 12 further 3-weekly cycles (with a duration of bevacizumab exposure of about 1 year), or until disease progression
	Standard chemotherapy (n = 764)		6 3-weekly cycles of IV carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m² of body surface area)
Endpoints and definitions	Progression-free survival (primary endpoint)	PFS	Calculated from the date of randomisation to the date of the first indication of disease progression or death, whichever occurred first. There was no independent central radiologists' panel review on progression
	Overall survival (secondary endpoint)	OS	Calculated from the date of randomisation to the date of death from any cause
	Response to therapy	-	-
	Disease progression		Disease progression was assessed by investigators according to RECIST 2000 guidelines, and needed radiological, clinical or symptomatic evidence of progression
	Quality of life	QoL	Quality of life was assessed with the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-OV28 questionnaires
	Safety	-	NR
Database lock	NR		
Results and analysis			
Analysis description	**Primary analysis** Intent to treat (included all patients randomly assigned to treatment) The primary analysis used an unstratified log-rank test to compare OS between randomised groups. Treatment effects were estimated from Cox regression analyses when proportional hazards could be assumed. With evidence of non-proportionality, flexible parametric survival models were used to smooth survival curves and estimate survival differences during a 5-year period, which is the approximate follow-up if patients were enrolled midway through the recruitment period and remained in follow-up at the end of the study.		
Analysis population	Inclusion		❖ Age ≥ 18 years ❖ Newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer ❖ ECOG performance status 0–2 ❖ FIGO 1988 stage IIb–IV or high risk (grade 3 or clear cell histology) stage I–IIa disease ❖ Patients who had undergone debulking cytoreductive surgery or, in advanced disease, had a biopsy with no further surgery planned ❖ Adequate coagulation parameters and liver, renal and bone marrow function

Title: Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase III randomised trial [18, 19, 23, 37]						
Study identifier	ISRCTN91273375, NCT00483782, EudraCT number 2005-003929-2, ICON-7					
Analysis population *(continuation)*	Exclusion	❖ Having other tumour types ❖ Previous systemic therapy ❖ Planned surgery ❖ Uncontrolled hypertension				
	Baseline characteristics		All		High risk	
			Bevacizumab (n = 764)	Standard therapy (n = 764)	Bevacizumab (n = 248)	Standard therapy (n = 254)
		Age, median (range) Years	57 (24–80)	57 (18–81)	60 (26–80)	60 (18–81)
		Race, n (%)				
		White	730 (96)	737 (96)	237 (96)	242 (95)
		Asian/Black/Other	34 (4)	27 (4)	11 (4)	12 (5)
		ECOG PS, n (%)				
		0	335 (45)	360 (48)	100 (41)	98 (39)
		1	366 (49)	354 (47)	123 (50)	135 (53)
		2	45 (6)	41 (5)	21 (9)	20 (8)
		Unknown	18	9	4	1
		Origin of cancer, n (%)				
		Ovary (epithelial)	673 (88)	667 (87)	207 (83)	210 (83)
		Fallopian tube	27 (4)	29 (4)	6 (2)	5 (2)
		Primary peritoneal	50 (7)	56 (7)	28 (11)	32 (13)
		Multiple sites	14 (2)	12 (2)	7 (3)	7 (3)
		Histology, n (%)				
		Serous	525 (69)	529 (69)	186 (75)	195 (77)
		Mucinous	19 (2)	15 (2)	6 (2)	4 (2)
		Endometroid	60 (8)	57 (7)	17 (7)	14 (6)
		Clear cell	67 (9)	60 (8)	6 (2)	6 (2)
		Mixed	40 (5)	48 (6)	14 (6)	14 (6)
		Other	53 (7)	55 (7)	19 (8)	21 (8)
		FIGO stage, n (%)				
		I/IIA	67 (9)	75 (10)		
		IIB/IIC	70 (9)	70 (9)		
		III	18 (2)	14 (2)	6 (2)	6 (2)
		IIIA	22 (3)	32 (4)	2 (0.8)	2 (0.8)
		IIIB	45 (6)	44 (6)	6 (2)	8 (3)
		IIIC	438 (57)	432 (57)	130 (52)	141 (56)
		IV	104 (14)	97 (13)	104 (42)	97 (38)
		Grade, n (%)				
		Grade 1	41 (5)	56 (7)	5 (2)	10 (4)
		Grade 2	175 (23)	142 (19)	70 (29)	45 (18)
		Grade 3	538 (71)	556 (74)	169 (69)	195 (78)
		Unknown	10	10	4	4
		Debulking surgery				
		Inoperable	13 (2)	17 (2)	13 (5)	17 (7)
		> 1 cm residual	196 (26)	199 (26)	194 (78)	194 (76)
		0–1 cm residual	194 (25)	175 (23)	20 (8)	19 (7)
		0 cm residual	361 (47)	373 (49)	21 (8)	24 (9)

Abbreviations: AUC = area under the curve, CA-125 = cancer antigen 125, ECOG = Eastern Cooperative Oncology Group, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, IV = intravenous, n = number, NA = not applicable, NR = not reported, OS = overall survival, PFS = progression-free survival, RECIST = Response Evaluation Criteria In Solid Tumors, QLQ-C30 = quality of life questionnaire – core 30, QLQ-OV28 = quality of life questionnaire – ovarian cancer module, QoL = quality of life

Table 6: Characteristics of the GOG-218 trial

Title: **Incorporation of bevacizumab in the primary treatment of ovarian cancer [20, 38]**			
Study identifier	NCT00262847, GOG-0218 trial		
Design	International, multicentre, double-blind, placebo-controlled phase III trial		
	Duration of main phase:		2005-10 to 2009-6 (enrolment)
	Complete data sweep:		2010-01-02
Hypothesis	Superiority A sample size of 1,800 was estimated to provide 90% statistical power to detect a 23% reduction in the hazard for progression with either of the 2 bevacizumab-containing regimens versus the control regimen while limiting the overall one-sided type I error for both comparisons to 2.5%. The final analysis was planned to be conducted after at least 375 patients in the control group died or had disease progression.		
Funding	National Cancer Institute and Genentech		
Treatments groups	Bevacizumab initiation (n = 625)		Paclitaxel IV 175 mg/m² of body surface area and carboplatin IV (AUC 6) for cycles 1 through 6 + bevacizumab IV (15 mg/kg of body weight) added in cycles 2 through 6 + placebo added in cycles 7 through 22
	Bevacizumab throughout (n = 623)		Paclitaxel IV 175 mg/m² of body surface area and carboplatin IV (AUC 6) for cycles 1 through 6 + bevacizumab IV (15mg/kg) added in cycles 2 through 22
	Control (n = 625)		Paclitaxel IV 175 mg/m² of body surface area and carboplatin IV (AUC 6) for cycles 1 through 6 + placebo added in cycles 2 through 22
Endpoints and definitions	Overall survival	OS	Defined as the observed length of life from entry into the study to death, regardless of cause or the date of last contact. Primary endpoint was initially specified as OS but was changed to PFS during the trial.
	Progression-free survival	PFS	Defined as the period from study entry until disease progression (according to RECIST criteria 2000), an increase in the CA-125 level according to Gynecologic Cancer InterGroup criteria, global deterioration of health, death or date of last contact
	Quality of life	QoL	FACT-O TOI Score
	Safety	-	AEs were reported until 30 days after the last study treatment had been administered and were summarised for patients who received at least one cycle of bevacizumab or placebo
Database lock	2010-02-05		
Results and analysis			
Analysis description	**Primary analysis** Intent-to-treat analysis		
Analysis population	Inclusion		❁ Patients with previously untreated, incompletely resectable stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian tube cancer histologically confirmed by the GOG Pathology Committee after standard abdominal surgery with maximal debulking effort within 12 weeks of study entry ❁ A GOG performance status score of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about more than 50% of waking hours) ❁ No history of clinically significant vascular events or evidence of intestinal obstruction ❁ Adequate bone marrow function, platelet count, renal function, hepatic function and blood coagulation parameters

Title: Incorporation of bevacizumab in the primary treatment of ovarian cancer [20, 38]					
Study identifier	NCT00262847, GOG-0218 trial				
Analysis population *(continuation)*	Exclusion	❖ Patients with a current diagnosis of borderline epithelial ovarian tumour or recurrent invasive epithelial ovarian, primary peritoneal, or fallopian tube cancer treated with surgery only ❖ Prior radiotherapy to any portion of the abdominal cavity or pelvis ❖ Prior chemotherapy for any abdominal or pelvic tumour, including neoadjuvant chemotherapy for ovarian, primary peritoneal or fallopian tube cancer ❖ Patients who had received any targeted therapy or hormonal therapy for management of their epithelial ovarian or primary peritoneal cancer ❖ Patients with serious non-healing wound, ulcer, or bone fracture ❖ Patients with active bleeding or pathologic conditions that carry a high risk of bleeding ❖ Clinically significant cardiovascular disease			
	Characteristics		Bevacizumab initiation (n = 625)	Bevacizumab throughout (n = 623)	Control (n = 625)
		Median age (range), years	60 (24–88)	60 (22–89)	60 (25–86)
		Race or ethnic group, n (%) Non-Hispanic white Asian Non-Hispanic black Hispanic Other or unspecified	 519 (83.0) 37 (5.9) 28 (4.5) 28 (4.5) 13 (2.1)	 521 (83.6) 39 (6.3) 27 (4.3) 25 (4.0) 11 (1.8)	 526 (84.2) 41 (6.6) 25 (4.0) 21 (3.4) 12 (1.9)
		GOG performance status, n (%) 0 1 2	 315 (50.4) 270 (43.2) 40 (6.4)	 305 (49.0) 267 (42.9) 51 (8.2)	 311 (49.8) 272 (43.5) 42 (6.7)
		Stage/debulking status, n (%) III (macroscopic, ≤ 1 cm) III (> 1 cm) IV	 205 (32.8) 256 (41.0) 164 (26.2)	 216 (34.7) 242 (38.8) 165 (26.5)	 218 (34.9) 254 (40.6) 153 (24.5)
		Histologic type, n (%) Serous adenocarcinoma Endometrioid Clear cell Mucinous Other or not specified	 519 (83.0) 14 (2.2) 23 (3.7) 5 (0.8) 64 (10.2)	 524 (84.1) 24 (3.9) 20 (3.2) 8 (1.3) 47 (7.5)	 541(86.6) 21 (3.4) 12 (1.9) 6 (1.0) 45 (7.2)
		Tumour grade, n (%) 3 2 1 Not graded	 465 (74.4) 86 (13.8) 28 (4.5) 46 (7.4)	 460 (73.8) 97 (15.6) 18 (2.9) 48 (7.7)	 445 (71.2) 102 (16.3) 36 (5.8) 42(6.7)

Abbreviations: AUC = area under the curve, FACT-O TOI = Trial Outcome Index of the Functional Assessment of Cancer Therapy – Ovary, GOG = Gynecologic Oncology Group, HR = hazard ratio, IV = intravenous, n = number, NA = not applicable, NR = not reported, OS = overall survival, PFS = progression-free survival, QoL = quality of life