AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: Bevacizumab (Avastin®) at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer
June 2019

KEY FINDINGS

Report background

Bevacizumab at a dose of 15 mg/kg, in combination with paclitaxel and carboplatin, has marketing authorisation for the front-line treatment of adults with advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer[1,2]. In 2013, this regimen was not recommended by the National Institute for Health and Care Excellence (NICE) based on grounds of cost effectiveness[3].

Bevacizumab at a dose of 7.5 mg/kg is not a licensed dose for the first-line treatment of advanced ovarian cancer and so its use is off-label. Commissioning representatives and patient experts have confirmed that bevacizumab at the unlicensed dose of 7.5 mg/kg is the dose most commonly used in NHS England for the treatment of advanced ovarian cancer. Bevacizumab 7.5 mg/kg is on the Cancer Drugs Fund in England for patients with FIGO stage III debulked but residual disease more than 1.0 cm or stage IV disease, or stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction[4].

A cohort of patients was identified in Wales based on data from individual patient funding request panels. Clinicians in Wales considered there to be an unmet need and based on these two factors this medicine was deemed suitable for a One Wales Interim Commissioning decision.

In August 2016, a One Wales decision was taken not to support the use of bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel within NHS Wales for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. In August 2017, this decision was re-assessed including newly published evidence, and the original decision to not support the use of this bevacizumab regimen was endorsed. In January 2019 the Interim Pathways Commissioning Group (IPCG) reviewed the evidence published subsequent to the second One Wales decision and deemed that there was not sufficient new evidence to warrant a full review. In April 2019 a simple Patient Access Scheme (PAS) providing bevacizumab at reduced cost to the NHS in England and Wales was agreed; the IPCG consider this information is significant and warrants a full re-assessment[5].

Clinicians in Wales consider that the group of patients who are most likely to benefit from treatment are those defined as high-risk based on the criteria applied by the Cancer Drugs Fund (see above). This evidence status report therefore focuses on this high-risk population.

Efficacy/Clinical Effectiveness

- In the high-risk subgroup of patients in the International Collaboration on Ovarian Neoplasms 7 (ICON7) trial, the addition of bevacizumab 7.5 mg/kg to standard chemotherapy increased progression-free survival by 4.1 months compared with standard chemotherapy alone, based on the restricted mean data in the final analysis[6].
- The addition of bevacizumab 7.5 mg/kg to standard chemotherapy also improved overall survival in the high-risk for progression subgroup, increasing overall survival by 4.8 months (from 34.5 to 39.3 months) based on the restricted mean data in the final analysis[6].
- The UK observational study, OSCAR, reports on 299 patients, all high-risk for progression; 93% received 7.5 mg/kg bevacizumab in combination with chemotherapy. Results report median progression-free survival of 15.4 months, this is consistent with those reported for ICON7[7].

Safety
Adding bevacizumab to standard chemotherapy was associated with more adverse events[8]. In the ICON7 trial, adverse events of grade 3 or higher were reported in 56% of the women in the standard chemotherapy group and in 66% of women in the bevacizumab plus standard chemotherapy group. Treatment with bevacizumab plus standard chemotherapy appeared to be associated with: an increase in bleeding, particularly grade 1 or 2 mucocutaneous bleeding (7% versus 36%); hypertension ≥ grade 2 (2% versus 18%); thromboembolic events of ≥ grade 3 (3% versus 7%); and ≥ grade 3 gastrointestinal perforations (< 1% versus 1%)[8]. No new safety signals were reported in the OSCAR observational study or in an audit conducted by Ipswich NHS Trust[9,10]. Both studies report adverse events of grade 3–4, comparable to those reported in ICON7[6,9].

Patient factors
Adding bevacizumab to standard chemotherapy was not associated with a decrease in quality of life for high-risk patients[11].

Cost effectiveness
According to one published model-based cost-utility analysis using the mature results of the high-risk subgroup of ICON7, a cost reduction of between 67% and 46% would be required to reach the willingness to pay thresholds of £20,000 and £30,000 respectively[12]. [Confidential data removed.]

Budget impact
Based on previous calculations it is estimated that 30 patients are eligible for treatment with bevacizumab annually in Wales[13]. With the agreed PAS price the medicine acquisition cost for bevacizumab for 30 patients weighing between 60 kg and 66 kg is [confidential data removed] in subsequent years.

Commercial agreement
The PAS agreed with NICE is a simple PAS, this makes bevacizumab available to NHS Wales at a discount.

Impact on health and social care services
Based on the number of patients accessing treatment, the impact on the service is expected to be minimal.

Innovation and/or advantages
Bevacizumab in combination with paclitaxel and carboplatin offers an additional treatment option.

BACKGROUND

Target group

Bevacizumab is licensed at a dose of 15 mg/kg, in combination with carboplatin and paclitaxel, for the front-line treatment of adult patients with advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer[1].

The indication being considered is bevacizumab at a dose of 7.5 mg/kg for those patients deemed to be high-risk for progression: patients with FIGO stage III debulked but residual disease more than 1.0 cm or stage IV disease, or stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction.

Technology

Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, on the surface of endothelial cells[1]. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth[1].

Marketing authorisation date: Not applicable, off-label

Bevacizumab is not licensed at a dose of 7.5 mg/kg to treat advanced ovarian, fallopian tube or primary peritoneal cancer; therefore its use at this dose for this indication is off label.

Dosing

Bevacizumab is administered in addition to carboplatin and paclitaxel for up to six cycles of treatment followed by continued use of bevacizumab as a single agent for an additional 12 cycles (18 cycles in total) or until disease progression or unacceptable toxicity occurs[1].

It is administered at an off-label dose of 7.5 mg/kg of body weight once every three weeks as an intravenous infusion[4,8].

Clinical background

Ovarian cancer is the leading cause of death from gynaecological cancer in the UK[14]. The outcome for women with ovarian cancer is generally poor, with an overall five-year survival rate of 46.2%[15]. This is because most women with ovarian cancer present with advanced disease (FIGO stage III and IV) despite experiencing symptoms for, on average, 12 months[14,16]. The five-year net survival has increased from 25.1% in 1980 to 46.2% in 2010[17]. Women with stage III or IV ovarian cancer have a five-year survival rate of 18.6% and 3.5%, respectively[17].

Incidence/prevalence

Ovarian and fallopian tube cancer is the seventh most common cancer in women in Wales, with 400 new cases being reported in 2016[13].

Current treatment options

Treatment of ovarian cancer involves surgery and chemotherapy[18]. Chemotherapy with paclitaxel and carboplatin is the current standard clinical practice in the NHS in England and Wales for the first-line treatment of advanced ovarian cancer (FIGO stages II–IV) after debulking surgery[3]. Three cycles of chemotherapy may be given before surgery for some patients expected to have residual disease left after surgery[3].

Guidance and related advice

- European Society for Medical Oncology (ESMO) and European Society of Gynaecological Oncology. Consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease (2019)[19].

- Scottish Intercollegiate Guidelines Network (SIGN). SIGN Guideline 135. Management of epithelial ovarian cancer (2018)[20].
- ESMO eUpdate – Ovarian cancer treatment recommendations (2016)[21].
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN guidelines®). Ovarian cancer including fallopian tube cancer and primary peritoneal cancer (2015)[22].
- National Institute for Health and Care Excellence (NICE). Technology Appraisal (TA) 284. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (2013)[3].
- ESMO. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2013)[23].
- NICE. Quality Standard (QS) 18. Ovarian cancer (2012)[14].
- NICE. Clinical Guideline (CG) 122. Ovarian cancer: The recognition and initial management of ovarian cancer (2011)[16].

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) identified five publications which detailed the use of bevacizumab at a dose of 7.5 mg/kg in the treatment of ovarian cancer. The publications include: a randomised controlled trial (ICON7) with final overall survival and quality of life data reported separately[6,8,11]; a retrospective study in South West Wales[24]; and one abstract describing audit results of the use of bevacizumab in the Cancer Drugs Fund setting in Ipswich NHS Trust[10]. The manufacturer provided the manuscript for a real-world UK study (OSCAR) ahead of publication; these data are confidential. Interim results of the OSCAR study are published in conference abstracts[9,25]. These studies are described below.

Efficacy

International Collaboration on Ovarian Neoplasms-7 (ICON7) trial
This was a multicentre, open-label, controlled, phase III trial designed to investigate the addition of bevacizumab to standard chemotherapy in the first-line treatment of ovarian cancer following debulking surgery[8].

Patients (n = 1,528) were randomised 1:1 to receive either standard chemotherapy (n = 764) consisting of carboplatin (area under the curve of 5 or 6 mg/ml per minute) and paclitaxel (175 mg/m^2 of body surface area), given every three weeks for six cycles or the same regimen in combination with bevacizumab 7.5 mg/kg (n = 764) given every three weeks for five or six cycles[8]. Bevacizumab was continued for an additional 12 cycles or until disease progression[8].

The baseline characteristics in the two treatment groups were well balanced. The median age was 57 years, and 94% of the patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 90% had epithelial ovarian cancer; 9% had high-risk early-stage disease; 30% were at high risk for progression; 21% had FIGO stage III, IIIA, or IIIB disease; 70% had FIGO stage IIIC or IV disease; 69% had serous histologic type; and 26% had more than 1.0 cm of residual disease after surgical debulking[8].

The primary endpoint was progression-free survival but the study was also powered to detect a difference in overall survival[8]. At the time of the primary progression-free survival analysis overall survival data were immature. We report data published by Oza et al. 2015 for the final overall survival and updated progression-free analysis[6]. The analyses were carried out in the intention-to-treat (ITT) patient group and a pre-specified subgroup of women considered to be at high-risk for progression with advanced ovarian cancer who had FIGO stage III and

more than 1.0 cm of residual disease after debulking surgery or who had FIGO stage IV disease (n = 465)[6,8].

The median follow-up at the end of the trial (data cut-off date 31 March 2013) was 48.9 months and there were 714 deaths: 352 in the standard chemotherapy group and 362 in the bevacizumab plus standard chemotherapy group[6]. There was no clinical significant difference in overall survival between the two groups, although non-proportional hazards were evident (p = 0.02). In detecting non-proportional hazards the conventional hazard ratio is not meaningful. In an attempt to better estimate the effect of bevacizumab on progression-free survival, restricted mean values were estimated. The restricted mean overall survival showed an improvement with the addition of bevacizumab to standard chemotherapy of 0.9 months. An updated analysis of progression-free survival showed no difference between the two groups when using data for all patients[6].

In the high-risk for progression subgroup (n = 502), there were 332 deaths: 174 in the standard chemotherapy group and 158 in the bevacizumab plus standard chemotherapy group[6]. Overall survival was longer in those patients who received bevacizumab plus standard chemotherapy (p = 0.03), however, non-proportional hazards were evident (p = 0.01). The restricted mean overall survival in this subgroup showed a significant improvement of 4.8 months with the addition of bevacizumab to standard chemotherapy compared with standard chemotherapy alone (p = 0.03). The absolute difference in survival was 4.4% (95% CI: –4.1 to 12.9) at 5 years[6]. In line with the primary results for progression-free survival, the analysis indicated a statistically significant improvement in median progression-free survival of 5.5 months with bevacizumab plus standard chemotherapy treatment in the high-risk for progression subgroup (p = 0.001)[6].

Table 1 shows the results of the final primary analysis of overall survival and updated analysis of progression-free survival in both the ITT population and in the high-risk for progression subgroup.

Table 1. Results of the final primary analysis of overall survival and updated analysis of progression-free survival with standard chemotherapy alone versus bevacizumab plus standard chemotherapy[6].

	All patients		High-risk for progression subgroup	
	Standard chemotherapy (n = 764)	Bevacizumab + standard chemotherapy (n = 764)	Standard chemotherapy (n = 254)	Bevacizumab + standard chemotherapy (n = 248)
OS				
No. of events	352 (46%)	362 (47%)	174 (69%)	158 (64%)
Median OS, months (95% CI)	58.6 (53.5 to 67.5)	58.0 (52.4 to 66.9)	30.2 (27.0 to 34.3)	39.7 (36.0 to 44.2)
Treatment difference, months	–0.6		9.5	
HR (95% CI)	0.99 (0.85 to 1.14) p = 0.85*		0.78 (0.63 to 0.97) p = 0.03*	
Restricted mean OS time, months (95% CI)*	44.6 (43.2 to 45.9)	45.5 (44.2 to 46.7)	34.5 (32.0 to 37.0)	39.3 (37.0 to 41.7)
Restricted mean OS time difference, (95% CI)	0.9 (–0.8 to 2.6)		4.8 (1.5 to 8.1)	
PFS				
No. of events	526 (74%)	554 (73%)	228 (90%)	223 (90%)
Median PFS, months (95% CI)	17.5 (15.7 to 18.7)	19.9 (19.1 to 22.0)	10.5 (9.3 to 12.0)	16.0 (14.2 to 17.8)
Treatment difference, months	2.4		5.5	
HR (95% CI)	0.93 (0.83 to 1.05) p = 0.25		0.73 (0.61 to 0.88) p = 0.001	
Restricted mean PFS time, months (95% CI)*	27.7 (26.1 to 29.2)	29.2 (27.7 to 30.7)	15.9 (14.1 to 17.7)	20.0 (18.1 to 21.8)
Restricted mean PFS time difference (95% CI)	1.6 (–0.6 to 3.7)		4.1 (1.4 to 6.7)	

CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival
* Restricted at five years.

ICON7 quality of life sub-study

In a sub-study, quality of life was measured using the European Organisation for Research and Treatment of Cancer quality of life questionnaire ovarian cancer module (QLQ-OV28) and QLQ-C30 questionnaires[11].

Patients completed the quality of life questionnaires on their own prior to the administration of treatment or medical consultation at baseline, before each chemotherapy cycle, then every six weeks for the rest of year one and every three months in year two unless there was disease progression[11]. A scheduled quality of life data collection for all patients still alive at three years is to be reported in the future[11].

At 54 weeks, a small but clinically relevant difference in the mean global quality of life score of 6.4 points was observed favouring standard chemotherapy compared with bevacizumab plus standard chemotherapy (76.1 versus 69.7; 95% CI: 3.7 to 9.0; $p < 0.0001$)[11]. The number of women whose global quality of life score improved by at least 10 points between baseline and 54 weeks was also higher in the standard chemotherapy group compared with

the bevacizumab plus standard chemotherapy group (66% [221/333] versus 56% [250/444]; odds ratio: 0.58; 95% CI: 0.42 to 0.80; p = 0.001)[11].

After completion of 18 weeks of standard chemotherapy, a small clinically relevant difference in the mean global quality of life score of 5.1 points was observed favouring standard chemotherapy compared with bevacizumab plus standard chemotherapy (64.4 versus 59.2; 95% CI: –7.4 to 2.9; p < 0.0001)[11]. Exploratory analyses of QLQ-C30 and QLQ-OV28 demonstrated that the addition of bevacizumab to standard chemotherapy was associated with clinically small but statistically significant reductions in role functioning, financial worries, attitudes to disease or treatment, hormonal symptoms, and rash (all p < 0.01)[11].

Data are available up to week 76 for those patients without disease progression; global quality of life scores did not differ significantly between groups (p = 0.43). In exploratory analysis for high-risk patients there was again no significant difference in quality of life scores (p = 0.36). Although the number of high-risk patients assessed was small (n = 70) sensitivity analyses (where scores were assigned to those patients with missing data) indicated these data to be robust. A small difference in quality of life was noted for non-high-risk patients, favouring treatment with standard chemotherapy (treatment difference -5.1; 95% CI: -9.4 to -0.7; p = 0.02)[11].

Bevacizumab for ovarian cancer at high risk of progression: reproducibility of trial results in 'real-world' patients

This study investigated patient characteristics, treatment patterns, adverse events and progression-free survival in 'real-world' patients in South West Wales treated with at least one dose of bevacizumab for advanced (FIGO stage III-IV) epithelial ovarian, fallopian tube or primary peritoneal cancer[24]. Patients were eligible for bevacizumab if considered at high risk for disease progression i.e. if they had FIGO stage IV disease, or suboptimally debulked FIGO stage III disease. Bevacizumab was given at a dose of 7.5 mg/kg every three weeks, initially in combination with chemotherapy and then continued as maintenance therapy until disease progression, death or discontinuation due to side effects[24].

A total of 60 patients with ovarian cancer treated with bevacizumab as part of their first-line chemotherapy were included in the study[24]. Fifteen patients had undergone primary debulking surgery and 45 interval debulking surgery after three or more cycles of neoadjuvant chemotherapy before starting bevacizumab. After completion of first-line chemotherapy (median of seven cycles, range 1–10 cycles), 31 patients (51.7%) were in complete remission, 23 (38.3%) had achieved a partial response, five (8.3%) had stable disease and response could not be assessed in one patient. At the time of data analysis (April 2016), patients had received a median of 12 (range 1–49) doses of bevacizumab, with a median treatment duration of 8 (range 0–34) months. In 45 patients (75%) disease had progressed and 34 patients (56.7%) had died. The median progression-free survival was 16 months (95% CI 14.4 to 17.6 months). Thirteen patients (21.7%) were still receiving bevacizumab at the time of analysis, while 47 had discontinued it due to disease progression (n = 35; 58.3%), death without previous documented progression (n = 3, 5%), toxicity (n = 7, 11.7%), patient's decision (n = 1, 1.7%) or clinician's decision (n = 1, 1.7%); the latter was regarding a woman who was still in complete remission 34 months after starting bevacizumab[24].

Observational study of bevacizumab as first line treatment for advanced ovarian cancer (OSCAR)

This was a single-arm study designed to assess the efficacy and safety of front-line bevacizumab combined with chemotherapy in patients with high-risk stage IIIB–V advanced ovarian cancer in the UK real-world setting[7]. Between 10 May 2013 and 28 April 2015, 299 patients from 29 centres in England and Wales started bevacizumab-containing therapy. Patients received bevacizumab (7.5 or 15 mg/kg every three weeks typically for up to 12 months) combined with standard front-line chemotherapy, and then continued as single-

agent maintenance therapy. The primary endpoints were progression-free survival and safety; secondary endpoints included overall survival and quality of life. The median age was 64 years. Only 57% of patients had undergone surgery (primary debulking in 21% and interval debulking in 36%).The majority of patients (90%) matched the Medical Research Council definition of high risk in ICON7. Most patients (93%) received bevacizumab 7.5 mg/kg every three week with carboplatin and paclitaxel. The median duration of bevacizumab therapy was 10.5 months [confidential data removed][7].

The median progression-free survival recorded in 250 patients (84%) at the data cut-off date (14 May 2018) was 15.4 months (95% confidence interval [CI] 14.5 to 16.9)[7]. [Confidential data removed.] Subgroup analyses according to prior surgery showed median progression-free survival of 20.8 months (95% CI 17.4 to 25.5) in 62 patients who underwent primary debulking surgery, 16.1 months (95% CI 14.6 to 19.4) in 109 patients who underwent interval debulking, and 13.6 months (95% CI 11.3 to 14.9) in 128 patients who had no surgery. The 1-year overall survival rate in the overall population was 94% (95% CI 90 to 96). No conclusions could be drawn from the quality of life data due to limited patient participation[7].

An audit of the use of bevacizumab in advanced ovarian cancer

An audit of patients in Ipswich NHS Trust eligible for bevacizumab according to the Cancer Drugs Fund criteria is described in a conference abstract[4,10]. Between August 2012 and December 2016, of 48 eligible patients, 28 (58%) received bevacizumab. Three patients received the maximum number of bevacizumab cycles and 57% commenced treatment at non-standard times. Median progression-free survival was 13.6 months and overall survival was 19.1 months compared with 16.0 months and 39.7 months respectively for the high risk for progression sub-population in the ICON7 study[8,10]. The author suggests that this difference may be due to the large proportion of patients (82%) with inoperable disease at presentation compared with ICON7 patients (6%)[10].

Ongoing studies

One ongoing study, ICON8B, recruited a small number of patients with ovarian cancer from a number of centres across Wales[26]. ICON8B is a multicentre study investigating differing regimens of paclitaxel and carboplatin with and without bevacizumab 7.5 mg/kg as first line treatment for ovarian cancer (FIGO stage IC-IV). ICON8B includes high-risk patients with FIGO stage III–IV epithelial ovarian, fallopian tube or primary peritoneal cancer with more than 1.0 cm residual disease or with planned primary chemotherapy with or without delayed primary surgery[27]. ICON8B is an extension to the ICON8 study investigating differing regimens of paclitaxel and carboplatin which completed in June 2017[26].

Safety

The Summary of Product Characteristics lists adverse events that may be associated with bevacizumab treatment[1]. These adverse events include, but are not limited to, gastrointestinal (GI) perforations and fistulae; wound healing complications; dose-dependent hypertension; posterior reversible encephalopathy syndrome; proteinuria; arterial and venous thromboembolism; haemorrhage (predominantly tumour-related and minor mucocutaneous haemorrhage); pulmonary haemorrhage and haemoptysis; congestive heart failure; neutropenia and infections; hypersensitivity and infusion reactions; osteonecrosis of the jaw and eye disorders[1]. In May 2013, the manufacturer of bevacizumab (Roche Products Ltd) warned about the risk of necrotising fasciitis in a letter to healthcare professionals, the condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation[28].

In the ICON7 trial, almost all patients experienced at least one adverse event[8]. Adverse events of grade 3 or higher were reported in 56% of the women in the standard chemotherapy group and in 66% of women in the bevacizumab plus standard chemotherapy group. Treatment with bevacizumab plus standard chemotherapy appeared to be associated

with: an increase in bleeding, particularly grade 1 or 2 mucocutaneous bleeding (7% versus 36%); hypertension ≥ grade 2 (2% versus 18%); thromboembolic events of ≥ grade 3 (3% versus 7%); and ≥ grade 3 GI perforations (< 1% versus 1%)[8].

In the ICON7 trial, there were five deaths related to treatment or to treatment and disease[8]. One death due to central nervous system ischaemia occurred in the standard chemotherapy group. Four deaths occurred in the bevacizumab plus standard chemotherapy group. These were due to GI perforation; intracerebral haemorrhage; recurrent bowel perforation and ovarian cancer; and neutropenic sepsis and ovarian cancer[8].

In the South West Wales retrospective study, the most common toxicities reported included proteinuria (66.7%, all grade 1) and grade 1–2 hypertension (15%)[24]. Cardiovascular accidents, two of which were fatal, occurred in 6.7% of patients. Seven patients whose disease had not yet progressed discontinued bevacizumab because of side-effects. These included colovesical fistulisation, stroke, haemoptysis, grade 2 hypertension, worsening leg ulcers, elevation of liver function tests, and athralgia in one patient each. Three patients died without documented progression during treatment with bevacizumab: one died of a myocardial infarction while still in complete remission after 29 months of treatment; the second died of a stroke after first dose; and the third died of unknown causes after receiving bevacizumab for eight months[24].

In the OSCAR study, almost all patients (99%) experienced at least one adverse event[7]. Grade 3 or 4 adverse events were reported in 54% of patients. The most common grade ≥ 3 adverse events were hypertension (16%) and neutropenia (5%). There were seven grade 5 adverse events (deaths) [confidential data removed]. Overall, 35 patients (12%) discontinued bevacizumab therapy because of adverse events, most often proteinuria (2%) or pulmonary embolism (1%)[7].

No new safety issues were reported in the Ipswich NHS Trust audit; reported adverse events of grade 3–4 were comparable to those reported in ICON7[8,10].

Clinical effectiveness issues

Evidence from the ICON7 trial suggests that the addition of bevacizumab to standard chemotherapy improved progression-free survival in women with ovarian cancer[8]. The benefits with respect to both progression-free survival and overall survival were greater among those at high risk for disease progression[8]. It should be noted that the ICON7 trial was not powered to assess the outcomes of patients considered to be at high risk for progression. The post hoc high-risk for progression subgroup analyses in the ICON7 trial were hypothesis generating and not able to test a scientific question; however ICON7 was a large trial and showed similar results to patients in the GOG-0218 study in which the licensed 15 mg/kg bevacizumab dose was used and all patients had cancer stage III or IV disease[8,29]. The improvement in restricted mean progression-free survival observed with bevacizumab was 3.6 months in the ICON7 high-risk subgroup and 3.8 months in GOG-0218 patients[8].

Patients receiving neoadjuvant chemotherapy were not included in the studies (patients were eligible for study inclusion if they had no plans for further surgery before disease progression)[8,30].

There were some limitations to the open-label design of the ICON7 trial that allowed both clinicians and patients to know if they were receiving bevacizumab in addition to standard chemotherapy; therefore, there may have been some systematic differences in the care provided to the patients in the standard chemotherapy group other than the intervention under investigation (performance bias) in favour of bevacizumab[31].

A large proportion (94%) of the women enrolled in the ICON7 trial had an ECOG performance status score of 0 or 1 meaning that they were asymptomatic or symptomatic but completely ambulatory[8]. They also had adequate coagulation values, bone marrow, liver and renal function[8].

The original results of the ICON7 quality of life sub-study included women with all stages of ovarian cancer before disease progression with no separate analysis for those patients at high risk for progression[11]. However data presented up to week 76 indicated that patients with high-risk disease receiving bevacizumab had similar quality of life scores to those receiving standard chemotherapy[11]. It would have been useful however to have seen these data earlier in the study when more patients were in the trial.

The South West Wales study is the first report of 'real-word' use of bevacizumab in the first-line treatment of patients with high-risk, advanced, ovarian cancer in the UK[24]. There were differences in the baseline characteristics of the patients included in this study compared to those included in the ICON7 trial; ICON7 patients were on average younger (median age 60 at final analysis compared to 66 years), had better performance status (41% World Health Organization performance status of zero compared to 18%) and had a lower rate of FIGO stage IV disease (42% compared to 58%)[6,24]. In ICON7 all patients received combination chemotherapy with carboplatin and paclitaxel; 15% of patients in the South West Wales study were not considered fit enough for combination chemotherapy and were treated with single-agent carboplatin. The authors of the South West Wales study note that despite these differences that predict worse outcomes in patients in their study, similar progression-free survival was reported between this study and ICON7 trial, with a median of 16 months in both cohorts. However, the authors stated that the maximum duration of bevacizumab therapy in the ICON7 was 15 months (figure not verified), whereas patients in the South West Wales study were allowed to continue maintenance treatment until progression. As a consequence, 16.7% of patients in the South West Wales study received bevacizumab for longer than 15 months. Additionally, 45 (75%) patients received three or more cycles of neoadjuvant chemotherapy after interval debulking surgery before starting bevacizumab[24]. Neoadjuvant chemotherapy was not allowed in ICON7[8].

The safety profile of bevacizumab and the reported progression-free survival results in the observation UK-based real-world OSCAR study are consistent with those reported in ICON7[7]. In the OSCAR study, median progression-free survival was shortest in patients who received no surgery and longest in patient who underwent primary debulking surgery. [Confidential data removed.]

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

Two cost-effectiveness analyse are presented below, one from the perspective of the NHS based on the high-risk subgroup in the ICON7 trial [12] and the second a Belgian study using data from the ICON7 and GOG-0218 studies[32].

Cost-effectiveness evidence

Context

Hinde et al published a UK study which reported a cost-utility analysis based on the mature results of the high-risk group in ICON7[12]. A three-state partition survival model with a lifetime horizon and one-week cycles was used to estimate the cost-effectiveness of the addition of 7.5 mg/kg bevacizumab to carboplatin plus paclitaxel chemotherapy. Clinical outcomes (overall survival and progression-free survival), health-related quality of life (HRQOL; based on the three-level EuroQol five-dimensional questionnaire responses) and healthcare resource use (including medication, treatments, clinical investigations and laboratory tests) were drawn directly from the ICON7 trial results and extrapolated beyond the trial period

using assumptions based on published data. Scenario analyses and probabilistic sensitivity analyses are performed to test the impact of input and assumption uncertainty on the resulting incremental cost-effectiveness ratio (ICER)[12].

The Belgian cost-utility analysis used a lifetime horizon Markov model to investigate the cost effectiveness of bevacizumab in first- and second-line treatment of ovarian cancer. For first-line treatment results of two trials, ICON7 and GOG-0218, were used[32]. The results generated using GOG-0218 data will not be discussed further as the dose used in this study was 15 mg/kg body weight.

Results

The results of the base case analysis reported by Hinde et al. 2016[12] suggest that the addition of low dose bevacizumab (7.5 mg/kg) to carboplatin plus paclitaxel chemotherapy results in 0.381 incremental quality-adjusted life years (QALYs) per patient over a lifetime horizon[12]. The Belgian study calculated the incremental QALY gains for the high risk sub population of the ICON7 patients to be 0.33 over the lifetime horizon[32]. The analysis by Hinde et al used the list price of bevacizumab in the model which resulted in a base case ICER of £48,975 per QALY gained. Scenario analyses were performed and the authors concluded that cost differences are mainly driven by bevacizumab acquisition and administration costs and the increased cost of continued care caused by improved survival in the bevacizumab arm[12].

Probabilistic sensitivity analysis suggests that the probabilities of low dose bevacizumab in combination with carboplatin plus paclitaxel being cost-effective compared to chemotherapy alone at willingness to pay (WTP) thresholds of £20,000 and £30,000 are 0.01% and 0.13%, respectively[12]. The authors suggest that a price reduction of 67% and 46% would be required to reach the WTP thresholds of £20,000 and £30,000, respectively[12]. [Confidential data removed.]

Health economic issues

The methodology reported in Hinde et al. 2016 appears robust and valid and the incremental QALYs per patient over a lifetime was in line with that calculated in the Belgium paper[12,32]. Both model inputs are based on actual mature results of 502 patients categorised as high risk in the ICON7 trial[6]. In the analysis by Hinde et al. assumptions regarding the extrapolation of parameters beyond the trial period are tested appropriately using scenario analyses and probabilistic sensitivity analysis. It can be considered the best health economic evidence to date for the use of low dose bevacizumab in high-risk advanced ovarian cancer.

However, all of the cost-effectiveness results should still be interpreted with caution as several caveats must be considered:

- The clinical trial results used to inform the model had to be extrapolated beyond the trial duration to the model lifetime horizon. Extrapolation of progression-free survival was based on a Weibull curve fitted to data from the ICON3 trial[33]. Overall survival was extrapolated using published data from a 10-year survival analysis study[34]. While extrapolation is necessary to adequately capture the benefits of bevacizumab on longer-term survival, differences in the study population and methodological heterogeneity are likely to introduce bias.
- The model does not appear to take into account costs and impact on quality of life of adverse events which could cause a slight overestimation of effect and underestimation of costs associated with bevacizumab.
- The model itself was not available for review by AWTTC. Therefore, the structural validity and appropriateness of calculations cannot be verified. Also this means that AWTTC is unable to re-run the model using the discounted PAS price.

BUDGET IMPACT

Using Welsh Cancer Intelligence Surveillance Unit data and the NICE costing template for TA 284 it is estimated that there are 30 newly treated women with high-risk advanced ovarian cancer in Wales per year[3,13]. Bevacizumab is provided in two vial sizes: 16 ml (400 mg) and 4 ml (100 mg)[1]. For a patient weighing between 60 kg and 66.6 kg a 16 ml and 4 ml vial would be required in combination (assuming wastage). The suggested regimen would be bevacizumab in combination with paclitaxel and carboplatin for six cycles and then on its own for an additional 12 cycles or until disease progression (maximum of 18 cycles in total). Bevacizumab is administered by intravenous infusion in a chemotherapy delivery suite, with input from a hospital pharmacist. Administration costs in an outpatient setting amount to £3,156 per patient per year. It is assumed in the budget impact analysis that all patients receive the maximum of 18 cycles of low dose bevacizumab. As one cycle is given every three weeks, it is assumed that 17 cycles fall in Year 1 while the last cycle will be administered in Year 2.

Table 2 details the prediction for the budget impact in Wales. This excludes VAT and any local contracting agreements.

Table 2. Estimated 2-year budget impact in Wales

	Year 1	Year 2	Year 3
Number of patients	30	30	30
Medicine acquisition costs*	¶¶	¶¶	¶¶
Medicine administration costs	£94,687	£100,256	£100,256
Overall net cost	¶¶	¶¶	¶¶
*For patients who weigh between 60 kg and 66.6 kg ¶¶ Confidential figure removed			

Budget impact issues

The budget impact results should be considered with caution as several caveats apply:

- The budget impact assumes that all patients receive the maximum number of cycles and does not consider the discontinuation of therapy and mortality rates. It thus assumes that all patients respond (100% success rate) for up to two years. This will overestimate the budget impact as mortality rate is high for women with advanced ovarian cancer. However, the effect is likely to be small considering that 62% of women in the ICON7 trial went through cycle 18 with a median number of administered cycles of 16 and 17 for women starting chemotherapy before 4 weeks after surgery and more than 4 weeks after surgery, respectively[8].
- Costs of treating adverse events of bevacizumab are not included due to lack of available data which will underestimate the budget impact.

Commercial agreement

In April 2019 a simple PAS providing bevacizumab (Avastin®) at reduced cost to the NHS in England and Wales was agreed.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Bevacizumab is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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