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

AWMSG Secretariat Assessment Report

Bevacizumab (Avastin®) 25 mg/ml concentrate for solution for infusion

Reference number: 5044

Resubmission

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report

Bevacizumab (Avastin®) 25 mg/ml concentrate for solution for infusion

1.0 Key facts

Assessment details	Resubmission of bevacizumab (Avastin®) for use in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix. The applicant company suggest AWMSG focus on bevacizumab for use only in combination with cisplatin and paclitaxel, as the company perceive this to be most representative of current standard of care in Wales.
Current clinical practice	Current management is usually palliative chemotherapy and consists of a platinum agent (usually carboplatin) plus paclitaxel up to a total of six cycles. Cisplatin can also be used in place of carboplatin; however, it is associated with more adverse events, especially in those with other co-morbidities (such as renal failure). The All Wales Therapeutics and Toxicology Centre (AWTTC)-sought clinical expert opinion indicates there are limited treatment options available for cervical cancer and there is no routine established treatment for second line chemotherapy. Due to lack of progress in new treatments, there remains an unmet need for the treatment of advanced cervical cancer patients.
Clinical effectiveness	The main evidence comes from a phase III, randomised, open-label, multicentre study (GOG-0240) which showed that the addition of bevacizumab to chemotherapy improves overall survival (OS) and progression free survival. The results of the OS subgroup analysis for the individual chemotherapy regimens were in general consistent with the overall estimate. A median OS gain of 2.5 months was observed in patients who received bevacizumab in addition to cisplatin plus paclitaxel; this difference was not statistically significant but the study was not powered to detect such differences. In addition, Health Related Quality of Life (HRQoL) data did not indicate any major deterioration of QoL by adding bevacizumab to chemotherapy.
Cost-effectiveness	A cost-utility analysis compares bevacizumab in combination with cisplatin and paclitaxel to carboplatin plus paclitaxel in the first-line treatment of adult patients with persistent, recurrent, or metastatic cervical cancer. The company base case suggests that bevacizumab in combination with cisplatin and paclitaxel is [commercial in confidence text removed] more costly and produces an additional [commercial in confidence text removed] quality-

	adjusted life-years (QALYs) gained resulting in an ICER of [commercial in confidence text removed] per QALY gained. Based on sensitivity and scenario analyses provided by the company, AWTTC considers the most plausible incremental cost-effectiveness ratio (ICER) range to be between [commercial in confidence text removed] per QALY gained. The cost-utility analysis is subject to considerable uncertainty around data inputs (in particular costs, utilities and long-term survival).
Budget impact	The company estimates that seven patients are eligible to receive treatment with bevacizumab in Wales in Year 1, increasing to 20 patients in Year 5. The company base case suggests an additional cost of [commercial in confidence text removed] in Year 1, increasing to [commercial in confidence text removed] in Year 5. The base case also predicts additional NHS resource use valued at [commercial in confidence text removed] in Year 1, increasing to [commercial in confidence text removed] in Year 5. This results from additional administration costs and management of adverse events. Sensitivity analysis changing uptake rates by 20% resulted in 5-year budget impact estimates between [commercial in confidence text removed] and [commercial in confidence text removed]. The budget impact analysis is subject to considerable uncertainty around patient numbers and costs.
Additional factors to consider	Bevacizumab is the first targeted therapy licensed for use in this group of patients and is used as add-on treatment to existing chemotherapy regimens. The company suggests that bevacizumab should be classed as an ultra-orphan medicine. However, considering all licensed indications, AWTTC does not consider bevacizumab eligible to be considered as an ultra-orphan medicine. The company suggests that bevacizumab should be classed as a life-extending, end-of-life medicine. However, considering that the most plausible ICER estimates do not exceed £30,000 per QALY gained, AWTTC does not consider bevacizumab to be eligible for application of end-of-life criteria. Bevacizumab (Avastin®) has a restricted recommendation for this indication in Scotland and is available in combination with paclitaxel and either cisplatin or carboplatin via the Cancer Drugs Fund for untreated recurrent or metastatic cervical cancer in England.

This assessment report is based on evidence submitted by Roche Products Ltd and an evidence search conducted by AWTTC on 15 February 2022[1].

2.0 Background

2.1 Condition and clinical practice

Cervical cancer causes approximately 857 deaths per year in the UK (59 in Wales), accounting for an estimated 1% of deaths from cancer in women[2]. Nearly half of women with cervical cancer are diagnosed with stage I disease, which is largely curable with radical surgery and chemotherapy, but prognosis worsens with increasingly advanced disease stage[3,4]. For patients with stage IV disease (which includes those with persistent, recurrent or distant metastases), cancer survival official statistics for Wales reported one-year survival of 38% between 2014 and 2018[5].

Patients with persistent, recurrent or metastatic cervical carcinoma are currently treated with palliative chemotherapy comprising a platinum agent (cisplatin or carboplatin) and paclitaxel[3]. Topotecan in combination with paclitaxel is considered in patients who cannot tolerate platinum-based therapies[6].

Vascular endothelial growth factor (VEGF) is an important therapeutic target in many solid tumours[3,7]. Bevacizumab binds to VEGF, inhibiting tumour angiogenesis, a process that correlates directly with the extent of disease and inversely with survival[3]. Although bevacizumab is licensed for use in combination with either paclitaxel and cisplatin or paclitaxel and topotecan, the applicant company request that bevacizumab is considered for use only in combination with cisplatin and paclitaxel, as the company perceive this to be most representative of current standard of care in Wales (see Section 3.4 for further details)[1].

2.2 Medicine

Bevacizumab (Avastin) is a recombinant humanised monoclonal antibody that inhibits angiogenesis by neutralising all isoforms of VEGF and by blocking their binding to VEGF receptors[6].

Bevacizumab (Avastin) was initially authorised in the European Union on 12 January 2005 for the treatment of metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine-based chemotherapy[6]. Extension of indication to include treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix for bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan was granted marketing authorisation by the European Medicines Agency (EMA) in April 2015[6].

The All Wales Medicines Strategy Group (AWMSG) has previously appraised bevacizumab for this indication and issued a negative recommendation in September 2017 because the case for cost-effectiveness was not proven[8]. This resubmission is based on a new Patient Access Scheme (PAS).

2.3 Comparators

The comparators included in the company submission were:

- cisplatin and paclitaxel
- carboplatin and paclitaxel
- topotecan and paclitaxel

Bevacizumab is considered as an add-on to existing chemotherapy regimens in persistent, recurrent or metastatic carcinoma of the cervix (although it is not licensed

for use in combination with carboplatin and paclitaxel. See Section 3.2 and 3.4 for further details).

2.4 Guidance and related advice

- National Comprehensive Cancer Network. Cervical Cancer, Version 1.22 (2022)[9].
- European Institute of Oncology. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2017)[10].
- Scottish Medicines Consortium Advice No. 1135/16 (2016)[11].
- American Society of Clinical Oncology (ASCO): Management and Care of Women with Invasive Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline (2016)[12].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, bevacizumab (Avastin®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 Clinical effectiveness

The company submission compared the safety and efficacy of bevacizumab plus chemotherapy with chemotherapy alone. A randomised controlled trial was submitted as evidence of the effectiveness of bevacizumab as an addition to cisplatin plus paclitaxel or topotecan plus paclitaxel. A network meta-analysis was also conducted to indirectly estimate the effectiveness of bevacizumab plus cisplatin plus paclitaxel versus carboplatin plus paclitaxel.

3.1 GOG-0240

GOG-0240 was a phase III, randomised, open-label, multicentre study that assessed the efficacy and safety of bevacizumab plus chemotherapy in patients with persistent, recurrent or metastatic (stage IVB) cervical carcinoma[7]. In the GOG-0240 study, 452 patients were randomised to one of four treatment arms:

- cisplatin plus paclitaxel
- cisplatin plus paclitaxel plus bevacizumab
- topotecan plus paclitaxel
- topotecan plus paclitaxel plus bevacizumab

Doses were 15 mg/kg on day one for bevacizumab, 50 mg/m^2 on day one or two for cisplatin, 135 or 175 mg/m^2 on day one for paclitaxel and 0.75 mg/m^2 on days one to three for topotecan. Treatment cycles were repeated every 21 days until disease progression, unacceptable toxicity or complete response[7].

All patients were aged 18 years or over and had persistent, recurrent or stage IVB cervical carcinoma and a Gynecologic Oncology Group (GOG) performance status of zero to one (where zero indicates that the person is fully active and one indicates the person is ambulatory but restricted in physically strenuous activities). Patients previously treated with any anti-VEGF therapy were excluded from the study.

The primary endpoint of the study was overall survival (OS), defined as the time from randomisation until death from any cause[7]. OS and secondary endpoints were analysed after 288 deaths (83% of total recorded deaths) for the primary analysis; an additional analysis of OS was also conducted after 350 deaths (the follow up analysis)[7].

The primary analysis showed that median OS was extended by 3.9 months in patients treated with bevacizumab plus chemotherapy (topotecan plus paclitaxel or cisplatin plus paclitaxel) compared with chemotherapy alone[7]. For the follow-up analysis, the difference in median OS between bevacizumab plus chemotherapy and chemotherapy alone was 3.5 months (Table 1)[7].

Table 1. Overall survival of patients treated with bevacizumab plus chemotherapy or chemotherapy alone[1]

Analysis	Median OS, months (95% CI)		
	Chemotherapy* (n = 225)	Bevacizumab plus chemotherapy (n = 227)	HR (95% CI), p-value
Primary	12.9 (10.9–15.0)	16.8 (14.1–19.0)	0.74 (0.58–0.94), 0.0132
Follow up	13.3 (10.9–15.8)	16.8 (14.8–19.0)	0.76 (0.62–0.94), 0.0126

*Cisplatin plus paclitaxel or topotecan plus paclitaxel.
Primary analysis was undertaken after 147 and 141 OS events in the chemotherapy and bevacizumab plus chemotherapy groups respectively. The median duration of follow up was 47.3 and 57.1 months respectively.
Follow-up analysis was conducted after 180 and 170 OS events in the chemotherapy and bevacizumab plus chemotherapy groups respectively. The median duration of follow up was 52.6 and 70.0 months respectively.
OS; Overall survival. HR; Hazard ratio. CI; Confidence interval

Subgroup analyses were carried out for the individual chemotherapy regimens used in the trial. A median OS gain of 2.5 months was observed in patients who received bevacizumab in addition to cisplatin plus paclitaxel; this difference was not statistically significant (Table 2)[1,6]. An increase in median OS of 4.2 months was also observed with bevacizumab plus topotecan plus paclitaxel treatment compared with topotecan plus paclitaxel; this difference was also not statistically significant[1,6]. It should be noted that the study was only powered to detect a statistically significant difference in OS for the pooled analysis (i.e. the entire study cohort) and not in the individual chemotherapy cohorts.

Secondary endpoint data was reported for the primary analysis dataset[1]. Addition of bevacizumab to chemotherapy treatment significantly increased progression-free survival (PFS) compared with chemotherapy alone; median PFS was 8.3 months and 6.0 months respectively (hazard ratio [HR] 0.66 [95% CI: 0.54–0.81]; $p < 0.0001$). In subgroup analyses by type of chemotherapy, a median PFS gain of 2.2 months with bevacizumab plus cisplatin plus paclitaxel treatment compared to cisplatin plus paclitaxel was demonstrated (9.1 vs 6.9 months, HR 0.57 [95% CI: 0.42–0.78]; $p = 0.0003$) (Table 2)[1].

Table 2. Overall survival and progression free survival of patients treated with cisplatin plus paclitaxel with or without bevacizumab[1]

Treatment	Median OS, months (95% CI)	OS HR (95% CI) p-value	Median PFS, months (95% CI)	PFS HR (95% CI) p-value
Cisplatin plus paclitaxel (n = 114)	15.0 (10.9–17.5)	0.75 (0.55–1.01) p = 0.0584	6.9 (5.9–8.3)	0.57 (0.42–0.78) p = 0.0003
Bevacizumab plus cisplatin plus paclitaxel (n = 115)	17.5 (14.9–23.0)		9.1 (7.2–10.8)	
OS analysis was conducted after 350 deaths had occurred (follow-up analysis dataset). PFS analysis was undertaken after 385 (85.2%) PFS events in the ITT population (primary analysis dataset). ITT; Intention-to-treat. OS; Overall survival. PFS; Progression free survival. HR; Hazard ratio. CI; Confidence interval				

Health Related Quality of Life (HRQoL) was assessed using three instruments[1]. Physical and functional well-being, assessed using mean scores from the Trial Outcome Index of the Functional Assessment of Cancer Therapy (FACT)–Cervix survey, were lower in the bevacizumab plus chemotherapy group compared with the group treated with chemotherapy alone (difference −1.84 [95% CI: −3.53 to −0.16; p = 0.0322]). This difference was not statistically significant, and the difference was not considered clinically meaningful based on the minimum important differences benchmark[13]. The FACT-GOG Neurotoxicity 4-item subscale decreased (indicating higher neurotoxicity) from baseline by a similar amount for both treatment groups. Pain, assessed using the Brief Pain Inventory, decreased (indicating less pain) at a similar magnitude from baseline in both treatment groups[1].

3.2 Indirect comparison with carboplatin plus paclitaxel

In the absence of trials directly comparing the clinical effectiveness of bevacizumab plus cisplatin plus paclitaxel with carboplatin plus paclitaxel, the company estimated comparative clinical effectiveness from a network meta-analysis[1]. A systematic review was conducted to identify evidence on the clinical efficacy and safety of available treatments in adult patients with cervical cancer[14]. The population included in the systematic review were adult patients with persistent, recurrent, or metastatic (mainly stage IVB) cervical cancer. Interventions included, but were not limited to, chemotherapy, bevacizumab, radiotherapy or surgery; comparisons to placebo and best supportive care were also considered eligible. Outcomes of interest included OS, PFS, response rate, tolerability, HRQoL and safety[14].

The systematic review identified a phase III randomised controlled trial, JCOG0505[15], which directly compared cisplatin plus paclitaxel with carboplatin plus paclitaxel as treatments for metastatic or recurrent cervical cancer. This trial provided an indirect link with GOG-0240 through the common control arm cisplatin plus paclitaxel, and also provided a direct estimate of the effectiveness of cisplatin plus paclitaxel versus carboplatin plus paclitaxel[1].

Results of the indirect treatment comparison showed that bevacizumab plus cisplatin plus paclitaxel treatment improved OS and PFS compared to carboplatin plus paclitaxel (HR 0.75 [95% credible interval [CrI]: 0.50–1.13] and HR 0.55 [95% CrI: 0.37–0.83]), although the difference in OS was not statistically significant[1]. The

company also report results from JCOG0505, which demonstrated that carboplatin plus paclitaxel treatment was non-inferior to cisplatin plus paclitaxel in terms of OS (17.5 months vs 18.3 months respectively; HR 0.994 [95% CI: 0.79–1.25]; p = 0.032) and PFS (HR 1.041 [95% CI: 0.80–1.35])[15]. Indirect comparison of carboplatin plus paclitaxel to cisplatin plus paclitaxel produced similar results (OS HR 0.994 [95% Cr 0.76–1.317]; PFS HR 1.039 [95% Cr 0.80–1.35]).

3.3 Safety information

The safety population in GOG-0240 comprised all randomised patients who received at least one full or partial dose of any component of their treatment, from randomisation to primary analysis data cut-off[7]. Compared with chemotherapy alone, the bevacizumab plus chemotherapy group had a greater incidence of serious adverse events (AEs) (50.0% and 36.5% respectively) and grade ≥ 3 AEs (75.7% and 58.1% respectively). AEs leading to discontinuation of any treatment were greater in the bevacizumab-containing arms, despite a similar duration of exposure. Most common AEs were typically associated with components of the chemotherapy and were broadly similar in both groups. Grade ≥ 3 hypertension occurred in a higher proportion of patients in the bevacizumab and chemotherapy group compared with chemotherapy alone (11.5% and 0.5% respectively). Venous thromboembolic events were higher than seen in previous trials of bevacizumab in other indications, with increased numbers of events in the bevacizumab and chemotherapy group compared to chemotherapy only (7.8% vs 4.1% respectively). The incidences of gastrointestinal (GI) perforations and non-GI fistula/abscess were similarly higher in GOG-0240 than in previous trials; incidence of both was increased in the bevacizumab and chemotherapy group compared to chemotherapy only (9.6% vs 0.9% and 4.1% vs 2.7% respectively)[1,7].

3.4 AWTTC critique

- Bevacizumab is licensed 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 patients who cannot receive platinum therapy[16]. These patients have a poor prognosis; current treatment is systemic chemotherapy, often given with a palliative rather than curative aim[6]. Bevacizumab is the first targeted therapy licensed for use in this group of patients.
- Bevacizumab (Avastin®) currently has a restricted recommendation for this indication in Scotland for use in combination with paclitaxel and cisplatin[11]. It is also available in combination with paclitaxel and either cisplatin or carboplatin (off-label) via the Cancer Drugs Fund for recurrent or metastatic cervical cancer in England[17].
- AWMSG has previously appraised and issued a negative recommendation (due to the case for cost-effectiveness not being proven) for the indication under consideration. Since then, bevacizumab has a new PAS in place which is the basis for this resubmission. In addition, there are now biosimilar bevacizumab available[8].
- The applicant company request that bevacizumab is considered for use only in combination with cisplatin and paclitaxel. The company perceive chemotherapy comprising a platinum agent plus paclitaxel to be the current standard of care for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix in Wales, with carboplatin being the most widely used platinum agent in this group of patients. Carboplatin has largely replaced cisplatin as it results in fewer adverse events and is simpler to administer than cisplatin[15,18]. However, bevacizumab is not licensed for use in combination

with carboplatin. The company claim, based on clinical expert opinion, that if bevacizumab was recommended in this indication, clinical practice would be adjusted so that bevacizumab was used in combination with cisplatin and not carboplatin[1].

- Evidence from GOG-0240 indicates that the addition of bevacizumab to chemotherapy improves OS and PFS. Patients in this trial received chemotherapy comprising either paclitaxel plus cisplatin or paclitaxel plus topotecan. Subgroup analysis by individual chemotherapy regimen demonstrated improvements in OS and PFS of similar magnitude to those observed for the whole study population. The OS differences between treatment groups were not statistically significant in subgroup analyses, but the study was not powered to detect such differences.
- A network meta-analysis was conducted to compare bevacizumab to carboplatin plus paclitaxel (the current standard of care in Wales). This included the study JCOG0505[15], which directly compared cisplatin plus paclitaxel and carboplatin plus paclitaxel, thereby providing an indirect link with GOG-0240 (both included cisplatin plus paclitaxel as a common treatment arm). Median OS for patients treated with cisplatin plus paclitaxel differed between the two studies (15.0 months in GOG-0240; 17.5 months in JCOG0505[15]), suggesting that patients in GOG-0240 may have had a poorer underlying prognosis than those in JCOG0505[15]. Consistent with this, patients in GOG-0240 had poorer performance status than those in JCOG0505[15].
- Results of the network meta-analysis suggest that bevacizumab plus cisplatin plus paclitaxel improves OS and PFS by similar magnitudes when compared to either carboplatin plus paclitaxel or cisplatin plus paclitaxel. The network meta-analysis did not report any other outcomes comparing bevacizumab plus cisplatin plus paclitaxel to carboplatin plus paclitaxel.
- Patients treated with bevacizumab in addition to paclitaxel plus cisplatin may be at increased risk of venous thromboembolic events, GI perforation and gastrointestinal-vaginal fistulae[1,6,16]. However, results of GOG-0240 suggest that the addition of bevacizumab to chemotherapy does not adversely affect HRQoL compared to chemotherapy alone.
- GOG-0240 was conducted in 164 sites across the US and Spain, and background treatment was chosen according to the US standard of care, which is cisplatin plus paclitaxel. As noted above, carboplatin has largely replaced cisplatin in the UK. No UK sites were included in the trial but the company suggests that, apart from the differences in the platinum agent used, the care provided to patients in the trial is broadly reflective of Welsh clinical practice.

4.0 Cost-effectiveness

4.1 Context

The company submission includes a cost-utility analysis (CUA) of bevacizumab 15 mg/kg body weight as intravenous infusion in combination with cisplatin and paclitaxel compared to carboplatin and paclitaxel for the first-line treatment of adult patients with persistent, recurrent, or metastatic cervical cancer[1].

A Markov model with an NHS perspective simulates disease progression based on patient level data from the GOG-0240 study in weekly cycles[7]. The model includes the three health states progression-free survival, progressed disease and death, which is the absorbing state. Patients enter the model in the progression-free survival health state. After every cycle, patients can remain in their current health state or

move to a worse state. The model base case adopts a 15-year time horizon and 3.5% discounting is applied to both costs and benefits. Most clinical data for the bevacizumab arm is taken directly from the GOG-0240 trial[7]. Baseline demographics (age, height, weight, diagnosis and previous treatments) are derived from the baseline characteristics of the 229 women treated with cisplatin plus paclitaxel (with or without bevacizumab) in GOG-0240. Survival was based on the observed values within the trial period (final analysis), which reported a median OS gain of 2.5 months in women treated with bevacizumab and cisplatin plus paclitaxel compared to cisplatin and paclitaxel alone (17.5 vs 15.0 months, HR: 0.75; 95% CI: 0.55–1.01; p = 0.0584). Log logistic functions were fitted to the Kaplan Meier curves to generate survival estimates beyond the clinical trial period and are adjusted after 5 years using the Surveillance, Epidemiology, and End Results (SEER) database estimates to account for a small proportion of patients with recurrent, persistent or metastatic cervical cancer who survive long-term[19]. A Gamma distribution was used to extrapolate the median trial PFS gain of 2.2 months with bevacizumab (9.1 vs. 6.9 months, HR: 0.57; 95% CI: 0.42–0.78; p = 0.0003) beyond the trial period. To estimate survival for patients treated with the comparator carboplatin plus paclitaxel, a HR of 0.994 is applied to the OS observed with cisplatin and paclitaxel and an HR of 1.039 is applied to the PFS. These HRs are taken from the indirect comparison of carboplatin-paclitaxel versus cisplatin-paclitaxel as part of the network meta-analysis described in Section 3.2. Treatment duration in the base case was based on the observed Kaplan Meier curves for the full duration of the study with an exponential function for the intervention arm and Gamma function for the control arm fitted to the tail after the follow-up period to ensure no patients were left on treatment indefinitely. To derive the treatment duration with carboplatin plus paclitaxel, the HR for PFS of carboplatin plus paclitaxel (1.039) is applied to the cisplatin plus paclitaxel duration data[18]. The model takes into account AEs with an incidence of 3% or more and a severity of grade 3 and 4 with frequency of AEs in each arm based on the pivotal study[15].

Costs included in the model comprise drug acquisition costs, drug administration costs, costs associated with the management of AEs and routine care costs (including palliative care) of patients in PFS and progressive disease (PD) health states. Cost of treatment is taken from the British National Formulary and adjusted according to the agreed Patient Access Scheme (PAS) discount of [commercial in confidence text removed][20]. Drug acquisition costs were based on the actual dose received by patients in the GOG-0240 trial assuming no vial sharing. Due to lack of data for the comparator, the dose of paclitaxel was assumed to be the same as in the GOG-0240 study whilst the dose of carboplatin was based on the licensed dose. Administration costs (including pharmacy dispensing) and AE costs are taken from published unit costs[21,22]. AE costs are averaged to a weekly cost based on the total AE follow-up period and were applied to all patients while on treatment taking into account the higher incidence of AEs with bevacizumab. Costs of routine care received during follow-up are based on NICE guidelines for recurrent ovarian cancer and include clinical assessments by the consulting oncologist every month and a computed tomography (CT) scan every 2 months[23]. These are costed using NHS reference costs[22]. Patients in the PD state are assumed to be treated with palliative care according to NICE guidance for patients with platinum-resistant ovarian cancer and costed using published costs for cancer of the uterus[24,25].

A mapping algorithm was used to translate HRQoL measured by the FACT-General (FACT-G) instrument during the GOG-0240 study into EQ-5D utility scores[26]. Accordingly, a baseline utility of 0.79 was used during the PFS state with an

assumed 20% decrement in the PD state (0.63). Disutilities of AEs were not considered in the model.

Extensive deterministic and probabilistic sensitivity analyses were undertaken to assess parameter uncertainty. Scenario analyses were used to explore the effect of alternative costing scenarios, the impact of assuming proportional hazards and assumptions about routine care palliative care costs on the results.

4.2 Results

The results of the base case analysis are summarised in Table 3. The analysis suggests that the addition of bevacizumab to cisplatin plus paclitaxel chemotherapy results in [commercial in confidence text removed] per patient over a 15-year time horizon compared to [commercial in confidence text removed] in the carboplatin plus paclitaxel arm. This is achieved at an incremental cost of [commercial in confidence text removed] per patient [commercial in confidence text removed]. This gives an incremental cost-effectiveness ratio (ICER) of [commercial in confidence text removed] gained. The model projects that the use of bevacizumab in combination with cisplatin plus paclitaxel results in 0.497 more life years gained compared to the carboplatin arm with an ICER of [commercial in confidence text removed] per life-year saved. Due to the similar efficacy of cisplatin and carboplatin, cost differences are mainly driven by bevacizumab acquisition and administration costs and the increased incidence of AEs.

Table 3. Results of the base case analysis (PAS applied)

	Bevacizumab plus cisplatin plus paclitaxel	Carboplatin plus paclitaxel	Difference
Total cost per patient	¶¶	¶¶	¶¶
Mean cost of PFS	¶¶	¶¶	¶¶
Drug acquisition: bevacizumab	¶¶	¶¶	¶¶
Drug acquisition: chemotherapy	¶¶	¶¶	¶¶
Drug administration	¶¶	¶¶	¶¶
Adverse events	¶¶	¶¶	¶¶
Routine care	¶¶	¶¶	¶¶
Mean cost of PD	¶¶	¶¶	¶¶
Total life-years gained per patient	**2.461**	**1.964**	**0.497**
Total QALYs per patient	¶¶	¶¶	¶¶
Cost per life year gained	¶¶		
ICER (cost/QALY gained)	¶¶		

¶¶ commercial in confidence figure removed
PFS; Progression-free survival health state. PD; Progressive disease health state.
ICER: Incremental cost effectiveness ratio. QALY; Quality-adjusted life-year.

In deterministic sensitivity analysis, the ICERs for bevacizumab plus cisplatin and paclitaxel compared to carboplatin and paclitaxel ranged from [commercial in confidence text removed]. The results of the deterministic sensitivity analyses indicate that the ICER is most sensitive to the use of alternative mapping algorithms for PFS utility, discount rate, time horizon, utility decrement in the PD state and administration costs. The results of the scenario analyses are assessed in order of plausibility in Table 4.

Probabilistic sensitivity analysis suggests that the model results are robust, as the mean results are comparable to the base case results. The probabilities of bevacizumab in combination with cisplatin plus paclitaxel being cost-effective compared to carboplatin plus paclitaxel at willingness to pay thresholds of £20,000 and £30,000 are [commercial in confidence text removed] and [commercial in confidence text removed], respectively.

Table 4. Results of the scenario analyses

Scenarios	ICER	Plausibility
Alternative extrapolation methods for OS data	Proportional hazard assumption: ¶¶	These scenarios are plausible as Log normal and Gamma parametric functions were the second closest fit and considered clinically plausible.
	Log normal: ¶¶	
	Gamma: ¶¶	
	Log normal + SEER data: ¶¶	These scenarios are plausible as Log normal and Gamma parametric functions were the second closest fit and considered clinically plausible.
	Gamma + SEER data: ¶¶	
Alternative extrapolation method for PFS data	Weibull: ¶¶	This scenario is plausible as the Weibull function was the second closest fit and considered clinically plausible.
Alternative HR used to extrapolate model inputs for carboplatin plus paclitaxel	Assuming HR of OS is 1: ¶¶	These scenarios are plausible considering the reported similarity in efficacy of cisplatin and carboplatin.
	Assuming HR of PFS is 1: ¶¶	
	Assuming HR of OS and PFS are both 1: ¶¶	
Different discount rates	0%: ¶¶ 6%: ¶¶	A discount rate of 3.5% was applied in the base case. These scenarios are plausible, dependant on the preference for the discount rate.
Alternative mapping algorithms used to extrapolate utility values in PFS state	Cheung et al[27] (0.80): ¶¶	The plausibility of these scenarios is uncertain due to the serious limitations of the algorithms and the bias this will cause.
	Dobrez et al[28] (0.73): ¶¶	
	Longworth et al[29] (0.68): ¶¶	
Alternative decrements assumed to estimate utility values in PD state	10% decrement (0.71): ¶¶	The plausibility of these scenarios is uncertain as they are based on assumptions (as is the base case).
	30% decrement (0.55): ¶¶	
Alternative extrapolation	KM + exponential: ¶¶	These scenarios are plausible as exponential and

Scenarios	ICER	Plausibility
methods for time to treatment discontinuation	KM + Gamma: ¶¶ KM + Weibull: ¶¶	Gamma functions were the second closest fit.
Different drug doses (all doses changed simultaneously)	Actual dose with vial sharing: ¶¶	The plausibility of these scenarios depends on the routine clinical practice.
	Planned dose without vial sharing: ¶¶	
	Planned dose with vial sharing: ¶¶	
	Planned individual dose without vial sharing: ¶¶	
	Planned individual dose with vial sharing: ¶¶	
Bevacizumab in combination with carboplatin and paclitaxel	¶¶	The plausibility of this scenario depends on routine clinical practice (considering that use of this combination is off label).
Different time horizons	10 years: ¶¶	Considering that after 5 years 88% and after 7 years 93% of the model population had died, the time horizon of 20 years is implausible.
	20 years: ¶¶	
No PAS applied	¶¶	This scenario is implausible as the PAS is in place for bevacizumab.
¶¶ commercial in confidence figure removed KM; Kaplan Meier. SEER; Surveillance, Epidemiology, and End Results database. PAS; Patient Access Scheme. HR; hazard ratio. OS; overall survival. PFS; progression free survival. PD; progressive disease.		

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The model used to calculate cost-effectiveness is well constructed, clearly and logically arranged, and appears to be robust and valid.
- The company generally provides a detailed and transparent account of methods and results.
- The company uses extensive sensitivity and scenario analyses to assess the effect of parameter uncertainty on the results.

Limitations:

- The chosen base case time horizon of 15 years is excessive considering a median OS of 15 months for the condition in question. The company states that a small proportion of patients with recurrent, persistent or metastatic cervical cancer survive for a long time, which is why they chose a time horizon that captures these long-term survivors and believe that 15- or 20-year horizons should both be considered as appropriate scenarios. However, after five years, the model calculates that 87.7% of bevacizumab-treated patients would have died. This increases to 91.0% after seven years and 93.6% after ten years. At 20 years, 96.8% of patients have died. This means that, while the difference in life years and QALYs will only be slightly affected due to the high mortality rate early in the model, the high upfront costs of bevacizumab will be artificially diluted by the long-time horizon chosen. Furthermore, the OS curves used in the model are based on extrapolation beyond the duration of the trial. The longer the period of extrapolation, the greater the uncertainty and potential for bias in the predicted survival rates. Increasing the time horizon has a disproportionate effect on the ICER compared to the change in patient numbers, which are also subject to considerable uncertainty by this stage. This approach will therefore reduce the ICER from [commercial in confidence text removed] when applying a 5-year time horizon, to [commercial in confidence text removed] at 10 years, [commercial in confidence text removed] at 15 years (base case) and [commercial in confidence text removed] at 20 years. AWTTC suggests a time horizon of 10 years that would give an ICER of [commercial in confidence text removed] would therefore be more realistic than the base case. At 10 years, the probability of bevacizumab being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 is [commercial in confidence text removed] and [commercial in confidence text removed], respectively.
- The GOG-0240 study was powered to detect a statistically significant difference in OS for patients treated with chemotherapy (cisplatin plus paclitaxel or topotecan plus paclitaxel) with or without bevacizumab. However, the economic analysis is based on the subgroup analysis of bevacizumab in combination with cisplatin plus paclitaxel. Survival benefit for this subgroup analysis was not statistically significant. The company argues that the direction and magnitude of treatment effect between the entire study population and subgroup analyses across endpoints supports the suggestion of survival benefit with bevacizumab in combination with cisplatin plus paclitaxel. However, this cannot be verified.
- The company conducted a literature search for utility values in patients with advanced cervical cancer but could not identify studies that related the EQ-5D values to the health states PFS and PD. They therefore used a published mapping algorithm[26] to estimate utility scores from the FACT-G responses

collected in the GOG-0240 trial. While the company have made considerable effort to use the best available data, the mapping approach has several limitations that will cause uncertainty, especially as the model proved sensitive to the mapping approach chosen:
    - The mapping algorithm was developed for breast, lung and colorectal cancer and was not validated for cervical cancer patients.
    - Sample size was relatively small (n = 367; 184 development set, 183 validation set) and generalisability was limited by differences in patient gender, age, ethnicity, disease stage and mean FACT-G scores.
    - As the FACT-G instrument did not show significant differences in HRQoL between treatment arms and subgroups, utilities were mapped using pooled analysis across the control and intervention arms using the ITT population.
- Disutilities associated with AEs were not included in the model as they were assumed to be negligible, despite a higher rate of AEs in the bevacizumab arm. The company argues that the impact of AEs on HRQoL would have been captured within the mean estimates obtained from the trial FACT-G data. This approach might result in an overestimation of utilities.
- The GOG-0240 trial did not collect sufficient data to appropriately estimate the costs of subsequent anti-cancer treatments received by patient's post-progression. While the company argues that these costs can be assumed to be negligible due to the poor prognosis of women with recurrent, persistent or metastatic cervical cancer, exclusion of these treatments might underestimate the total costs.
- No information about the actual dose of carboplatin plus paclitaxel was available in the JCOG0505[15] trial. The comparator was therefore costed using the same dose of paclitaxel as in the GOG-0240 trial whilst the dose of carboplatin was based on the planned dose as indicated in the SPC. This will introduce bias if the dosing differs in routine clinical practice.
- Only cost inputs were updated to 2020 prices in the resubmission compared to the original submission in 2016. Clinical inputs, such as long-term survival and utilities are still based on pre-2016 publications even though more recent data are available which will cause bias if changes occurred.
- No cost data was available for palliative care of patients with recurrent cervical cancer. The model therefore uses costs for patients with cancer of the uterus. While the company states that these costs are more reflective of routine practice for patients with cervical cancer than the costs associated with ovarian cancer, any differences in costs will cause uncertainty in the results.
- All costs were adjusted to 2019–2020 price levels instead of 2022 prices. This will underestimate the actual cost of treatments.

4.4 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-utility of bevacizumab in combination with cisplatin plus paclitaxel chemotherapy compared to carboplatin plus paclitaxel for the first-line treatment of adult patients with persistent, recurrent, or metastatic cervical carcinoma. However, two CUAs were identified that compared bevacizumab plus cisplatin plus paclitaxel to cisplatin plus paclitaxel alone; these reported ICERs of $155,148 and $133,559, respectively[30,31]. Two CUAs compared chemotherapy (cisplatin plus paclitaxel and topotecan plus paclitaxel) to chemotherapy plus bevacizumab and reported ICERs of $252,996 and $280,380, respectively[32,33]. All analyses were conducted in the USA, based on results from the GOG-0240 trial and can be considered very low-quality evidence due to severe limitations.

5.0 BUDGET IMPACT

5.1 Context and methods

In 2006, the 1-year prevalence of cervical cancer was 143 women in Wales[34]. However, according to an audit in England[35], only 3.8% of these women have stage IVB or stage IV "otherwise not specified" disease, which is equivalent to five patients in Wales. Based on company-sought clinical expert opinion it is estimated that a quarter of patients with cervical cancer (34 patients in Wales) have recurrent or persistent disease and that 80% of all women with recurrent, persistent or metastatic cervical cancer in Wales are suitable to receive platinum-based chemotherapy and would therefore be eligible for combination treatment with bevacizumab. This results in 33 eligible patients in Wales in year 1. The budget impact model does not take into account yearly incidence or mortality but assumes an eligible population of 33 throughout the 5-year period. The company assumes an uptake of 20% in year 1 increasing to 60% in years 4 and 5, resulting in seven patients receiving bevacizumab combination therapy in year 1 and 20 in years 4 and 5. The model includes incremental costs expected as a consequence of the introduction of bevacizumab, and the difference in chemotherapy platinum agent between arms. The net annual acquisition cost for the bevacizumab arm is [commercial in confidence text removed] per patient [commercial in confidence text removed] based on the actual dose and treatment duration of bevacizumab as observed in the GOG-0240 trial[7]. Additional administration costs of £210 and increased AE treatment costs of £259 are assumed for the bevacizumab arm based on the cost-effectiveness model output for year 1.

The company supplied a basic sensitivity analysis that estimates the effects of different market shares on the results.

5.2 Results

The estimated net budget impact as presented by the company is shown in Table 5. The introduction of bevacizumab in combination with cisplatin plus paclitaxel is estimated to result in additional costs of [commercial in confidence text removed] in year 1 increasing to [commercial in confidence text removed] in year 5. The total predicted budget impact over 5 years is [commercial in confidence text removed].

Table 5. Company-reported costs associated with use of bevacizumab

	Year 1	Year 2	Year 3	Year 4	Year 5
Sub-population of eligible patients (indication under consideration)	33	33	33	33	33
Uptake of new medicine (%)	20%	51%	59%	60%	60%
Number of patients receiving new medicine allowing for discontinuations*	7	17	19	20	20
Medicine acquisition costs in a market without new medicine§	£0	£0	£0	£0	£0
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs¶	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£3,084	£7,865	£9,098	£9,253	£9,253
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶ commercial in confidence figure removed

*Discontinuation is included in the drug acquisition costs as this is based on dose and treatment duration as observed in the GOG-0240 trial

§ Bevacizumab regarded as add-on treatment. Cost differences between cisplatin and carboplatin not taken into account.

¶ Including additional administration costs and management of adverse events.

†A PAS discount of ¶¶ is applied to the list price of bevacizumab.

Sensitivity analysis based on different uptake rates for bevacizumab indicates a total budget impact between [commercial in confidence text removed] and [commercial in confidence text removed] if only acquisition costs are considered.

5.3 AWTTC critique

- The patient number calculations presented by the company in the budget impact model lack face validity. The company proposes that the prevalence of all cervical cancer cases in Wales is 143 patients, which is inconsistent with the presented incidence data of 164/100,000 population[34]. The prevalence rate is based on patients in Wales with cervical cancer for 1 year or less, but

the same publication lists a prevalence of 2,279 for patients with cervical cancer for up to 20 years.

- The budget impact analysis further assumes that patients are treated for 1 year only and then drop out of the model. In each subsequent year, a new set of patients are introduced, who then also all drop out before the start of the next year. That all patients drop out of the model after 1 year is a reasonable assumption considering the short OS and the median time on treatment in the economic model (4–5 months). However, to assume that the number of new patients in each year is based on the prevalence of patients with cervical cancer for less than 1 year does not appear plausible. Therefore, the analysis does not appear to present realistic prevalence and incidence estimates over the 5-year time horizon.
- The use of clinical expert opinion to estimate the proportion of cervical cancer patients who are eligible for bevacizumab introduces uncertainty and bias into the analysis.
- Clinical experts consulted by AWTTC estimated patient numbers to be broadly similar to company estimates (estimates ranged from 11 to 50 eligible patients per year). However, given the uncertainties surrounding the number of eligible patients, and the high cost of treatment, even small differences in patient numbers will have the potential to considerably affect the budget impact.
- The difference in cost of cisplatin and carboplatin are not taken into account which will introduce bias.
- As costs are derived from the economic model, the limitations of the economic model therefore also apply to the budget impact estimates.
- Yearly uptake rates are assumed by the company and are subject to uncertainty as in all budget impact analyses. Any difference in actual uptake will affect the budget impact.
- Overall, there is considerable uncertainty associated with the results of the budget impact analysis.

6.0 Additional factors to consider

6.1 AWMSG's policy for life-extending, end-of-life medicines

The applicant company has indicated that bevacizumab may be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[36]. The AWMSG criteria for appraising life-extending, end-of-life medicines and a discussion of the extent to which bevacizumab may meet these criteria are provided in Table 6.

Considering that all criteria must be fulfilled to apply the EoL policy and the most plausible ICER estimates do not exceed £30,000 per QALY gained (see Table 6), AWTTC does not consider bevacizumab to be eligible for application of end-of-life criteria.

Table 6. End-of life considerations for NMG/AWMSG

AWMSG criteria for application of the EoL policy (all must apply)[36]	Bevacizumab considerations
The most plausible ICER estimate exceeds £30,000 per QALY	The base case ICER presented by the company for bevacizumab in combination with cisplatin plus paclitaxel versus carboplatin plus paclitaxel is [commercial in confidence text removed] per QALY. Probabilistic sensitivity analysis estimated that the probability of the addition of bevacizumab being cost- effective at a £30,000 threshold was [commercial in confidence text removed]. AWTTC considers the time horizon chosen for the base case to be unrealistic. Considering that median OS is less than 15 months, the 15-year time horizon artificially dilutes the high upfront costs of bevacizumab without adding considerable life years or QALYs. The ICER therefore decreases with increasing length of time horizon. AWTTC suggests that a 10-year time horizon would be more plausible, which would result in an ICER of [commercial in confidence text removed].
The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).	GOG-0240 reports a median OS of 13.3 months (95% CI: 10.9–15.8) for patients on chemotherapy alone[7]. Median OS in the JCOG0505 trial was 18.3 months (95% CI: 16.1–22.9) for patients who received cisplatin plus paclitaxel and 17.5 months (95% CI: 14.2–20.3) for patients who received carboplatin plus paclitaxel[15].
There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression-free survival or overall survival.	Median OS of patients with persistent, recurrent or metastatic cervical carcinoma treated with bevacizumab is estimated from GOG-0240. Analysis is available for different subgroups and at several different follow up points. Median OS was reported in the company submission based on the follow up analysis, which covers the longest available follow up time. The company request that bevacizumab is considered for use only in combination with cisplatin and paclitaxel. In the subgroup of patients in GOG-0240 receiving cisplatin plus paclitaxel, the follow up analysis estimated that median OS was extended by 2.5 months (17.5 months vs. 15.0 months; HR 0.75, 95% CI: 0.55–1.01, p = 0.0584). This difference was not statistically significant, although it should be noted that the study was not powered to detect differences between subgroups.
EoL; End-of-life. ICER; Incremental cost-effectiveness ratio. OS; Overall survival. QALY; Quality-adjusted life years.	

6.2 Medicines developed to treat rare diseases

The applicant company suggests that bevacizumab, for the indication under consideration, meets the AWMSG criteria for an ultra-orphan medicine. AWMSG defines an ultra-orphan medicine as a medicine that has been granted EMA designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[37].

The company suggests that bevacizumab is designated an orphan medicine by the European Medicines Agency (EMA). However, AWTTC were unable to verify the EU population size as bevacizumab is not registered on the EMA website as having orphan designation for this indication.

The company has estimated the population for the licensed indication as covered in this submission (recurrent, persistent or metastatic cervical cancer) as 33 patients, as detailed in Section 5.2. However, the full licensed indication for bevacizumab includes the treatment of adult patients with metastatic carcinoma of the colon or rectum, metastatic breast cancer, unresectable advanced, metastatic or recurrent non-small cell lung cancer, advanced and/or metastatic renal cell cancer, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer and persistent, recurrent, or metastatic carcinoma of the cervix. The company has not provided patient numbers for the full licensed indication but this is likely to exceed 60 patients in Wales. AWTTC does not consider bevacizumab eligible to be consider as an ultra-orphan (or equivalent) medicine.

The criteria for assessing clinical effectiveness and cost-effectiveness of orphan and ultra-orphan medicines and medicines specifically developed for rare diseases are the same as those applied to other medicines, but recognises that the evidence base may be weaker. If the medicine is considered to meet the criteria as an ultra-orphan, orphan or equivalent medicine, NMG and AWMSG may consider additional criteria for appraising these medicines (see Table 7), if the cost per QALY is above the normal thresholds applied.

Table 7. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases: considerations for NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	The 3-year relative cervical cancer survival rate in Europe between 2000 and 2007 was 68% (95% CI: 67-68%)[4]. Survival data differentiated by stage of disease are not available for Wales, but are reported as 1-year survival of 50% for stage IV disease in England with long-term survival estimates of a 3-year survival rate of less than 50% reported in other countries[38-40]. Women with recurrent, persistent or metastatic cervical cancer who are suitable to receive chemotherapy will usually receive platinum-based chemotherapy (cisplatin or carboplatin plus paclitaxel or topotecan)[41]. However, the survival benefit of current chemotherapy treatments is modest with a median OS no greater than 13 months[18].
Whether the medicine addresses an unmet need (e.g. no other licensed medicines).	Bevacizumab is the first targeted therapy granted a licence for treatment of patients with cervical carcinoma. Current standard treatment relies on platinum-based chemotherapy and combination regimens which have shown limited survival benefit compared with monotherapy. The main treatment goals for patients with cervical cancer are prolongation of life, delay of disease progression, prevention or control of symptoms, and improvement or maintenance of HRQoL.
Whether the medicine can reverse, rather than stabilise the condition.	Bevacizumab will not reverse or cure the condition.
Whether the medicine may bridge a gap to a “definitive” therapy (e.g. gene therapy), and that this “definitive” therapy is currently in development.	Bevacizumab does not bridge a gap to definitive therapy.
The innovative nature of the medicine.	The company suggests that cisplatin has been the preferred treatment for recurrent cervical cancer for the last thirty years and no new treatments of increased efficacy for recurrent, persistent or metastatic cervical cancer have become available in the last ten years. Bevacizumab is the first targeted therapy granted a licence for treatment in patients with cervical carcinoma. Treatment with bevacizumab plus chemotherapy demonstrated a significant improvement in median OS of 3.5 months compared with chemotherapy alone (16.8 vs 13.3 months, HR 0.76, 95% CI: 0.62–0.94, p = 0.013). A 2.3 month gain in median PFS was also demonstrated in the ITT population (8.3 vs 6.0 months, HR 0.66, 95% CI: 0.54–0.81, p < 0.0001).

Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	Women diagnosed with gynaecological cancer (ovarian, endometrial, and cervical) have significantly lower QoL scores compared with age-matched controls from the general population with a significantly greater impact of progressive or recurrent disease on patient QoL[42]. Effective therapies, especially in progressive or recurrent disease, could therefore potentially increase QoL and improve long-term survival. In GOG-0240[7], patient QoL showed no clinically meaningful improvement with bevacizumab plus cisplatin-paclitaxel compared with cisplatin plus paclitaxel alone. Other specific domains of added value were not quantified by the company.
Added value to the patient's family (e.g. impact on a carer or family life).	Cervical cancer is associated with a considerable impact on patients' and carers' psychological well-being and QoL, most notably anxiety and depression, and a decline in physical health, including fatigue, eating disorders and hypertension[43]. Duration and morbidity of the illness is associated with decreased QoL scores for both patients and caregivers[44]. However, these effects were not quantified by the company.
QALY: quality-adjusted life-year; QoL: quality of life; HRQoL: health related quality of life; ITT; Intention-to-treat	

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