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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

BEVACIZUMAB IN THE TREATMENT OF OVARIAN CANCER

KCE REPORT 285
HEALTH TECHNOLOGY ASSESSMENT

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
95%CI	95% confidence interval
AEs	Adverse events
AESIs	Adverse events of special interest
APR-DRG	All Patient Refined Diagnosis Related Group
ATC	Anatomical Therapeutical Chemical (classification)
AUC	Area Under the Curve
B	Bevacizumab
BCR	Belgian Cancer Registry
BFM-BMF	Budget financiële middelen - budget des moyens financiers (Budget of Financial Means)
C	Carboplatin
C&E	Costs and effects
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CNS	Central nervous system
CoI	Conflict of interest
CRD	Centre for Reviews and Dissemination
CT	Computer tomography
CUA	Cost-utility analysis
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-OV28	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module 28
EQ-5D	EuroQol five dimensions questionnaire

ERG	Evidence Review Group
EUnetHTA	European Network for Health Technology Assessment
FACT-O TOI	Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index
FIGO	International Federation of Gynaecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy-Ovarian Symptom Index
G	Gemcitabine
GOG	Gynecologic Oncology Group
GRADE	Grades of Recommendation Assessment, Development and Evaluation
HR	Hazard ratio
HTA	Health Technology Assessment
IC	Incremental cost
ICD-O	International classification of diseases for oncology – 3rd edition
ICER	Incremental cost-effectiveness ratio
IE	Incremental effect
IMA – AIM	InterMutualistisch Agentschap – Agence Intermutualiste
INAHTA	International Network of Agencies for Health Technology Assessment
INSZ – NISS	Identificatie Nummer voor de Sociale Zekerheid – Numéro d'Identification à la Sécurité Sociale (National Number for Social Security)
IV	Intravenous
KCE	Belgian Health Care Knowledge Centre
KM	Kaplan Meier
KSZ – BCSS	Kruispuntbank van de Sociale Zekerheid – Banque Carrefour de la Sécurité Sociale (Crossroads Bank for Social Security)
LYG	Life-year gained
mB	Maintenance bevacizumab
MD	Mean difference

MDT	Multidisciplinary team
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MS	manufacturer's submission
MZG – RHM	Minimale Ziekenhuisgegevens – Résumé Hospitalier Minimum
NICE	National Institute for Health and Care Excellence (United Kingdom)
NIHDI	National Institute for Health and Disability Insurance (RIZIV – INAMI)
OR	Odds ratio
OS	Overall survival
P	Paclitaxel
PD	Progressive disease
PF-LYS	Progression-free life-year saved
PFS	Progression-free survival
PLD	Pegylated liposomal doxorubicin
POP	Planned and Ongoing Projects
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
QA-PFY	Quality-adjusted progression-free years
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
RIZIV – INAMI	Rijksinstituut voor ziekte-en invaliditeitsverzekering – Institut National d'Assurance Maladie Invalidité (National Institure for Health and Disability Insurance - NIHDI)
RR	Relative risk
SD	Standard deviation

SMD	Standardized mean difference
TCT	Technische cel – Cellule technique (Technical cell) –
TNM	Tumour – Node – Metastasis
UK	United Kingdom
US(A)	United States (of America)
VEGFA	Vascular endothelial growth factor A
VEGFR2	Vascular endothelial growth factor receptor 2
VPF	Vascular Permeability Factor
WHO	World Health Organization
X	Missing Stage

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

The KCE clinical practice guideline on the diagnosis, first-line treatment and follow-up of ovarian cancer was published on 29 April 2016.[1] During the elaboration of this guideline, it was decided to investigate the role of bevacizumab in this cancer treatment in a separate HTA project, which is the subject of the present report.

1.2 Scope and objectives

This study aims to evaluate the safety, clinical effectiveness and cost-effectiveness of bevacizumab in two situations: first, in addition to first-line chemotherapy for ovarian cancer; second, in the treatment of recurrent ovarian cancer (platinum-sensitive or platinum-resistant).

2 HEALTH PROBLEMS

HTA CORE MODEL DOMAIN: CUR1

2.1 Population and condition

In Belgium, ovarian cancer is the eight most frequent female cancer and the fifth one in terms of female cancer mortality.[2] In 2014, 848 women were diagnosed with ovarian cancer (ICD-O C56). The mean age at diagnosis is 66.7 years. Around 71.7% of all ovarian cancers are diagnosed in an advanced stage when the tumour has already spread outside the pelvic area, to the retroperitoneal lymph nodes or beyond the peritoneum (stage III-IV), which explains why ovarian cancer is called a silent killer.[3] The global relative five-year survival is 42.6%, but only 23.8% for stage IV (Belgian Cancer Registry calculation on 2009-2013, personal communication). More details on women who had no other cancer than ovarian cancer can be found in Chapter 4.

Epithelial carcinomas account for over 90% of all ovarian tumours, far before germ cell and stromal tumours. Most common histological subtypes of epithelial carcinomas are serous, mucinous, endometrioid and clear-cell carcinomas. Brenner and mixed mullerian tumours are less common.

It has been suggested that the majority of assumed ovarian cancers originate from the fallopian tube epithelium rather than from the ovary itself. In advanced stages, it is difficult to distinguish tumours that originated from the ovary, fallopian tube or the peritoneal surface. Historically, although there may be behavioural and prognostic differences, the therapeutic approach of women suffering from epithelial ovarian, fallopian or primitive peritoneal cancer has been similar.[1] Strictly speaking, the population included in clinical studies and targeted by reimbursement conditions (see sections 4 and 0) is hardly larger than the target population in the present report, which includes only women with ovarian cancer. In any case, the number of cases actually diagnosed and registered with a primary fallopian tube cancer (ICD-O C57.0) is much more limited: 59 cases in 2013 (Belgian Cancer Registry calculation on 2009-2013, personal communication). As for primary peritoneal cancer (ICD-O C48.1), it is definitely a rare cancer: 12 cases diagnosed in 2013, far below the thresholds used in Europe or in the United States of America to define a rare cancer (< 6 per 100 000).[4]

2.2 Current treatment guidelines

Most women suffering from ovarian cancer are treated by surgery and/or chemotherapy, depending of the tumour stage, the patient's health status and the tumour response to antineoplastic agent.

Treatment of apparent early-stage disease is essentially surgical. Comprehensive staging includes thorough inspection of the abdominal cavity, peritoneal washings, multiple blind peritoneal biopsies, bilateral salpingo-oophorectomy, hysterectomy, infracolic omentectomy and bilateral pelvic and para-aortic lymphadenectomy. Histopathological examination of the removed specimens allows for precise diagnosis and staging and assessment of the need for adjuvant therapy. Platinum-based adjuvant chemotherapy should be offered to clinically fit stage IA, grade 2-3 or stage IB-IC, grade 1-3 patients, whether or not the tumour is optimally staged.[1]

In advanced stage, which characterizes the majority of patients, cytoreductive surgery and chemotherapy are used. Since the nineties, the standard first-line chemotherapy combination is carboplatin-paclitaxel.[1] For second-line chemotherapy, this combination may be re-used in platinum-sensitive patients, and carboplatin may also be switched to cisplatin. In case of allergy to platinum-based compounds, or non-response of the tumour to platinum-based chemotherapy (platinum-refractory tumour) or in case of relapse within 6 months after this kind of chemotherapy (platinum-resistant tumour), paclitaxel alone, pegylated liposomal doxorubicin hydrochloride (PLD), topotecan or gemcitabine represent possible options.[5-7]

2.3 Belgian recommendations of good practice

Diagnosis, first-line treatment and follow-up have been addressed in the guideline published by the KCE in March 2016 (recurrence treatment is not covered). Recently, the KCE also published a report on the organisation of care for rare cancers, including epithelial ovarian, fallopian or primitive peritoneal cancer.[4]

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS

HTA CORE MODEL DOMAIN: TEC

3.1 Bevacizumab

Bevacizumab, marketed as Avastin by Roche, is a drug used as a targeted cancer treatment (Anatomical Therapeutic Chemical (ATC) code L01XC07).[a] It is a recombinant humanised (93% human/7% murine) monoclonal antibody that recognizes and attaches ("targets") the vascular endothelial growth factor A (VEGFA). VEGFA is a protein present in the blood, responsible for angiogenesis (the development of new blood vessels from pre-existing blood vessels). This factor plays an essential role in the embryonic development, the human growth and more generally every time new blood vessels are needed (e.g. wound healing). VEGFA allows, among others, the angiogenesis, vasculogenesis and growth of endothelial cells by binding to the tyrosyne kinase receptor VEGFR2. Not only does it play a role in normal angiogenesis, but also in pathological angiogenesis as this factor is overexpressed in most human tumours. By binding to VEGFA, bevacizumab blocks the development of the tumour's blood vessels network, cutting its supply of oxygen and nutrients and therefore impeding its growth and dissemination. It is used in combination with chemotherapy as it increases chemotherapy uptake by the tumour.[9, 10]

Bevacizumab was derived from the research of Napoleone Ferrara at the biotechnological laboratory Genentech (San Francisco, USA). In 1989, Ferrara and his colleagues isolated and cloned VEGFA (which later confirmed to be the same molecule as the so-called Vascular Permeability Factor (VPF) identified by Senger et al. in 1983).[9]

Seven years later, they collaborated with other researchers including Peter Carmeliet (KU Leuven) to demonstrate the essential role of this cytokine in embryonic vasculogenesis and angiogenesis in the mouse. Ferrara's research went on around the turn of the century, studying in particular the effect of VEGF inhibitors on the human ovary angiogenesis.[11] It was the first anti-angiogenic agent approved by the FDA on 26 February 2004, in metastatic colorectal cancer. On 14 November 2014, the FDA approved bevacizumab in combination with chemotherapy for the treatment of platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Bevacizumab is available as a concentrate for solution for intravenous infusion, marketed in Europe by Roche (owner of Genentech since 2009) under the brandname Avastin, either as a single use vial of 100 mg/4 ml or a single use vial of 400 mg/16 ml.

The European Commission granted its marketing authorization on 12 January 2005. The European Medicines Agency authorized the use of Avastin in metastatic colorectal cancer as a first indication in 2006. Other indications were gradually proposed by Roche, and the current Avastin indications include metastatic colorectal cancer, metastatic breast cancer, unresectable advanced, metastatic or recurrent non-small cell lung cancer, advanced or metastatic renal cancer, advanced or recurrent epithelial ovarian, fallopian or primitive peritoneal cancer and persistent, recurrent or metastatic cervical cancer. For epithelial ovarian, fallopian or primitive peritoneal cancer, the front-line treatment in stage IIIB-IIIC-IV was authorized on 21 September 2011. This indication was extended to recurrent platinum-sensitive cancer on 20 September 2012 and to recurrent platinum-resistant cancer on 31 July 2014.

[a] It is also used in Belgium as an off-label drug in the treatment of age-related macular degeneration, as described in the recent KCE report on the use of off-label drugs.[8]

3.2 Belgian rules for the reimbursement of bevacizumab

Bevacizumab entered the Belgian reimbursement schedule on 1 December 2008 and is currently conditionally reimbursed in Belgium in the following tumours: metastatic colorectal cancer, advanced or metastatic renal cancer, metastatic breast cancer, recurrent or metastatic cervical cancer, and finally advanced or recurrent epithelial ovarian, fallopian or primitive peritoneal cancer (but not non-small cell lung cancer).

In Belgium, reimbursement for epithelial ovarian, fallopian or primitive peritoneal cancer can be allowed in three types of indications:

1. **First-line treatment** of **stage FIGO IV** epithelial ovarian, fallopian or primitive peritoneal cancer, in combination with carboplatin and paclitaxel for a maximum of 6 treatment cycles and then in monotherapy until either a maximum of 15 months in total, disease progression or unacceptable toxicity.
2. **First recurrence** of epithelial ovarian, fallopian or primitive peritoneal cancer, in adult patients **sensitive to platin salts** who have not yet been treated with bevacizumab or other VEGF inhibitors or other agents aiming at the VEGF receptor, in combination with carboplatin and gemcitabine during 6 to maximum 10 cycles and then in monotherapy until disease progression.
3. **Second-line** treatment of epithelial ovarian, fallopian or primitive peritoneal cancer, in adult patients **resistant to platin salts** who have not received more than 2 chemotherapy lines and have not been treated with bevacizumab or other VEGF inhibitors or other agents aiming at the VEGF receptor, in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin until disease progression or unacceptable toxicity.

In order to be reimbursed, bevacizumab treatment needs to be approved during a multidisciplinary team meeting prior to its administration. In any case, the patient must present neither with arterial thromboembolic history (cerebrovascular accident, transient ischemic attack, myocardial infarction, angina pectoris, peripheral arteriovascular insufficiency nor any other arterial thromboembolic event) nor with hypertension uncontrolled by a standard therapy.

Moreover, in case of platinum resistance, the patient should not show any sign of rectosigmoïd involvement on pelvic examination, intestinal involvement on computed tomography (CT) or clinical symptoms of intestinal obstruction.

Reimbursement is renewable for a maximum period of 15 months in first-line treatment and by periods of 36 months in second-line treatment, on request by the patient's oncologist.

The patient must be evaluated after 3 and 6 cycles. In case of second-line treatment, evaluation must then be done at least every 3 months. Treatment should be stopped in case of disease progression shown by CT or MRI.

The reimbursement tariffs are presented in Table 1.

Table 1 – Reimbursement tariffs for bevacizumab (all indications)

Billing code	Packaging	Ambulatory	Inpatient
00700420	4 ml solution Avastin 25mg/ml	333.67€	326.56€
00700521	16 ml solution Avastin 25mg/ml	1240.65€	1233.54€

Prices on February 2017.

Bevacizumab is not covered by the hospital pharmaceuticals lump sum. There is no patient share for bevacizumab as it is a category A pharmaceutical specialty (100% reimbursed).

The global annual reimbursement of Avastin, irrespective of the indication, amounted to € 38 million in 2014. For patients diagnosed with ovarian cancer prior to 2014, NIHDI reimbursements amounted to € 2.44 million in 2014.

The reimbursement terms in the case of epithelial ovarian, fallopian or primitive peritoneal cancer were negotiated based on article 81 of the Royal Decree of 21 December 2001,[12] according to which the Minister of Social Affairs and Public Health may allow the negotiation of a reimbursement contract (managed entry agreement) for some specific pharmaceuticals when the regular procedure did not result in the drug entry in the reimbursement schedule, until sufficient evidence is available to justify the requested reimbursement basis. On 1 March 2014, a first 3-year contract was concluded for the first-line treatment of stage IV (after a first refusal for stage IIIB, IIIC and IV in 2012) and the treatment of first recurrence in platinum-sensitive patients. A second 3-year contract was concluded on 1 July 2015 for the treatment of platinum-resistant patients.

This report should support the negotiations of these 3-year contracts of which the first one is ending in March 2017.

4 CURRENT USE

HTA CORE MODEL DOMAIN: CUR2

4.1 Methods

4.1.1 Data sources

Data were extracted from three databases that were coupled for the present study: the Belgian Cancer Registry (BCR), the Technical cell (TCT) database and the IMA – AIM database. The databases linkage and data delivery was authorized by the Sector Committee Social Security and Health on 16 February 2016[b].

The primary data selection was made on the BCR database and included ovarian cancers that were diagnosed between 1 January 2008 and 31 December 2013, for patients with an official residence in Belgium at the time of diagnosis for whom no cancer other than ovarian was diagnosed between 2003 and 2013. Tumour selection criterion was ICD-O C56 *Malignant neoplasm of ovary*. As explained in section 2.1, the primary fallopian tube and primary peritoneum cancers are much less frequent (respectively 13 times and 64 times less than ovarian cancer in 2013) and were not included in the data extraction. These data contained information on the tumour (FIGO stage, TNM, incidence date, morphology, laterality, etc.), the patient (age, WHO performance status, vital status, etc.) and the tumour treatments. The vital status is available in the BCR database from the Crossroad Bank of Social Security (Kruispuntbank van de Sociale Zekerheid / Banque Carrefour de la Sécurité Sociale) based on the patient unique social security number (INSZ – NISS).

[b] Dutch version: https://www.privacycommission.be/sites/privacycommission/files/documents/beraadslaging_AG_009_2016.pdf; French version: https://www.privacycommission.be/sites/privacycommission/files/documents/d%C3%A9lib%C3%A9ration_SS_009_2016.pdf.

In a second step, these selected data were coupled with the Technical cell (TCT) database 2008-2013 that contains the administrative, medical and billing data of all inpatient and day-care hospital stays in Belgian general hospitals. In particular, variables retrieved included the diagnoses, procedures, APR-DRG (version 15), severity of illness, length of stay as well as reimbursed amounts for honorarium fees, medical supplies, implants, pharmaceuticals and hospital lump-sums.

Finally, a coupling was made with the IMA – AIM database 2008-2014, that gathers all billing data from the Belgian sickness funds. These data cover all reimbursed services (consultations, pharmaceuticals, diagnostic and therapeutic procedures) and some patient socio-demographic characteristics.

4.1.2 Analysis

The next section presents descriptive statistics on the sample, using the SAS software package version 9.4[13] and R 3.3.2[14].

4.2 Results

4.2.1 Sample size

In the period 2008–2013, 4 282 patients were diagnosed with ovarian cancer according to the previously explained selection criteria. The correspondence between the three datasets is shown in Table 2. Of the 4 282 BCR-retrieved patients, 97.1% occurred in the IMA – AIM data sets. Of the non-linked, 80 were not in any of the IMA – AIM data sets. For 45 patients, IMA – AIM socio-demographic data but no reimbursement data was available.

For 94.9% of BCR patients, inpatient or day-care hospital admissions were found in the TCT data sets.

Table 2 – Number of patients per year in each data set after linkage.

Year	BCR	IMA – AIM	TCT
2008	761	740	701
2009	685	642	644
2010	754	730	729
2011	725	712	705
2012	699	688	659
2013	658	645	627

Unless otherwise specified, the remainder of the analysis was conducted on the entire sample for the period 2008–2013 with the addition of 2014 for IMA–AIM reimbursement data.

Of particular concern in the present study are patients receiving bevacizumab as part of their treatment. In our sample, the bevacizumab subsample is identified in the IMA–AIM reimbursement data by the package codes (CNK code) associated with ATC code L01XC07 (see also Table 1). Between 2008 and 2014, 152 patients had bevacizumab records in the IMA–AIM data set. The majority of these patients received their first session in 2014 (82.2%).

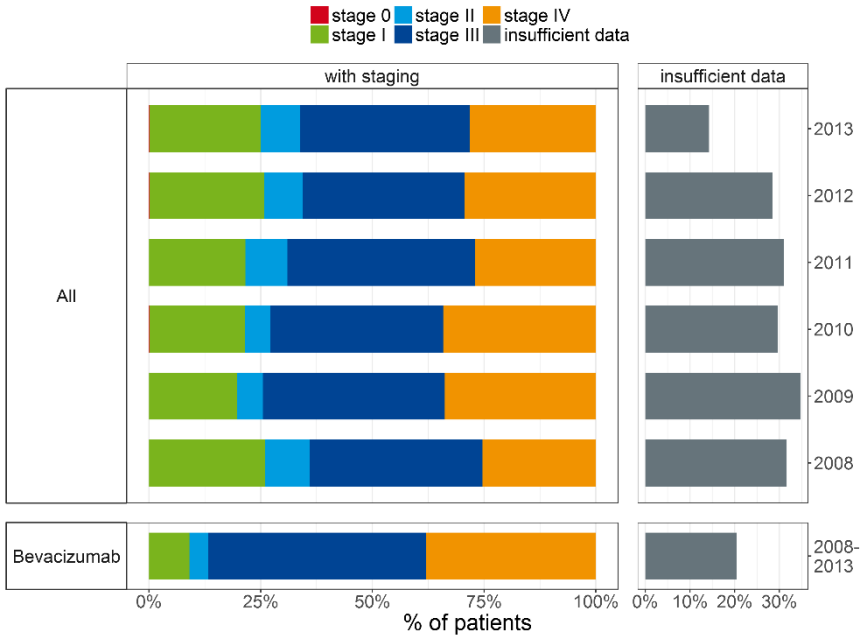
4.2.2 Staging levels

The distribution of patients per combined staging level is similar across years (see Figure 1). In 2013, the proportion of patients without staging information was about half that of previous years. The increase of staging information in 2013 spreads out over all staging levels, resulting in a similar distribution of patients to previous years across these levels.

The bevacizumab subsample has a higher proportion of patients in stage III and IV compared to the overall sample (stage III: respectively 48.8% vs. 38.9%; stage IV: respectively 38% vs. 29.6%; both for the years 2008–2013).

The number of patients staged with an in situ tumour is very low (less than eight). They are not removed from the analysis but for privacy reasons, their exact number is not reported and the in situ level is not shown in further analyses.

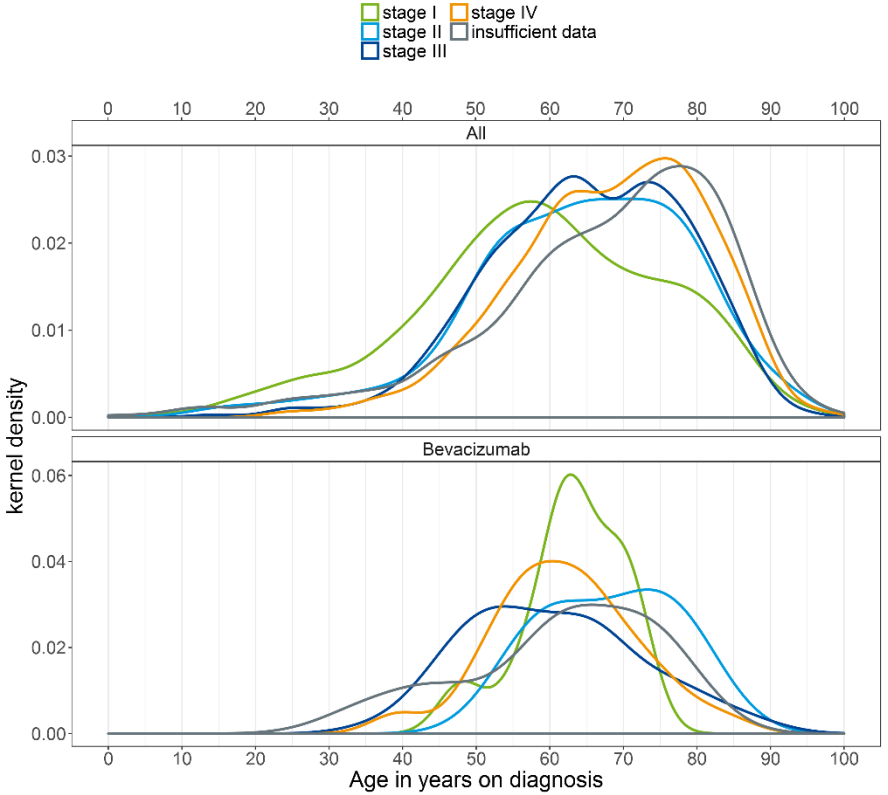
Figure 1 – Percentage of patients by combined stage per year for all and for bevacizumab patients.



4.2.3 *Age at diagnosis*

Overall, the mean age of patients in our sample is 65.3 years at diagnosis (SD: 15.2; median: 67; IQR: 21). For bevacizumab patients, the mean age is 61.5 years at diagnosis (SD: 11.1; median: 62; IQR: 15.2). Age distribution varies with staging, both overall and for the bevacizumab patients (see Figure 2).

Figure 2 – Distribution of age at diagnosis by combined stage for all and for bevacizumab patients.

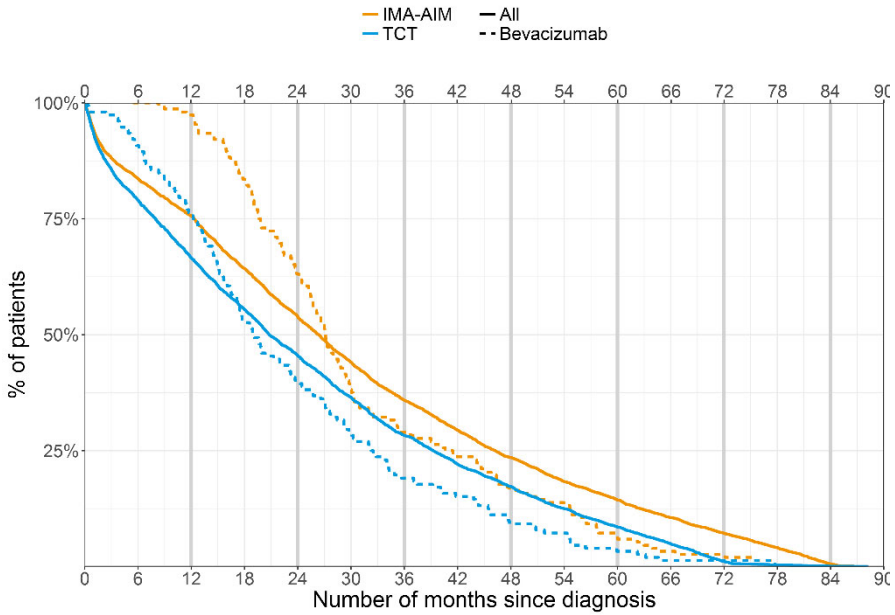


4.2.4 Available follow-up

For over 75% of the patients in our sample, at least one year of IMA–AIMdata is available following the diagnosis of ovarian cancer, with over two years for half of the patients (see Figure 3). This is lower for TCT data because 2014 was not yet available at the start of the study.

For most of the bevacizumab patients, at least one year of IMA–AIMdata is available. This is to be expected as 2013 was the last year available for diagnosis in BCR data, while the IMA–AIMdata extend to 2014. The small percentage of patients without a full year of IMA–AIMdata were deceased within one year of diagnosis. Comparable to the overall sample, TCT data provide a shorter follow-up in bevacizumab patients as well.

Figure 3 – Number of months of available follow-up by data set for all and for bevacizumab patients.



4.2.5 Adjuvant chemotherapy

4.2.5.1 Antineoplastic agents

Of the 4 282 patients in our sample, 3 124 patients (72.96%) received some form of chemotherapy (ATC L01 antineoplastic agents) after being diagnosed with ovarian cancer.

Considering all chemical substances within the ATC L01 group reimbursed on the same day as a chemotherapy session, we found 170 different combinations of chemical substances in use. The fifteen most common combinations are shown in Table 3.

Table 3 – Fifteen most common combinations of chemotherapy chemical substances used within a single session.

Chemo combination	N patients	% chemotherapy patients
carboplatin + paclitaxel	2 468	59.23%
carboplatin	911	21.86%
doxorubicin	812	19.49%
paclitaxel	626	15.02%
gemcitabine	559	13.41%
topotecan	499	11.98%
carboplatin + gemcitabine	491	11.78%
carboplatin + doxorubicin	217	5.21%
doxorubicin + trabectedin	167	4.01%
cisplatin	145	3.48%
cyclophosphamide	125	3.00%
fluorouracil	95	2.28%
bevacizumab	87	2.09%
celecoxib	84	2.02%
bevacizumab + carboplatin + gemcitabine	73	1.75%

Most patients received several different combinations during their treatment (median: 2 combinations; IQR: 3 combinations; see Figure 4). Patients with stage I ovarian cancer are the exception: over 50% received only one combination during their treatment trajectory.

We found 1936 different treatment trajectories with '6 sessions of carboplatin + paclitaxel' being the most common trajectory (13.8% of patients). When taking into account only the order of different substances, leaving out the exact number of sessions for each, there were 1314 different types of trajectories. The 15 most common are these are shown in Table 4.

Figure 4 – Number of different combinations of chemotherapy chemical substances within treatment trajectory by combined stage.

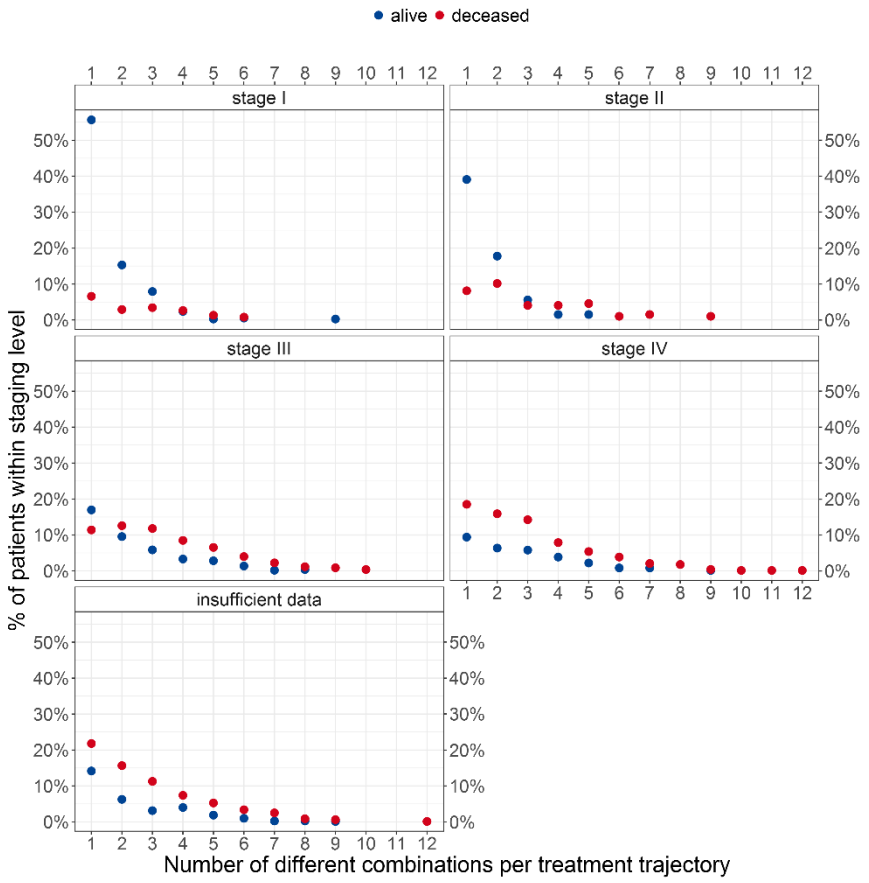


Table 4 – Fifteen most common chemotherapy trajectories ('+' means combination of the substances within a single session; '>' means next session(s)).

Chemotherapy trajectory	N patients	% chemotherapy patients
carboplatin + paclitaxel	758	24.26%
carboplatin	249	7.97%
carboplatin + paclitaxel > doxorubicin	102	3.27%
carboplatin + paclitaxel > carboplatin	71	2.27%
carboplatin + paclitaxel > topotecan	36	1.15%
carboplatin + paclitaxel > carboplatin + doxorubicin	35	1.12%
carboplatin + paclitaxel > paclitaxel > carboplatin + paclitaxel > paclitaxel > carboplatin + paclitaxel > paclitaxel > carboplatin + paclitaxel > paclitaxel > carboplatin + paclitaxel > paclitaxel	28	0.90%
carboplatin + paclitaxel > doxorubicin > topotecan	26	0.83%
carboplatin + paclitaxel > paclitaxel > carboplatin + paclitaxel	23	0.74%
carboplatin > doxorubicin	23	0.74%
carboplatin > carboplatin + paclitaxel	20	0.64%
doxorubicin	20	0.64%
carboplatin + paclitaxel > paclitaxel	18	0.58%
carboplatin > paclitaxel	16	0.51%
carboplatin + paclitaxel > carboplatin > carboplatin + paclitaxel	13	0.42%

4.2.5.2 Bevacizumab

Patients receiving bevacizumab during their treatment trajectory show a large variation in use of bevacizumab (see Figure 5, Figure 6, and Figure 7).[c] None of the chemotherapy trajectories started with bevacizumab as chemotherapy substance. There is however considerable variation as to when bevacizumab is introduced in the treatment trajectory. On average, bevacizumab was introduced at the 12th session, but with a standard deviation of 10.9 sessions (median: 9, IQR: 7.6). Sometimes bevacizumab was given as the single chemical substance in the session, but it was also frequently used in combination with other ATC L01 chemical substances as well (see also Table 3). Bevacizumab is also always part of treatment trajectories involving other ATC L01 chemical substances.

Patients received on average 5.5 bevacizumab sessions, either single or in combination (SD: 4.1; median: 4; IQR: 7).

[c] Because of privacy considerations, Figure 5, Figure 6, and Figure 7 do not show labels on the axes. The vertical axis corresponds to individual treatment trajectories. The horizontal axis corresponds to time. Moreover, some random noise has been added to the individual data points to eliminate the possibility to reidentify treatment trajectories but keeping the overall trajectories as close as possible to the original ones. Trajectories for other stages are not shown because of the low number of patients.

Figure 5 – Chemotherapy trajectories in bevacizumab patients with stage III ovarian cancer. [c]

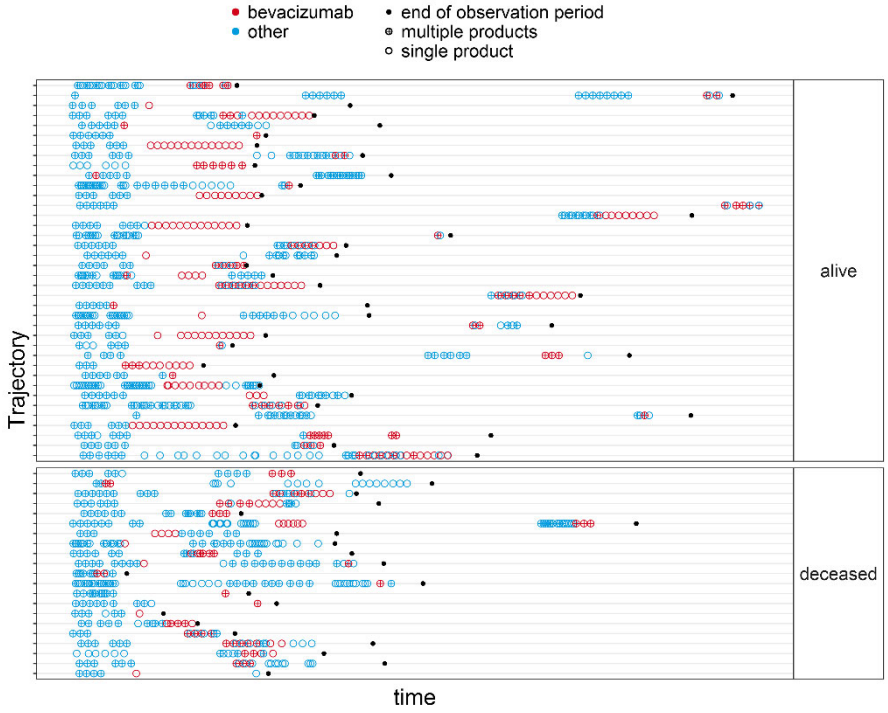


Figure 6 – Chemotherapy trajectories in bevacizumab patients with stage IV ovarian cancer. [c]

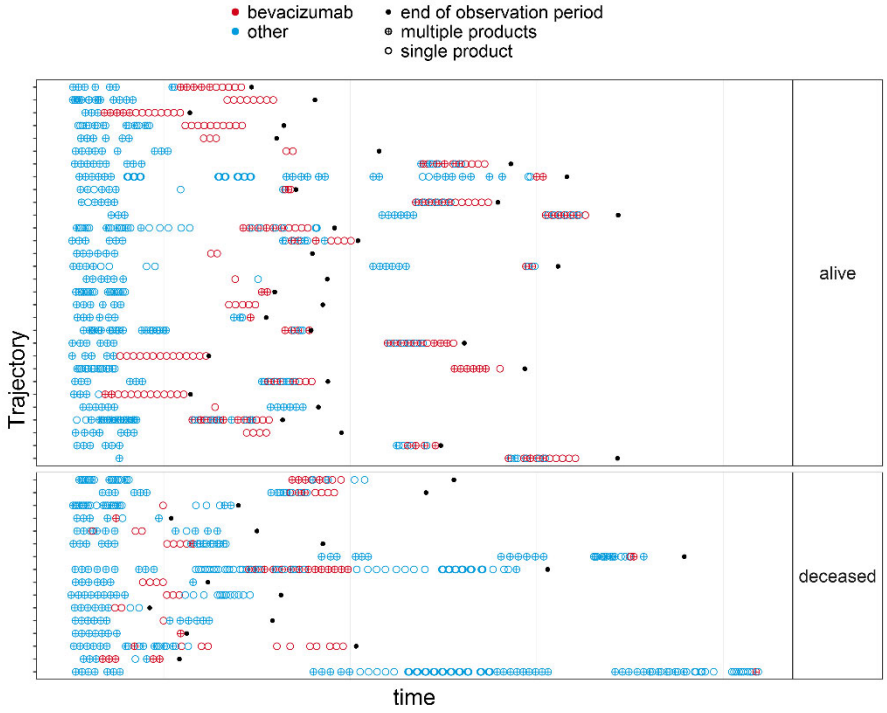


Figure 7 – Chemotherapy trajectories in bevacizumab patients with insufficient information on stage. [c]

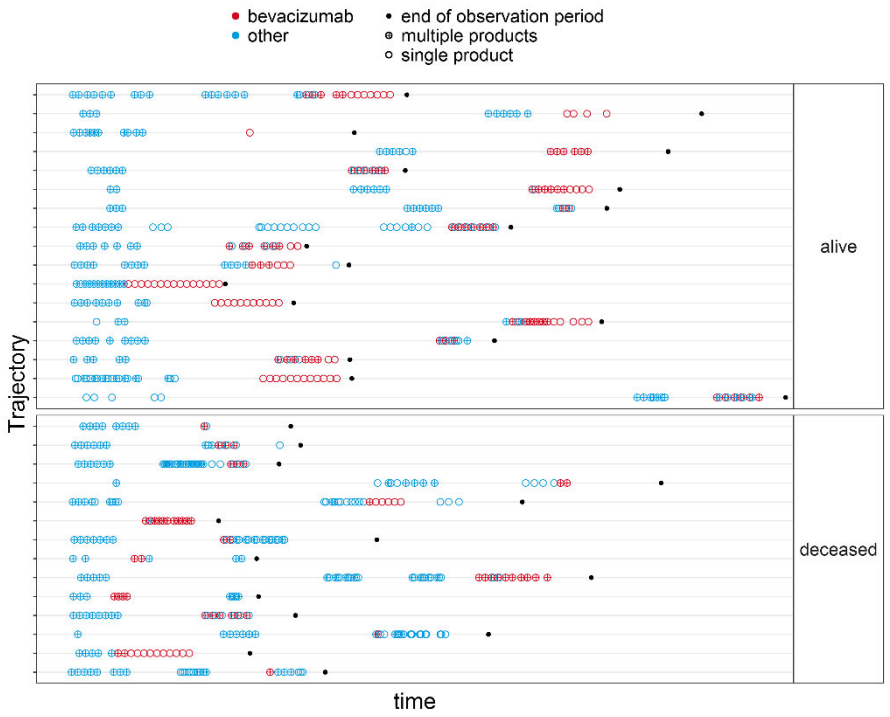
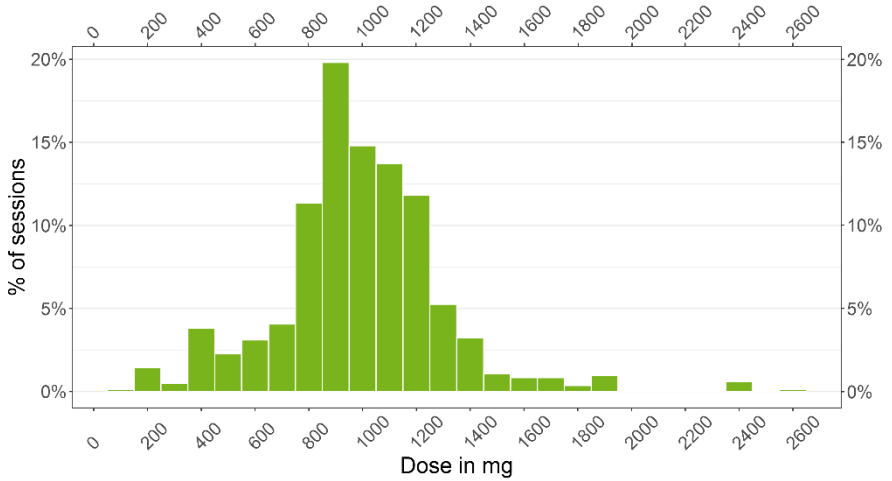


Figure 8 – Distribution of dose per session.



Bevacizumab dosage per session is related to the weight of the patient. The manufacturer reports a 15 mg/kg dose for treatment of ovarian cancer. Figure 8 shows the distribution of dosage per session. The majority of the sessions used a dose between 800 mg and 1200 mg, corresponding to a weight range of 53.4 kg to 80 kg. The lower doses could be explained by the recommended dose of 10 mg/kg for platinum-resistant recurring ovarian cancer. In that case, the doses 400 mg to 700 mg correspond to a weight range of 40 kg to 70 kg.

5 CLINICAL EFFECTIVENESS AND SAFETY

HTA CORE MODEL DOMAIN: EFF - SAF

5.1 Methods

This report was developed using a standard methodology based on a systematic review of the medical literature. Further details about the KCE methods are available at https://kce.fgov.be/content/kce-processes.

5.1.1 Clinical research question

The aim of the medical part of this report is to provide the evidence for the clinical effectiveness and safety of bevacizumab in patients with ovarian cancer. The clinical research question was formulated using the PICO (Participants–Interventions–Comparator–Outcomes) framework (Table 5).

Table 5 – Clinical research question

PICO item	Description
Population	Women with epithelial ovarian, fallopian or primary peritoneal cancer: • First-line setting: chemotherapy-naïve patients • Second-line setting: recurrence or progression after completion of front-line platinum-based chemotherapy o Platinum-sensitive disease o Platinum-resistant disease
Intervention	Bevacizumab
Comparator	No bevacizumab
Outcomes	Critical: • Overall survival • Progression-free survival • Quality of life Important: • Adverse events • Response to treatment

5.1.2 Literature search and study selection

A systematic literature review was performed by searching for (systematic reviews and meta-analyses of) randomized controlled trials (RCTs). The following databases were searched:

- The Cochrane Library (Cochrane Database of Systematic Reviews, DARE, HTA database, CENTRAL)
- Medline (including PreMedline)
- Embase

The search strategies are documented in the appendix.

HTA websites were also searched. In addition, the reference lists of included articles were checked for relevant publications that may have been missed. Included systematic reviews, meta-analyses and HTA reports only served as a source for primary studies.

To be eligible, a primary study had to:

- be a randomised trial;
- address the population, intervention and comparator as described in the PICO;
- evaluate at least one of the selected (critical and important) outcomes.

Study selection was performed by one researcher in two phases. Phase one consisted of screening the titles and abstracts of the retrieved studies and excluding studies for which it was obvious that they did not fulfill the inclusion criteria. Of the remaining studies (phase two), the full text was screened. If no full-text was available, the study was not taken into account. Studies published in a language other than English, Dutch or French were not included. A date limit was not imposed.

In addition to the search above, clinical experts and the manufacturer were asked to provide any information about unpublished trials and/or results. Furthermore, the FDA website and clinical trial registers were searched.

Since the identified RCTs contained very detailed information about adverse events, no separate search for safety data was carried out.

5.1.3 Quality appraisal and data extraction

Each study was appraised for methodological quality by one researcher. The quality of systematic reviews was assessed by the use of AMSTAR (http://amstar.ca/Amstar_Checklist.php).[15] For RCTs the Cochrane Collaboration's tool for assessing risk of bias was used.[16]

Data extraction was performed by one researcher and entered in evidence tables using standard KCE templates (see appendix 4). For each systematic review the following data were extracted: title and reference, funding sources, search date, databases being searched, number and types of included studies, details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics, details of the intervention and comparator groups that have been addressed in the review, results for the outcomes, and limitations and other comments regarding the review. For each RCT the following data were extracted: title, reference, source of funding, country and setting, sample size, duration and follow-up, details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics (including baseline comparability), details of the intervention and comparator (e.g. type, dose, duration, route of administration), results, and limitations and other comments regarding the study.

5.1.4 Statistical analysis

For dichotomous outcomes the risk ratio (RR) was used as the measure of treatment effect and for continuous outcomes the mean difference or – if applicable – the standardised mean difference. For time-to-event data, the hazard ratio (HR) was used.

Meta-analyses were performed according to the guidelines described in the Cochrane Handbook[17] and by the use of Review Manager software (RevMan 5.3). Results of studies that were sufficiently clinically homogeneous, i.e. sufficiently similar with respect to the patients, interventions, outcomes and timing of the follow-up measurements were combined by the use of a fixed-effect model. If the studies were statistically heterogeneous a random-effects model was used and – if sufficient studies available – heterogeneity was explored by subgroup analyses. Statistical heterogeneity was assessed by a combination of visual inspection of the forest plots, the Chi-square test for homogeneity (p-value set at 0.1 to increase the power of this test) and the I^2 statistic. The latter two statistics were interpreted in the light of the size of the studies included in the meta-analysis (e.g. if many large studies are included that have clinically irrelevant different effect estimates, the Chi-square test will become significant (due to high power) and I^2 will approach 100%; in that case the results of the visual inspection will dominate the judgment of heterogeneity).

In case of multiple publications about a specific study, the most recent data were used for meta-analysis.

5.1.5 GRADE

For each critical and important outcome, GRADE was used to grade the quality of the supporting evidence. For this report, GRADE for systematic reviews was used. For systematic reviews, quality of evidence refers to one's confidence in the estimates of effect. In systematic reviews each outcome is considered separately, in contrast to guidelines, where the evidence is assessed across all outcomes and studies for a particular recommendation.

Following the GRADE methodology, the quality of evidence was classified into four categories: high, moderate, low, and very low (Table 6 and Table 7). A more detailed description of the GRADE methodology can be found in the appendix and in the KCE process book. GRADE profiles are also reported in appendix 5.

Table 6 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 7 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

5.2 Results

5.2.1 Overview of selected studies

5.2.1.1 Systematic reviews, meta-analyses and HTA reports

Eight systematic literature reviews were included:[18-25]

- Four reviewed the effectiveness of bevacizumab as first-line treatment of ovarian cancer;[19, 21, 22, 24]
- Four reviewed the effectiveness of bevacizumab as second-line treatment of ovarian cancer;[18, 21, 22, 25]
- Eight reviewed the safety of bevacizumab.[18-25]

5.2.1.2 Randomised controlled trials

Five published RCTs were included, with a total of 4304 randomised women with epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer.[26-35] In addition, unpublished results of the GOG-0213 trial were provided by one of the clinical experts in the format of a powerpoint presentation (presented at the 2015 Annual Meeting on Women's Cancer in Chicago).[36]

Two multicentre trials evaluated bevacizumab in addition to standard chemotherapy as first-line treatment,[28-33] two multicentre trials evaluated bevacizumab in addition to standard chemotherapy as second-line treatment,[26, 27, 34] and one small single-centre study evaluated bevacizumab administered intraperitoneally in addition to standard intraperitoneal chemotherapy as first-line treatment.[35] The unpublished GOG-0213 trial evaluated bevacizumab in addition to standard chemotherapy +/- secondary cytoreductive surgery as second-line treatment (double randomisation). [36]

An overview of the bevacizumab IV treatment schedules is provided in Table 8.

Table 8 – Bevacizumab treatment schedules in RCTs evaluating IV treatment

Setting	Study	Bevacizumab schedule
First-line	GOG-0218	• Bevacizumab-initiation treatment: 15 mg/kg every 3 weeks for 5 cycles • Bevacizumab-throughout treatment: 15 mg/kg every 3 weeks for 21 cycles
	ICON7	7.5 mg/kg every 3 weeks for 5-6 cycles and continued for 12 additional cycles or until disease progression
Second-line	AURELIA	10 mg/kg every 2 weeks (or 15 mg/kg every 3 weeks in patients receiving topotecan in a schedule repeated every 3 weeks)
	OCEANS	15 mg/kg every 3 weeks
	GOG-0213	15 mg/kg every 3 weeks until disease progression or toxicity precludes further treatment

GOG-0218 trial

The GOG-0218 trial[28-30] randomised 1 873 women with previously untreated, incompletely resectable stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian-tube cancer to (1) six 3-week cycles of standard chemotherapy (carboplatin plus paclitaxel) plus placebo starting with cycle 2 and sixteen additional cycles of placebo, (2) six 3-week cycles of the same standard chemotherapy plus bevacizumab (15 mg/kg on day 1 starting with cycle 2) and sixteen additional cycles of placebo (bevacizumab-initiation group), or (3) six 3-week cycles of the same standard chemotherapy plus bevacizumab (15 mg/kg on day 1 starting with cycle 2) and sixteen additional cycles of bevacizumab (bevacizumab-throughout group). The primary endpoint was initially specified as overall survival, but was changed to progression-free survival during the trial. Other endpoints were quality of life (measured with the FACT-O TOI instrument) and adverse events.

The trial had an unclear allocation concealment. It was supported by Genentech, and several authors had financial links with Genentech. Attrition bias was present for quality of life and adverse events.

ICON7 trial

The ICON7 trial[31-33] randomised 1 528 women with early-stage (stage I or IIA) high-risk disease (clear-cell or grade 3 tumours) or advanced (stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer to six 3-week cycles of standard chemotherapy (carboplatin plus paclitaxel) with or without bevacizumab (7.5 mg/kg on day 1) given concurrently every three weeks for five or six cycles and continued for twelve additional cycles or until disease progression. Primary endpoints were progression-free and overall survival. Other endpoints were treatment response, quality of life (measured with the EORTC QLQ-C30 and QLQ-OV28 instruments) and adverse events.

It was unclear if the participants were blinded to treatment assignment. Attrition bias was present for quality of life and adverse events. The trial was supported by Roche, and several authors had financial links with Roche.

AURELIA trial

The AURELIA trial[26, 27] randomised 361 women with epithelial ovarian, fallopian tube, or primary peritoneal cancer that had progressed within six months of completing at least four cycles of platinum-based therapy (i.e. platinum-resistant) to single-agent chemotherapy (paclitaxel, pegylated liposomal doxorubicin or topotecan) with or without bevacizumab (10 mg/kg every 2 weeks, or 15 mg/kg every 3 weeks for practical reasons in patients receiving topotecan in a schedule repeated every 3 weeks). The primary endpoint was progression-free survival. Additional endpoints were overall survival, treatment response, quality of life (measured with the EORTC QLQ-C30, EORTC QLQ-OV28 and FOSI instruments) and adverse events. The authors hypothesized that chemotherapy would improve disease-related symptoms in some women, and that adding bevacizumab would be associated with greater improvements, particularly in women with abdominal symptoms and/or ascites at baseline.

The study was unblinded and had attrition bias for quality of life. It was supported by Roche, and several authors had financial links with Roche.

OCEANS trial

The OCEANS trial[34] randomised 484 women with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer and disease progression at least six months after completion of front-line platinum-based chemotherapy to six to ten 3-week cycles of second-line chemotherapy (gemcitabine plus carboplatin) plus placebo or the same chemotherapy plus bevacizumab (15 mg/kg on day 1). The primary endpoint was progression-free survival. Additional endpoints were overall survival, treatment response and adverse events.

The study was of good methodological quality. It was supported by Genentech, and several authors had financial links with Genentech.

GOG-0213 trial

The GOG-0213 trial[36] included 674 women with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer and disease progression at least six months after completion of front-line therapy. Prior treatment with bevacizumab was allowed. With a double randomisation method, surgical candidates were first randomised to surgery or no surgery and then to chemotherapy (carboplatin plus paclitaxel) with or without bevacizumab (15 mg/kg every 3 weeks until disease progression). In addition, non-surgical candidates were randomised to chemotherapy (carboplatin plus paclitaxel) with or without bevacizumab (also 15 mg/kg every 3 weeks until disease progression). The primary endpoint was overall survival. Additional endpoints were progression-free survival, quality of life (measured with the FACT-O TOI instrument), treatment response and adverse events.

Because the results were not yet published in a peer-reviewed journal at the time of the writing of this report, the methodological quality could not be assessed in full. However, the trial had an open design, and attrition bias was present for adverse events. The trial was supported by Genentech.

Zhao et al.

Zhao et al.35 randomised 58 women with stage IIC-IV ovarian epithelial cancer and malignant ascites to standard chemotherapy (paclitaxel and carboplatin every 3 weeks) and intraperitoneal cisplatin (every 2 weeks) with or without intraperitoneal bevacizumab (300 mg every 2 weeks). The primary endpoint was treatment response (according to the WHO's criteria). Additional endpoints were the performance status (assessed with the Karnofsky Performance Status) and adverse events.

The trial had an unclear allocation concealment. It was unclear if the participants, clinicians and assessors were blinded.

Table 9 – Quality of life instruments used in RCTs evaluating bevacizumab for ovarian cancer

Instrument	Generic / specific	Domains (items)	Domain description	Scaling & scoring / administration
EORTC QLQ-C30	Cancer-specific	10 (30)	Functional domains: Physical; Role; Emotional; Cognitive; Social; Global QoL Symptom domains: Fatigue; Nausea/vomiting; Pain Single-item domains: Dyspnea, appetite loss, sleep disturbance, constipation, diarrhea	Physical and role function, dichotomous (Yes/No); Global QoL, 7-point scale; Other items, 4-point Likert scale ranging from 1 (not at all) to 4 (very much) Scale scores = mean of item scores, rescaled to 0 to 100, with higher function subscale scores indicating less dysfunction and higher symptom subscale scores indicating more dysfunction Self-administered, interviewer-administered
EORTC QLQ-OV28	Disease-specific	7 (28)	Abdominal symptoms, peripheral neuropathy, other chemotherapy-related side effects, hormonal symptoms, body image, sexual functioning and attitudes towards disease and treatment	4-point Likert scale ranging from 1 (not at all) to 4 (very much) All scale scores are transformed into 0-100 from a recoded summation of item scores in each scale; a higher score reflects greater symptom burden Self-administered, interviewer-administered
FACT-O TOI	Disease-specific	3 (26)	FACT-G physical well-being subscale (7 items) FACT-G functional well-being subscale (7 items) FACT-O subscale (12 items): additional concerns	5-point scale ranging from 0 (not at all) to 4 (very much) Scale score = sum of subscale scores; a higher score represents better wellbeing Self-administered
FOSI	Disease-specific	1 (8)	Symptom response to ovarian cancer treatment	5-point scale ranging from 0 (not at all) to 4 (very much) Scale score = sum of scores; a higher score represents better wellbeing and less symptom burden Self-administered

5.2.2 Effectiveness in first-line

5.2.2.1 Progression-free survival

Two trials evaluated the effect of first-line intravenous bevacizumab on progression-free survival and could be combined (NB: for the GOG-0218 trial only the data of the bevacizumab-throughout group were used in the meta-analysis).[28, 31] The pooled estimate showed no significant effect on progression-free survival (HR = 0.85, 95%CI 0.70-1.02), although the data from the two trials were discordant (I^2 = 80%). A potential explanation for this discordance is the different definition for progression-free survival that was used and the less intensive schedule that was used in the ICON7 trial.[31] Since pooling was therefore considered inappropriate, individual results are presented: in the ICON7, a non-significant effect was found (HR = 0.93, 95%CI 0.83-1.05), while the GOG-0218 trial found a significant effect for the bevacizumab-throughout group (HR = 0.77, 95%CI 0.68-0.87; updated analysis). An analysis of progression-free survival, in which data for patients with increased CA-125 levels were censored, showed an even stronger effect in the bevacizumab-throughout group (HR = 0.65, 95%CI 0.55-0.76; primary analysis).

No significant effect was found in the bevacizumab-initiation arm of the GOG-0218 trial (HR = 0.91, 95%CI 0.80-1.04).[28] A comparison between the bevacizumab-initiation and bevacizumab-throughout group was not reported. Subgroup analyses showed a significant effect in the bevacizumab-throughout group for stage III cancer with a maximal residual lesion diameter ≤1 cm (HR = 0.62), stage III cancer with a maximal residual lesion diameter >1 cm (HR = 0.76) and stage IV cancer (HR = 0.70). No significant effect was found in the bevacizumab-initiation arm for these subgroups.

In the ICON7 trial,[31] based on a Cox regression analysis (reported in supplementary appendix, and predefined in the statistical plan), patients with a high risk for progression (FIGO stage IV disease, or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery) were found to have a better progression-free survival when treated with bevacizumab (HR = 0.73, 95%CI 0.61-0.88). Subgroup analyses for the predefined strata showed a significantly better progression-free survival when treated with bevacizumab for FIGO stages I-III and >1 cm of residual disease (HR = 0.72, 95%CI 0.54-0.95) and for FIGO stage III (inoperable) or IV (HR = 0.66, 95%CI 0.48-0.91).[32]

5.2.2.2 Overall survival

Two trials evaluated the effect of first-line intravenous bevacizumab on overall survival and could be combined (NB: for the GOG-0218 trial only the data of the bevacizumab-throughout group were used in the meta-analysis).[28, 31] The pooled estimate showed no significant effect (HR = 0.94, 95%CI 0.84-1.05), and no heterogeneity was found despite the difference in dosage. No significant effect was found in both trials separately. Both trials reported overall survival as a secondary outcome, and were not powered to detect a significant difference.

Also no significant effect was found in the bevacizumab-initiation arm of the GOG-0218 trial (HR = 1.078, 95%CI 0.919-1.270).[28] Again, a comparison between the bevacizumab-initiation and bevacizumab-throughout group was not reported. Subgroup analyses (published as an abstract) showed a significant effect in the bevacizumab-throughout group for stage IV cancer (HR = 0.72, 95%CI 0.53-0.97), but not for stage III cancer with a maximal residual lesion diameter ≤1 cm (HR = 0.97, 95%CI 0.70-1.34) or stage III cancer with a maximal residual lesion diameter >1 cm (HR = 0.98, 95%CI 0.77-1.26).[37] No significant effect was found in the bevacizumab-initiation arm for these subgroups.

In the ICON7 trial,[31] based on a Cox regression analysis (reported in supplementary appendix, and predefined in the statistical plan), patients with a high risk for progression (FIGO stage IV disease, or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery) were found to have a better overall survival when treated with bevacizumab (HR = 0.78, 95%CI 0.63-0.97). For the predefined strata, no results for overall survival were reported.

5.2.2.3 Treatment response

One trial reported the best overall response (RECIST criteria) to first-line intravenous bevacizumab,[32] which was defined as the best confirmed response recorded from the start of treatment until 70 days after the last dose of per-protocol treatment. The rate of complete or partial remission was 48% in the standard chemotherapy group and 67% in the bevacizumab group (MD = 19%, 95%CI 11-28%; p<0.001).

Another trial reported the overall response (according to the WHO's criteria) to first-line intraperitoneal bevacizumab.[35] The rate of complete response at 6 weeks was 41% in the control group and 58% in the bevacizumab group. The rate of partial response was 19% versus 32%.

5.2.2.4 Quality of life

Two trials reported the effect of first-line intravenous bevacizumab on quality of life. In the GOG-0218 trial quality of life was assessed with the FACT-O TOI instrument.[30] Both bevacizumab-arms reported lower QoL scores than those in the control group. The treatment differences were observed mainly at cycle 4, when the patients receiving bevacizumab (bevacizumab-initiation and bevacizumab-throughout) reported 2.72 points (98.3%CI 0.88-4.57; effect size = 0.18) and 2.96 points (98.3%CI 1.13-4.78; effect size = 0.20) lower QoL scores, respectively, than those in the control group. The difference in QoL scores between the control group and the bevacizumab-throughout group remained statistically significant up to cycle 7 (MD = -2.2; 95%CI -3.75 to -0.65). In the ICON7 trial quality of life was assessed with the EORTC QLQ-C30 and QLQ-OV28 instruments.[33] The mean EORTC QLQ-C30 global health QoL subscale score at 54 weeks was lower in the bevacizumab group than in the standard chemotherapy group (69.7 vs. 76.1 points; MD = -6.4, 95%CI -9.0 to -3.7, p<0.0001). In the assessment report of NICE (TA284) EQ-5D scores are also reported,[24] although these were never published in a peer-reviewed article (the study protocol stated that the EQ-5D assessment was part of the economic assessment). A log-rank test confirmed that there was no difference in utility values whilst patients were progression-free across the intervention and control arms. Furthermore, a trend test suggested that utility values did change over time.

Both trials could be pooled for global QoL at 18 and 54-60 weeks (NB: for the GOG-0218 trial only the data of the bevacizumab-throughout group were used in the meta-analysis). At 18 weeks a significant better QoL was found for the standard chemotherapy group (SMD = -0.21; 95%CI -0.29 to -0.13). At 54-60 weeks no significant difference was found (SMD = -0.13; 95%CI -0.52 to 0.26), although the data from the two trials were discordant (I^2 = 94% and non-overlapping confidence intervals).

One trial reported the effect of first-line intraperitoneal bevacizumab on the Karnofsky Performance Status, a functionality measure and not a QoL measure.[35] 94% in the bevacizumab group had an improvement vs. 48% in the control group (p=0.0068).

5.2.3 Effectiveness in second-line

5.2.3.1 Progression-free survival

Two published trials evaluated the effect of second-line intravenous bevacizumab on progression-free survival and could be combined.[26, 34] The pooled estimate showed a strong significant effect in favour of bevacizumab after a median follow-up of 13-24 months (HR = 0.48; 95%CI 0.41-0.57). The median progression-free survival in the bevacizumab groups of both trials was 12.4 and 6.7 months, respectively, versus 8.4 and 3.4 months in the control groups.

The unpublished GOG-0213 trial also reported a significant effect in favour of bevacizumab (HR = 0.61; 95%CI 0.52-0.72).[36] The median progression-free survival was 13.8 months in the bevacizumab group versus 10.4 months in the control group. Adding these data to the meta-analysis resulted in a slightly higher HR (0.54; 95%CI 0.48-0.61).

In a letter to the editor, subgroup analyses of the AURELIA trial were reported.[38] In all three predefined chemotherapy cohorts progression-free survival was significantly improved by adding bevacizumab to chemotherapy (paclitaxel: HR = 0.46, 95%CI 0.30-0.71; pegylated liposomal doxorubicin: HR = 0.57, 95%CI 0.39-0.83; topotecan: HR = 0.32, 95%CI 0.21-0.49).

5.2.3.2 Overall survival

Two published trials evaluated the effect of second-line intravenous bevacizumab on overall survival and could be combined.[26, 34] The pooled estimate showed no significant effect (HR = 0.93; 95%CI 0.77-1.12).

The unpublished GOG-0213 trial also reported no significant effect on overall survival, although there was at least a trend towards improved survival with bevacizumab (HR = 0.83; 95%CI 0.68-1.01).[36] Adding these data to the meta-analysis resulted in a slightly lower HR in favour of bevacizumab (0.88; 95%CI 0.77-1.01).

These trials reported overall survival as a secondary outcome, and were not powered to detect a significant difference.

Subgroup analyses of the AURELIA trial[38] showed that in none of the three predefined chemotherapy cohorts overall survival was significantly improved by adding bevacizumab to chemotherapy, although the effect in the paclitaxel cohort was more pronounced (paclitaxel: HR = 0.65, 95%CI 0.42-1.02; pegylated liposomal doxorubicin: HR = 0.91, 95%CI 0.62-1.36; topotecan: HR = 1.09, 95%CI 0.72-1.67).

5.2.3.3 Treatment response

Two published trials reported the best overall response to second-line intravenous bevacizumab (evaluated according to RECIST) and could be combined.[26, 34] The pooled estimate showed a significantly higher response rate with bevacizumab compared with standard chemotherapy (MD = 19%; 95%CI 13-26%).

The unpublished GOG-0213 trial also reported a significantly higher response rate with bevacizumab compared with standard chemotherapy (78.7% vs. 58.5%, p<0.0001). [36] However, the data could not be added to the meta-analysis because the absolute numbers were not available.

Our pooled results confirm those of the three identified systematic reviews that reported this outcome.[21, 22, 25]

5.2.3.4 Quality of life

One published trial reported the effect of second-line intravenous bevacizumab on quality of life.[27] As reported above, quality of life was measured with the EORTC QLQ-OV28, EORTC QLQ-C30 and FOSI instruments. Week 8/9 was predefined as the primary analysis time point, with week 16/18 as a secondary analysis time point. The primary hypothesis was that a higher proportion of women in the bevacizumab group would experience a ≥15% improvement in an abdominal/GI symptom subscale comprising items 31 to 36 of the EORTC QLQ-OV28 instrument. Prespecified secondary hypotheses were that similar proportions of women in the two treatment groups would experience ≥15% improvements in FOSI and in the EORTC QLQ-C30 physical, role, emotional, social functioning, and global health-related QoL subscales. A responder (improvement) analysis approach was adopted, with improvement defined as a 15-point (15%) absolute increase in the 100-point scale. In addition, a linear mixed-model repeated-measures (MMRM) analysis, adjusting for score at baseline, time, and a treatment-by-time interaction, was used to estimate the treatment effect over time.

At week 8/9, significantly more patients treated with bevacizumab reported a ≥15% improvement in abdominal/GI symptoms (21.9% vs. 9.3%; difference = 12.7%, 95%CI 4.4-20.9%; p=0.002). Similar results were reported at 16-18 weeks (15.5% vs. 5.6%; difference = 9.9%, 95%CI 2.9-17.0%; p=0.005). The MMRM analysis showed a 6.4-point difference favoring the bevacizumab arm (95%CI 1.3-11.6; p=0.015).

Significantly more patients treated with bevacizumab showed a ≥15% improvement in FOSI score at week 8/9 (12.2% vs. 3.1%; difference = 9.0%; 95%CI 2.9-15.2%; p=0.003). Similar results were reported at 16-18 weeks (9.0% vs. 1.3%; difference = 7.7%, 95%CI 2.6-12.9%; p=0.002). The MMRM analysis did not show an important treatment effect (estimated between-treatment group difference = 0.7; 95%CI -0.3 to 1.8; p=0.21).

Significantly more patients treated with bevacizumab showed at least 15% improvement on the global health item of the EORTC QLQ-C30 at 8-9 weeks (24.4% vs. 13.0%, p=0.011). The MMRM analysis of the EORTC QLQ-C30 global health QoL subscale showed no significant difference between treatment groups (estimated between-treatment group difference = 2.2; 95%CI -3.08 to 7.40).

Subgroup analyses[38] showed that in all three predefined chemotherapy cohorts numerically more patients receiving bevacizumab achieved ≥15% improvement in abdominal/GI symptoms at 8-9 weeks (paclitaxel: 25.0% vs. 13.0%, difference = 12.0%, 95%CI -4.9% to 28.9%; pegylated liposomal doxorubicin: 21.1% vs. 6.8%, difference = 14.3%, 95%CI 0.9% to 27.6%; topotecan: 20.0% vs. 8.8%, difference = 11.2%, 95%CI -3.2% to 25.7%).

The unpublished GOG-0213 trial showed no significant effect on quality of life measured with the FACT-O TOI instrument (mean score at 12 months post-cycle 1: bevacizumab 77.8 vs. no bevacizumab 77.0, p=0.479).[36]

5.2.4 Safety

5.2.4.1 Data from randomised trials

All included trials reported safety data, of which the data from the four published trials on intravenous bevacizumab could be pooled.[26, 28, 32, 34] Significant adverse events with bevacizumab were found for: gastrointestinal perforation (≥ grade 2: 4 studies, RR = 2.90, 95%CI 1.44-5.82), hypertension (≥ grade 2: 3 studies, RR = 5.36, 95%CI 2.36-12.15; ≥ grade 3: 2 studies, RR = 29.15, 95%CI 9.23-92.02), proteinuria (any grade: 2 studies, RR = 1.84, 95%CI 1.07-3.18; ≥ grade 3: 3 studies, RR = 4.31, 95%CI 1.74-10.68), pain (≥ grade 2: 1 study, RR = 1.13, 95%CI 1.00-1.28), thrombocytopenia (any grade: 1 study, RR = 1.36, 95%CI 1.01-1.83), venous thromboembolism (≥ grade 3: 2 studies, RR = 2.19, 95%CI 1.29-3.74), arterial thromboembolism (any grade: 4 studies, RR = 2.15, 95%CI 1.08-4.30), wound healing complication (any grade: 2 studies, RR = 2.34, 95%CI 1.31-4.16; ≥ grade 3: 3 studies, RR = 3.55, 95%CI 1.09-11.59), bleeding (any grade: 2 studies, RR = 2.78, 95%CI 1.13-6.85), non-CNS bleeding (≥ grade 3: 2 studies, RR = 3.55, 95%CI 1.46-8.61), and mucocutaneous bleeding (any grade: 1 study, RR = 5.07, 95%CI 3.87-6.65). These findings were confirmed by most of the included systematic reviews.[18, 19, 21-23] Only Huang et al. found significantly more fatal adverse events with bevacizumab, but did not include the results of the AURELIA trial.[20]

For several adverse events, the unpublished GOG-0213 reported data that could be added to the meta-analysis.[36] However, no substantial changes occurred (forest plots reported in appendix 6).

Zhao et al. reported no grade 3-4 complications with intraperitoneal bevacizumab.[35]

5.2.4.2 FDA data

On November 14, 2014, the Food and Drug Administration (FDA) approved bevacizumab, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (www.fda.gov, accessed on February 8, 2016). This approval was based on the results of the AURELIA trial.[26] However, no accompanying review was published on the FDA website.

5.2.5 Ongoing trials

The following trial registers were searched on February 8, 2016 to identify ongoing trials: www.clinicaltrials.gov, www.controlled-trials.com, **Error! Hyperlink reference not valid.**, http://www.who.int/ictrp/en/, and www.trialregister.nl. Six potentially relevant studies were identified (Table 10).

Table 10 – Overview of ongoing studies with bevacizumab in ovarian cancer

Trial	Target population	Intervention	Control	Estimated enrolment	Study completion date
First-line					
NCT01462890 (BOOST)	FIGO stage IIb-IV	Standard chemotherapy plus bevacizumab 15 mg/kg every 3 weeks up to 22 cycles	Standard chemotherapy plus bevacizumab 15 mg/kg every 3 weeks up to 44 cycles	N=800	November 2021
NCT01081262 (GOG-0241)	FIGO stage II-IV (new or recurrent chemonaïve) FIGO stage I (recurrent chemonaïve)	Carboplatin + paclitaxel + bevacizumab every 3 weeks up to 12 cycles (dose not reported) Oxaliplatin + capecitabine + bevacizumab every 3 weeks up to 12 cycles (dose not reported)	Carboplatin + paclitaxel Oxaliplatin + capecitabine	N=332	July 2020
ISRCTN10356387 (ICON8B)	High-risk FIGO stage III-IV	Dose-dense carboplatin + paclitaxel, plus bevacizumab 7.5 mg/kg every 3 weeks up to 18 cycles	Dose-dense carboplatin + paclitaxel Standard carboplatin + paclitaxel, plus bevacizumab 7.5 mg/kg every 3 weeks up to 18 cycles	N=2655	May 2022
Second-line					
NCT01802749	Recurrent or progressive disease Platinum-sensitive	Pegylated liposomal doxorubicin or gemcitabine or paclitaxel, plus bevacizumab 15 mg/kg every 3 weeks	Pegylated liposomal doxorubicin or gemcitabine or paclitaxel	N=400	July 2017
NCT00565851 (GOG-0213)	Recurrent disease Platinum-sensitive	Paclitaxel and carboplatin, plus bevacizumab 15 mg/kg every 3 weeks	Paclitaxel and carboplatin	N=1038	March 2019
UMIN000017247 (JGOG-3023)	Recurrent or progressive disease Platinum-resistant	Standard chemotherapy + bevacizumab (dose not reported)	Standard chemotherapy	N=106	Not reported

5.3 Conclusions

First-line bevacizumab

Progression-free survival

- If only the **GOG-0218** trial is considered, which evaluated a more intensive schedule with bevacizumab than the ICON7 trial, a significant effect on progression-free survival is seen *(according to the GRADE system, there is a moderate confidence in the effect estimate, which is due to methodological constraints).*
- In the **ICON7** trial, no significant effect on progression-free survival was found *(according to the GRADE system, there is a moderate confidence in the effect estimate, which is due to methodological constraints)*. However, a subgroup analysis in **patients with a high risk for progression** (FIGO stage IV disease, or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery) showed a significantly better progression-free survival in the group treated with bevacizumab *(according to the GRADE system, there is a low confidence in the effect estimate, which is due to methodological constraints)*.
- When the results of both published studies (**GOG-0218 and ICON7**) are combined, the pooled estimate shows no significant effect of bevacizumab on progression-free survival in patients with previously untreated advanced stage epithelial ovarian, primary peritoneal, or fallopian-tube cancer *(according to the GRADE system, there is a very low confidence in the effect estimate, which is mainly due to the imprecision of the estimate and the inconsistency between the two trials, making pooling inappropriate).*

Overall survival

- When the results of both published studies (**GOG-0218 and ICON7**) are combined, the pooled estimate shows no significant effect of bevacizumab on overall survival in patients with previously untreated advanced stage epithelial ovarian, primary peritoneal, or fallopian-tube cancer. This is also the case for both trials individually. Both trials reported overall survival as a secondary outcome, and were not powered individually to detect a significant difference. *(According to the GRADE system, there is a moderate confidence in these effect estimates, which is due to methodological constraints).*
- A subgroup analysis of the **GOG-0218** trial (published as an abstract) showed a significant effect on overall survival for **patients with stage IV cancer** (a*ccording to the GRADE system, there is a low confidence in the effect estimate, which is due to methodological constraints and imprecision of the estimate).*
- In the **ICON7** trial, a subgroup analysis in **patients with a high risk for progression** (FIGO stage IV disease, or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery) showed a significantly better overall survival in the group treated with bevacizumab *(according to the GRADE system, there is a low confidence in the effect estimate, which is due to methodological constraints).*

Quality of life

- When the results of both published studies (**GOG-0218 and ICON7**) are combined, the pooled estimate shows that bevacizumab is associated with an early (at 18 weeks) worse quality of life in patients with previously untreated advanced stage epithelial ovarian, primary peritoneal, or fallopian-tube cancer. This also the case for both trials individually. *(According to the GRADE system, there is a moderate confidence in the effect estimates, which is due to methodological constraints).*
- This negative effect on the quality of life disappears in the long run (at 54-60 weeks) *(according to the GRADE system, there is a very low confidence in the effect estimate, which is mainly due to the imprecision of the estimate and the inconsistency between the two trials).* In the **GOG-0218** trial no effect was found at 60 weeks, while in the **ICON7** trial a persistent worse quality of life was found at 54 weeks *(according to the GRADE system, there is a moderate confidence in these effect estimates, which is due to methodological constraints).*
- Quality of life results were not reported for subgroups.

Second-line bevacizumab

Progression-free survival

- Bevacizumab has a positive effect on progression-free survival in patients with recurrent epithelial ovarian, primary peritoneal, or fallopian-tube cancer, both in platinum-sensitive (**OCEANS** trial) and platinum-resistant populations (**AURELIA** trial).
  (According to the GRADE system, there is a moderate confidence in the effect estimate, which is due to methodological constraints).

Overall survival

- Bevacizumab has no significant effect on overall survival in patients with recurrent epithelial ovarian, primary peritoneal, or fallopian-tube cancer. The conclusion holds, both in platinum-sensitive populations (**OCEANS** trial) and platinum-resistant populations (**AURELIA** trial). Both trials reported overall survival as a secondary outcome, and were not powered individually to detect a significant difference.
  (According to the GRADE system, there is a moderate confidence in the effect estimate, which is due to methodological constraints).

Quality of life

- Bevacizumab increases the proportion of patients achieving a 15% improvement in patient-reported abdominal/gastrointestinal symptoms (measured with EORTC QLQ-OV28) during chemotherapy in patients with recurrent platinum-resistant epithelial ovarian, primary peritoneal, or fallopian-tube cancer. This treatment effect extends until 30 weeks.
  (According to the GRADE system, there is a very low confidence in the effect estimate, which is due to methodological constraints and the imprecision of the estimate).
- No differences in quality of life were found with other instruments (FOSI and EORTC QLQ-C30).

Safety of bevacizumab in patients with epithelial ovarian, primary peritoneal, or fallopian-tube cancer

- Bevacizumab is associated with significant adverse events (gastrointestinal perforation, hypertension, proteinuria, pain, thrombocytopenia, venous thromboembolism, arterial thromboembolism, wound healing complication, bleeding, non-CNS bleeding, mucocutaneous bleeding) in patients with epithelial ovarian, primary peritoneal, or fallopian-tube cancer.
  (According to the GRADE system, there is a moderate confidence in the effect estimate, which is due to methodological constraints).

6 COST-EFFECTIVENESS OF BEVACIZUMAB IN OVARIAN CANCER: LITERATURE REVIEW

HTA CORE MODEL DOMAIN: ECO

6.1 Literature search

6.1.1 Search strategy

A systematic search for economic literature about the cost-effectiveness of bevacizumab for the treatment of ovarian cancer was performed by consulting various databases. First of all, reviews on this topic were searched by consulting the CRD (Centre for Reviews and Dissemination) HTA database and websites of HTA institutes mentioned on the INAHTA (International Network of Agencies for Health Technology Assessment) website. Websites of ex- or non-member HTA institutes such as NICE (National Institute for Health and Care Excellence) were also consulted. We also consulted the non-public POP database (Planned and Ongoing Projects) accessible to EUnetHTA partners (European Network for Health Technology Assessment).

The NHS EED (CRD's Economic Evaluation Database), Medline (OVID), and EMBASE databases were searched to retrieve both full economic evaluations and reviews of full economic evaluations of bevacizumab in ovarian cancer. No language restrictions were imposed.

The search strategy started in February 2016 by looking for HTA reports on websites of HTA institutes and consulting CRD's HTA database. In October 2016, CRD's databases, Medline (OVID), and EMBASE were searched. An overview of this search strategy and results is provided in Appendix.

6.1.2 Selection criteria

All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, comparator, and design (Table 11). For the population, intervention and comparator, we refer to the medical in- and exclusion criteria (see part 5.1.1). The design is restricted to full economic evaluations, i.e. studies comparing at least two alternative treatments in terms of costs and outcomes. Cost-minimization, cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses were eligible.

The selection of relevant articles was performed in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of a full-text assessment. Reference lists of the selected studies were checked for additional relevant citations. The primary full economic evaluations were summarized in an in-house data extraction sheet (see appendix). This in-house document is used as a reporting checklist to gather all relevant information. The data extraction sheets of all identified studies are working documents that provide the basis for summary tables and a critical assessment of identified economic evaluations.

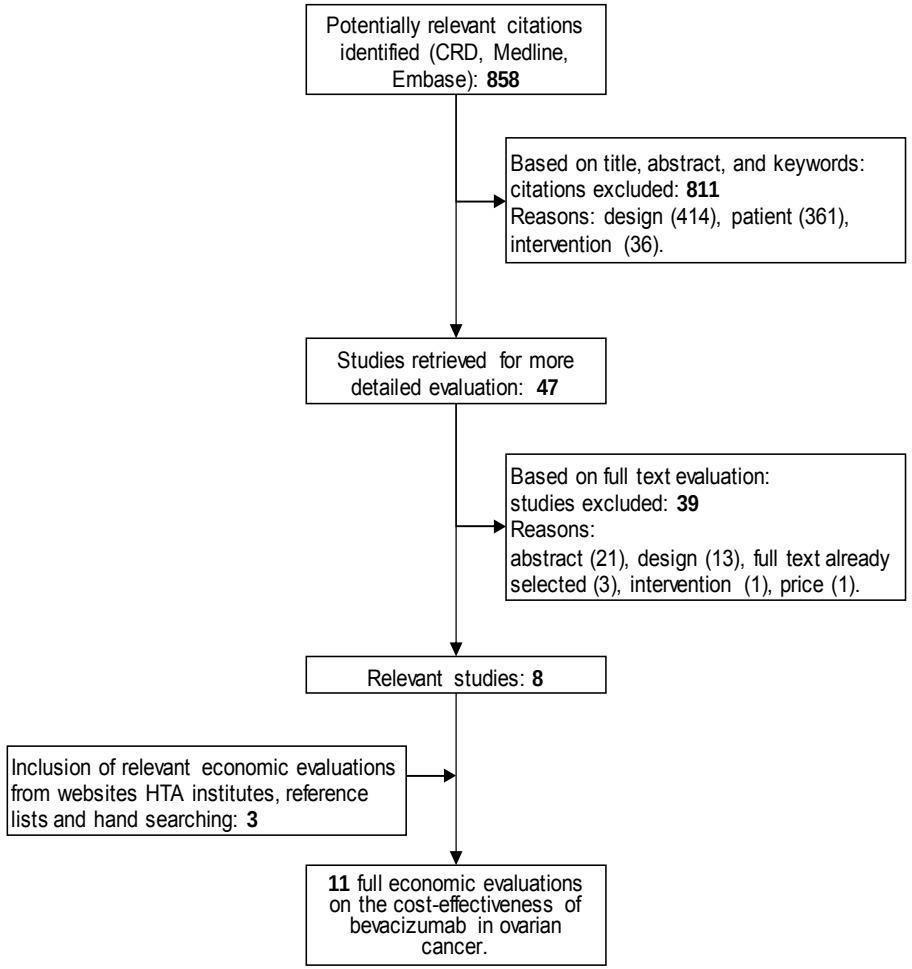
Table 11 – Economic evaluation selection criteria

	Inclusion criteria	Exclusion criteria
Population, Intervention and Comparator	See Table 5 in part 5.1.1	
Design	Full economic evaluations	Other designs such as cost calculations

6.2 Results of the economic search strategy

Figure 9 provides the flow chart of the selection process. Eight articles were identified in electronic databases.[39-46] Two manufacturer submissions published by NICE[47, 48] were included. The related Evidence Review Group (ERG) evaluations were also consulted.[49, 50] One extra reference was identified when searching for an article that initially could not be retrieved. It was found out that it was an abstract of an article that became published in October 2016.[51] The list of selected economic evaluations is provided in Table 12.

Figure 9 – Selection of relevant articles



CRD: Centre for Reviews and Dissemination; EED: Economic Evaluation Database; HTA: Health Technology Assessment.

Table 12 – List of selected economic evaluations

References
HTA reports
National Institute for Health and Care Excellence (NICE). Bevacizumab in combination with carboplatin and paclitaxel for the treatment of advanced ovarian cancer [TA284]; August 2012.[47] Cooper K, Pickett K, Frampton GK, Copley V, Bryant J. Bevacizumab in combination with carboplatin and paclitaxel for the first-line treatment of ovarian cancer. A Single Technology Appraisal. SHTAC. 2012[49]
National Institute for Health and Care Excellence (NICE). Bevacizumab for the treatment of recurrent advanced ovarian cancer [TA285]; September 2012.[48] Edwards SJ, Barton S, Thurgar E, Nherera L, Hamilton V, Karner C, Trevor N. Bevacizumab for the treatment of recurrent advanced ovarian cancer: A Single Technology Appraisal. BMJ-TAG, London, 2012.[50]
Articles
Barnett JC, Alvarez Secord A, Cohn DE, Leath CA, Myers ER, Havrilesky LJ. Cost effectiveness of alternative strategies for incorporating bevacizumab into the primary treatment of ovarian cancer. Cancer. 2013 30 Aug 2013;119(20):3653-61.[39]
Chan JK, Herzog TJ, Hu L, Monk BJ, Kiet T, Blansit K, et al. Bevacizumab in treatment of high-risk ovarian cancer: a cost-effectiveness analysis. Oncologist. 2014 09 Oct 2014;19(5):523-7.[40]
Chappell NP, Miller CR, Fielden AD, Barnett JC. Is FDA-Approved Bevacizumab Cost-Effective When Included in the Treatment of Platinum-Resistant Recurrent Ovarian Cancer? J Oncol Pract. 2016 Jul;12(7):e775-83.[41]
Cohn DE, Kim KH, Resnick KE, O'Malley DM, Straughn JM. At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. Journal of Clinical Oncology. 2011 07 Sep 2011;29(10):1247-51.[42]
Cohn DE, Barnett JC, Wenzel L, Monk BJ, Burger RA, Straughn JM, Jr., et al. A cost-utility analysis of NRG Oncology/Gynecologic Oncology Group Protocol 218: incorporating prospectively collected quality-of-life scores in an economic model of treatment of ovarian cancer. Gynecologic Oncology. 2015 Feb;136(2):293-9.[43]
Duong M, Wright E, Yin L, Martin-Nunez I, Ghatage P, Fung-Kee-Fung M. The cost-effectiveness of bevacizumab for the treatment of advanced ovarian cancer in Canada. Curr Oncol. 2016 Oct;23(5):e461-e7.[51]
Hinde S, Epstein D, Cook A, Embleton A, Perren T, Sculpher M. The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial. Value Health. 2016 Jun;19(4):431-9.[44]
Lesnock JL, Farris C, Krivak TC, Smith KJ, Markman M. Consolidation paclitaxel is more cost-effective than bevacizumab following upfront treatment of advanced epithelial ovarian cancer. Gynecologic Oncology. 2011 07 Mar 2012;122(3):473-8.[45]
Mehta DA, Hay JW. Cost-effectiveness of adding bevacizumab to first line therapy for patients with advanced ovarian cancer. Gynecologic Oncology. 2014 28 Feb 2014;132(3):677-83.[46]

6.3 Overview of economic evaluations

6.3.1 General information

The eleven included studies were carried out for the United States (7), United Kingdom (3), and Canada (1). To structure the discussion hereafter, the studies are ordered depending on the underlying clinical trial: the GOG-0218, ICON7, AURELIA or OCEANS study (Table 13). We notice that four US studies have one or two authors in common.[39, 41-43]

Both short and lifetime time horizons were applied. The analysis of Barnett et al.[39] and Chan et al.[40] reflected the duration of follow-up in the ICON7 trial: 39 months (~3 years) and 46 months (~4 years), respectively. A 10-year time horizon may approach a lifetime horizon depending on the underlying study population: the Evidence Review Group (ERG) of TA285 considers that the 10-year time horizon is likely to represent a lifetime time horizon for most patients in the model.[50] The ERG of TA284 notices that after ten years about 10% of patients are still alive.[49] Discounting was in most cases performed according to national guidelines: for both costs and effects, 3%, 3.5% and 5% in US, UK and Canadian studies, respectively.

Not all studies applied a 'traditional' economic evaluation expressing outcomes in incremental costs per life-year gained (LYG), or per quality-adjusted life years (QALYs) gained. In three US analyses (with common authors),[41-43] a disease-specific outcome "costs per progression-free life-year saved (PF-LYS)" was used. The first study of Cohn et al.[42] was based on data presented in abstract form and without inclusion of quality of life (QoL) data. In their updated study,[43] QoL data were incorporated and results were expressed in another disease-specific outcome of quality-adjusted progression-free years (QA-PFY) and QALYs. The majority of studies set up a three-state Markov model with a progression-free, progressed disease, and death health state.

The conflicts of interest (CoI) widely vary from all authors being affiliated or have involvement with Hoffmann–La Roche Ltd in the Canadian study of Duong et al.[51] to studies not mentioning any CoI. In case of the NICE TA284 and TA285 studies, both the manufacturer's submission (MS) and the summary and critique of the manufacturer's submitted economic evaluation by the ERG were considered. For the ERG, no CoI were present.

6.3.2 Population, intervention and comparator(s)

The average age and weight of the population were not always mentioned. Average age was around 60 years (minimum: 56 years; maximum: 63 years) and weight varied widely from 60kg in a UK study[47] up to 77kg in a US study.[45] The patient characteristics, if provided, do not always reflect the patient characteristics as in the original trials. The NICE TA284[47] and TA285[48] studies for example included the mean weight of a cohort of UK ovarian cancer patients[52] which has an influence on the calculated dose per patient.

Most studies model the results of the GOG-0218 or a subgroup of the ICON7 trial.

The GOG-0218 study included women with newly diagnosed stage III or IV ovarian cancer.[28] Bevacizumab in combination with carboplatin and paclitaxel (CPB) is compared with carboplatin and paclitaxel (CP). Paclitaxel (175mg/m²) and carboplatin (Area Under the Curve (AUC) of 6) are given six times three-weekly. In the GOG trial, the licensed dose of bevacizumab (15mg/kg body weight) is given every 3 weeks by intravenous infusion. During chemotherapy, bevacizumab is added in the second cycle. After chemotherapy, 16 cycles of maintenance bevacizumab are added.[d]

The studies of Cohn et al.[42, 43] also include an option in which six cycles of paclitaxel, carboplatin, and bevacizumab starting in cycle 2 (PCB), without bevacizumab maintenance therapy, is administered. The study of Lesnock et al.,[45] referring not only to the GOG-0218 but also the GOG 158 and 178

[d] The study of Mehta et al.[46] mentions to include 18 additional cycles of bevacizumab. This probably is a typing error since they also refer to the GOG-0218 trial including 16 cycles of maintenance therapy.

studies, also includes a treatment arm in which patients are treated with 6 cycles of CP followed by 12 cycles of P (CP+P).

The six studies referring to the ICON7 trial all compare standard chemotherapy alone to this treatment added with bevacizumab (B) and maintenance bevacizumab (mB) continued for 12 additional cycles or until disease progression. Standard chemotherapy consisted of 6 three-weekly cycles of carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m2 body surface area).[31] In the ICON7 study, bevacizumab is administered at a dose of 7.5mg/kg and 12 additional cycles (or until disease progression) after chemotherapy instead of 15mg/kg and 16 additional cycles in the GOG-0218 study.

All these studies refer to the 'high risk' subgroup of the ICON7 study, including all patients with stage IV disease, inoperable stage III disease, or suboptimally debulked (>1 cm) stage III disease.[31] One in three (502/1528) women included in the ICON7 trial were categorized into this subgroup. In this subgroup of advanced ovarian cancer patients at high risk of progression, a survival benefit was observed in the trial. The subgroup and the analysis were predefined, although the randomization was not stratified for it. Only Barnett et al.[39] also include concurrent and maintenance bevacizumab for all instead of only the high-risk subgroup of the ICON7 trial. Furthermore, they also include an option in which they explore "*the potential effectiveness and cost effectiveness of an SNP biomarker predictive test to direct the use of bevacizumab in the high-risk (suboptimally debulked or stage IV disease) population*"[39] (Table 15).

The AURELIA study included platinum-resistant ovarian cancer patients. Chappell et al.[41] compare cytotoxic chemotherapy (pegylated liposomal doxorubicin [PLD], paclitaxel once per week, or topotecan) with or without bevacizumab. Two separate models were constructed. In the first model, bevacizumab (10mg/kg) was given once every two weeks (when PLD, paclitaxel once per week, or topotecan once per week was the chemotherapy). In the second, bevacizumab (15mg/kg) was given every three weeks (when the every 3-week dosing of topotecan was used).[41]

Finally, in the NICE TA285 study,[48] the population cohort matches the inclusion criteria of the OCEANS trial. In this study, patients with platinum-sensitive recurrent ovarian cancer that progressed more than 6 months after completion of front-line platinum-based chemotherapy, received bevacizumab in combination with gemcitabine and carboplatin or gemcitabine and carboplatin.[34]

Table 13 – General information on the identified economic evaluations

Reference (country) Conflict of interest	Underlying study	Time horizon Discount rate	Analytic technique Design
NICE TA284, 2012 (UK) CoI: yes & no*	GOG 218 ICON7 subgroup	10 years 3.5% (C&E)	CUA Markov model
Cohn et al., 2011 (US) CoI mentioned	GOG 218	Not mentioned	CEA (dis. specific) decision tree
Cohn et al., 2015 (US) no CoI mentioned	GOG 218	60 months 3% (C&E)	CEA (dis. specific) + CUA Markov model
Mehta et al., 2014 (US) no CoI mentioned	GOG 218 ICON7 subgroup	Lifetime 3% (C&E)	CUA Markov model
Lesnock et al., 2011 (US) CoI mentioned	GOG 158, GOG 178 & GOG 218	10 years 3% (C&E)	CUA Markov model
Barnett et al., 2013 (US) CoI mentioned	ICON7	~3 year 3% (C&E)	CEA (CUA) Markov model
Chan et al., 2014 (US) CoI mentioned	ICON7 subgroup	~4 year not mentioned	CEA Markov model
Duong et al., 2016 (CAN) CoI mentioned	ICON7 subgroup	10 year 5% (C&E)	CUA Markov model
Hinde et al., 2016 (UK) CoI mentioned	ICON7 subgroup	Lifetime 3.5% (C&E)	CUA Markov model
Chappell et al., 2016 (US) no CoI mentioned	AURELIA	Not mentioned	CEA (dis. specific) decision tree
NICE TA285, 2012 (UK) CoI: yes & no*	OCEANS	10 years 3.5% (C&E)	CUA Markov model

C&E: costs and effects; CAN: Canada; CEA: cost-effectiveness analysis; CoI: conflict of interest; CUA: cost-utility analysis; dis. specific: disease specific
** The Evidence Review Group (ERG) has no CoI. They review a submission of the manufacturer (with CoI).*

Table 14 – Intervention and comparator of the identified economic evaluations (part 1/3)

Reference	Population	Intervention and comparator(s)
NICE TA284, 2012 (UK)	GOG 218 ICON7 subgroup Age: 56.34 years Weight: 60.49kg	1) CP: one cycle CP + five cycles CP & placebo + 16 cycles placebo. 2) CPB + mB: one cycle CP + five cycles CPB + 16 cycles B. GOG 218 → B: 15 mg/kg every 3 weeks ICON7 → B: 7.5 mg/kg every 3 weeks (12 cycles instead of 16)
Cohn et al., 2011+2015 (US)	GOG 218 Age: N/A Weight: N/A	1) CP 2) CPB 3) CPB + mB Bevacizumab: - CPB: six cycles B, 15 mg/kg 3-weekly - + mB: + 16 cycles B, 15 mg/kg 3-weekly
Mehta et al., 2014 (US)	GOG 218 ICON7 subgroup Age: 60 years Weight: N/A	1) CP (6 cycles) 2) CPB + mB: GOG 218 → CPB (6 cycles) + B (18* cycles) 3) CPB + mB: ICON 7 → CPB (6 cycles) + B (12 cycles)
Lesnock et al., 2011 (US)	GOG 158, GOG 178 & GOG 218 Age: 58 years Weight: 76.9kg	1) CP (6 cycles) 2) CP+P = CP (6 cycles) + P (12 cycles) 3) CPB+ mB = CP (1 cycle) + CPB (5 cycles) + B (16 cycles).

B: bevacizumab; C: carboplatin; G: gemcitabine; mB: maintenance bevacizumab; P: paclitaxel
** Mehta mentions 18 extra cycles, while 16 extra cycles are mentioned in the underlying trial. This is probably a typing error.*

Table 15 – Intervention and comparator of the identified economic evaluations (part 2/3)

Reference	Population	Intervention and comparator(s)
Barnett et al., 2013 (US)	ICON7 Age: N/A Weight: N/A	1) CP for all 2) CPB + mB for all 3) CPB + mB for high risk 4) test for bevacizumab responsiveness B: 7.5 mg/kg - concurrent bevacizumab during primary platinum-based chemotherapy followed by 12 cycles of maintenance therapy.
Chan et al., 2014 (US)	ICON7 subgroup: Age: 63 years Weight: N/A	1) CP every 3 weeks for 6 cycles versus 2) CPB + mB B: 7.5 mg/kg - continued for 12 additional cycles or until disease progression.
Duong et al., 2016 (Canada)	ICON7 subgroup Age: N/A Weight: 64.86kg	1) CP 2) CPB + mB B: concurrent 7.5 mg/kg body weight, starting at cycle 2 + additionally 12 three-weekly cycles of bevacizumab
Hinde et al., 2016 (UK)	ICON7 subgroup Age: 60 years Weight: N/A	1) CP 2) CPB + mB B: given concurrently (7.5 mg/kg of body weight) every 3 weeks and continued for 12 additional cycles or until disease progression if earlier.

Table 16 – Intervention and comparator of the identified economic evaluations (part 3/3)

Reference	Population	Intervention and comparator(s)
Chappell et al., 2016 (US)	AURELIA Age: N/A Weight: 70kg	1) chemo 2) chemo + B Chemo: pegylated liposomal doxorubicin [PLD], paclitaxel or topotecan. For Bevacizumab → two models: 1) 10mg/kg once every 2 weeks: when PLD, paclitaxel once per week, or topotecan once per week was the chemotherapy 2) 15 mg/kg once every 3 weeks: when the every 3-week dosing of topotecan was used.
NICE TA285, 2012 (UK)	OCEANS Age: 61.37 years Weight: 69.35kg	1) CG 2) CGB Bevacizumab: 15mg/kg until progression

6.3.3 Costs

An overview of the cost items and their valuation included in the identified economic evaluations is provided in Appendix. All economic evaluations are performed from the perspective of the healthcare payer. Cohn et al.[43] mentions no data exists regarding the impact of treatment with adjuvant and maintenance bevacizumab on lost patient and caregiver time (and thus the cost of this lost time). Nevertheless, one analysis[46] mentions to perform the analysis form a societal perspective. Indirect costs in the model included unpaid patient and caregiver time and costs assuming the time associated with informal caregiving to be 6.8 hours per day for the stable state and 10 hours per day for the progression state, which was valued at the mean hourly compensation of a home health aide.[46] No reference or value is mentioned for this compensation. Furthermore, the authors refer to a study published in 2001[53] to support this assumption. However, when checking the original reference, the following is mentioned: "*Those subjects reporting CT [having a diagnosis of cancer and receiving treatment in the last year] received an average of 10.0 hours of informal caregiving per week, as compared with 6.9 and 6.8 hours for those who reported NC [no history of cancer] and CNT [having a diagnosis of cancer but not receiving treatment for their cancer in the last year], respectively (P < .05). Accordingly, cancer treatment was associated with an incremental increase of 3.1 hours per week, which translates into an additional average yearly cost of $1,200 per patient.*"[53] The impact is thus expressed per week instead of per day. Probably this is a typing mistake in the study of Mehta.

The main difference in costs between the treatment arms is related to the administered drugs, which is more expensive when bevacizumab is included (Table 17).

Table 17 – Drug/treatment costs in the identified economic evaluations

	Treatments without bevacizumab	Treatments with bevacizumab
Drug cost per cycle[47]	Paclitaxel: £21.80 Carboplatin: £18.51	Bevacizumab: £2,229
Treatment costs per cycle[42]	PC: $1000	PCB: $6740 +mB: +$5940
Treatment costs per cycle[43]	PC: $449	PCB: $7127 +mB: +$6999
Drug cost per cycle[45]	Carboplatin: $268.75 Paclitaxel: $155.16	Bevacizumab: $2191.45
Treatment costs per cycle[39]	PC: $508	PCB: $3,266 +mB: $3,064
Treatment costs per cycle[40]	PC: $535	PCB: $3,760 +mB: $3,225
Drug cost per cycle[51]	PC: CAD153	PCB + mB: CAD2653
Trial drugs costs per day[e44]	PC: £20.19	PCB + mB: £72.67
Treatment cost per cycle[41]	chemo: $1,572	chemo + B: $10,933
Drug cost per cycle[48]	Gemcitabine: £21,53 Carboplatin: £155.43	Bevacizumab: £2,556

[e] Only Hinde et al.[44] provide no treatment costs per cycle but mean costs per day. The incremental difference in trial drug costs in this study eventually is £17,760.

The studies relying on the GOG-0218 or ICON7 trial include paclitaxel and carboplatin (PC) as chemotherapy. With the exception of one study,[46] all studies provide treatment or drug costs per cycle. The difference between treatment and drug costs may exist in administration and/or pharmacy costs. The difference in drug/treatment costs between chemotherapy and bevacizumab is clear. Large differences between studies for the same countries may exist for the bevacizumab treatment depending on the underlying source. For example, Lesnock et al included bevacizumab at the cost to the author's home institution (University of Pittsburgh Medical Center), which is less than the official values.[45] The difference in drug costs for carboplatin between the two NICE submission is somewhat strange: applying the same cost of £21.84 per 600mg vial results in very different costs per cycle: £18.51[47] versus £155.43[48].

The incremental difference in total drug costs is much larger than the extra cost per cycle due to the prolonged treatment with bevacizumab as maintenance therapy. In the GOG-0218 and ICON7 trials this is respectively for 12 or 16 additional cycles. The mean treatment duration is only explicitly mentioned in the NICE TA284 and TA285 studies. In the TA284, the ERG noted that the treatment duration used within the model was a maximum of one year, rather than 15 months as stated in the Summary of Product Characteristics (SPC) for bevacizumab for the GOG-0218 trial, which results in an underestimation of the cost of bevacizumab.[49] A mean treatment duration of 11.8 cycles was included instead of the expected number of 13.7 cycles in the GOG-0218 trial. The ERG solved this by providing an extra analysis with longer treatment durations.[49]

The total incremental costs are also influenced by a difference in complications. The occurrence of these AEs in the economic models is discussed in the following part. The costs for included AEs are also provided in Appendix. Some of the included AEs are perforations, hypertension and venous thromboembolism.

Next to the drug/treatment costs and costs for AEs, some studies also explicitly mention other costs: difference in follow-up/supportive care (including e.g. physician visits after administration, cancer antigen 125 immunohistochemistry tests, and computed tomography imaging examinations),[51] depending on the health state (pre- vs post-progression),[44, 51] inclusion of other drugs such as antiemetic medications or growth factors,[39, 42, 43] costs of salvage bevacizumab after failing chemotherapy,[41] palliative care,[47, 48] etc. For more details on the occurrence and valuation of these costs we refer to the full details provided in Appendix 6. For an overview of the total incremental costs we refer to part 6.3.8.

6.3.4 Adverse events

In general, the models included adverse events for which there was a relevant difference in costs between the treatment arms. This relevant difference could be caused by a large difference in occurrence of the adverse events (AEs) between the treatment arms or the combination of a difference in incidence with a high cost to treat the AEs. As mentioned by Duong et al., grades 1–2 AEs are considered mild to moderate in severity and require limited or no intervention. As a result, they would not affect an economic analysis.[51] In general, such AEs are thus not included in the economic evaluations.

Overall, more patients in the bevacizumab treatment arms experienced more AEs (Table 18 to Table 20). Exceptionally, the number of AEs does not differ between the modelled treatment arms in only one economic evaluation.[40]

The two studies for NICE[47, 48] are the most detailed studies. For these studies, only the incidence of adverse events costed in the model are included in Table 18 and Table 20. Other adverse events not receiving a cost per episode are not mentioned in these tables. The costs for treating the modelled AEs are mentioned in Appendix. In TA285, relying on the OCEANS trial, a larger proportion of patients in the bevacizumab group experienced an adverse event (i.e. Grade 3 and Grade 4 events, and adverse events of special interest (AESIs)) compared with the placebo group.[48] However, the incremental impact on costs was limited. The total average cost per patient used in the model for the chemotherapy + bevacizumab group was £224, while this was £146 for the chemotherapy group.

The inclusion of hypertension is somewhat different between the models. For example, Cohn et al. mention in their first analysis that "*the rate of grade 2 or greater hypertension was significantly higher in the arms containing bevacizumab (16.5% and 22.9% in PCB and PCB+B, respectively) compared with the control arm (7.2% in PC)*."[42] However, they considered the differential costs of this complication to be negligible and did not include this cost in their first analysis.[42] In their updated study and some other studies,[39, 43, 46, 48] this cost was modelled explicitly (Table 18 - Table 20). The US study of Mehta et al.[46] mentions "*cost of treating side-effects derived from the literature was weighted based on differential incidence of hypertension observed in the clinical trial. The cost of treating side-effects was accounted for during the first cycle and no side effect cost was incorporated for the remaining cycles.*"[46] Unfortunately, no details on incidence or costs are explicitly mentioned in the article and are thus not included in the overview tables. In contrast with all other models, the incidence of hypertension as a minor adverse event is higher in the placebo group in comparison with the placebo+bevacizumab group in one economic evaluation.[39]

The major adverse event "perforations" was also included in several economic evaluations.[39, 41, 42, 45] Other Modelled AEs were e.g. thromboembolic events[39] or neutropenia.[47, 48] However, as mentioned by Cohn et al.: "*The incidence of febrile neutropenia was shown to be relatively rare and not significantly different across all arms … as such, neither the relative differences in cost nor the overall cost of treatment of this complication would be expected to influence the overall model.*"[42]

The models only include the costs for these AEs during treatment. In contrast with the other models, Duong et al.[51] extrapolate the cost of treating patients with AEs beyond the trial follow-up by applying the average weekly AE cost by arm. This is rather controversial since this neglects the link between the occurrence of AEs and the underlying treatment.

Table 18 – Adverse events included in the identified economic evaluations (part 1/3)

Reference	Adverse events			
NICE TA284, 2012 (UK)	List of adverse events and summary of costs (GOG 218)			
	(only AEs with a cost per episode are mentioned in this table)			
			N (%) patients experiencing event	
			CP	CPB + mB
	Dehydration		14 (2.24)	21 (3.37)
	Diarrhoea		20 (3.2)	16 (2.57)
	Febrile Neutropenia		23 (3.68)	30 (4.82)
	Haemaglobin decreased		84 (13.44)	63 (10.11)
	Hypokalaemia		15 (2.4)	13 (2.09)
	Hyponatraemia		9 (1.44)	14 (2.25)
	Neutrophil count decreased		431 (68.96)	430 (69.02)
	Neutrophil count decreased (Grade 4)		354 (56.64)	387 (62.12)
	Platelet count decreased		78 (12.48)	100 (16.05)
	Platelet count decreased (Grade 4)		27 (4.32)	36 (5.78)
	White blood cell count decreased		300 (48)	311 (49.92)
	White blood cell count decreased (Grade 4)		22 (3.52)	28 (4.49)
	List of adverse events and summary of costs (ICON7)			
	(only AEs with a cost per episode are mentioned in this table)			
	Anaemia		7 (2.79)	4 (1.64)
	Dyspnoea		1 (0.40)	7 (2.87)
	Febrile Neutropenia		7 (2.79)	2 (0.82)
	Neutropenia		24 (9.56)	21 (8.61)
	Neutropenia (Grade 4)		12 (4.78)	9 (3.69)
	Pulmonary Embolism (Grade 4)		0 (0.00)	6 (2.46)
	Thrombocytopenia		5 (1.99)	9 (3.69)
Cohn et al., 2011 (US)		PC	PCB	PCB + B
	Intestinal perforation rate	1.2%	2.8%	2.6%
	% of fatal perforations	25%	25%	25%
Cohn et al., 2015 (US)		PC	PCB	PCB + B
	Grade 3–5 intestinal events	1.4%	3.2%	3.3%
	Grade 4 hypertension	0%	0.3%	0.5%
Mehta et al., 2014 (US)	No details provided			
Lesnock et al., 2011 (US)		Estimate	Range	
	Neuropathy | CP	7%	0.03 – 0.14	
	Neuropathy | CP+P	20%	0.10 – 0.40	
	Neuropathy | CPB+B	7%	0.03 – 0.14	
	Bowel Perforation | CPB+B	3%	0.015 – 0.10	
	Death | Bowel Perforation	50%	0.00 – 0.75	

Table 19 – Adverse events included in the identified economic evaluations (part 2/3)

Reference	Adverse events		
Barnett et al., 2013 (US)		Control Arm Rate % (range)	Bevacizumab Arm Rate % (range)
	Gastrointestinal Perforation	<1%	1%
	Venous Thromboembolism	3%	7%
	Minor Adverse Event (Hypertension)	18% (3-18)	2% (1-4)
Chan et al., 2014 (US)		PC	PCB + mB
	Severe complication rate	0.2 (0.1–0.3)	0.2 (0.1–0.3)
Duong et al., 2016 (Canada)	The AEs and toxicities were modelled from the ICON7 trial. AEs of grade 3 and greater, observed within 28 days after discontinuation of the clinical trial treatment, are included. The cost of treating patients with AEs was extrapolated beyond the trial follow-up by applying the average weekly AE cost by arm.		
Hinde et al., 2016 (UK)	AEs were not mentioned separately. Overall costs and QALYs were directly taken from the ICON7 trial.		

Table 20 – Adverse events included in the identified economic evaluations (part 3/3)

Reference	Adverse events		
Chappell et al., 2016 (US)		Chemo	Chemo + B
	GI perforation:	0%	2.2%
	Grade 2 hypertension:	7%	20%
	Paracentesis:	2%	17%
NICE TA285, 2012 (UK)	Incidence of adverse events costed in the model:	Placebo	Bevacizumab
	Thrombocytopenia	14 (5.58%)	15 (6.15%)
	Thrombocytopenia (grade 4)	8 (3.19%)	15 (6.15%)
	Leukopenia	7 (2.79%)	8 (3.28%)
	Neutropenia	30 (11.95%)	40 (16.39%)
	Neutropenia (grade 4)	9 (3.59%)	14 (5.74%)
	Hypertension	1 (0.4%)	33 (13.52%)
	Anaemia	13 (5.18%)	14 (5.74%)
	Neutrophil count decreased	8 (3.19%)	5 (2.05%)
	Neutrophil count decreased (Grade 4)	3 (1.2%)	5 (2.05%)
	White blood cell count decreased	6 (2.39%)	1 (0.41%)

6.3.5 Quality of life

The published RCTs usually did not include a generic utility instrument in their protocol. Measures of quality of life (QoL) with such an instrument can provide result in utility weights which can be used in economic evaluations. The lack of QoL data measured with a generic utility instrument results in different approaches and assumptions across identified economic evaluations.

In the studies relying on the GOG trial, QoL was not included in the first analysis of Cohn. In their updated analysis in 2015, QoL was added. They mention that "*bevacizumab was found to compromise QOL during chemotherapy, as measured by the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy—Ovary (FACT-O) [FACT-O TOI] (before cycle four, there was an approximately three point decrease in QOL with bevacizumab compared to the control arm), but had no impact after chemotherapy was completed*[30]." These FACT subscale scores, measured at baseline, prior to cycle 4, cycle 7, cycle 13 and cycle 21, and 6 months following completion of treatment, were converted to utilities. "*As there was no QOL data beyond the 6-month post-treatment time point, QOL was assumed to be equivalent between treatment arms from the final measured time point to the date of progression or 60 months.*"[43] This study does not extrapolate after progression since their endpoint is 'progression-free (quality-adjusted) years'. We remark, however, that utilities were modelled as a normal distribution for which a large part of the probability distribution exceeds 1, which is the upper limit for utilities (see further in part 6.3.7).

In the study of Mehta et al.,[46] the utility weights in the bevacizumab arm are somewhat lower than in the CP arm. The utility values gradually increase in both treatment arms. Utility weights were also adjusted in the CP arm for a period of 12 months for residual neurotoxicity due to chemotherapy cycles.[46] If the disease is stable after more than 12 months, a utility weight of 0.85 is taken into account. Once the disease has progressed, a much lower utility value of 0.63 is modelled (Table 21). In table 1 in the original publication, the authors refer to eight other studies to justify the applied values. Unfortunately, utility values were not measured in the underlying GOG-0218 trial and the values from the other referred studies are often based on expert

opinion (e.g. reference is made to the study of Lesnock which is discussed further).

In the NICE TA284 study, the manufacturer's submission includes QoL values for two health states (PFS and progression). Only the ICON7 trial included a measurement of patients' HRQoL through EQ-5D.[f] The ERG notes that "*the EQ-5D data used in the model are from the ICON7 trial, which employed a lower dose of bevacizumab than in the NICE scope. Any AEs caused by the higher dose of bevacizumab as specified in the NICE scope would not be captured using the utility data from the ICON7 trial.*"[49] In the appendix of the report, it is also mentioned that "*some women receiving bevacizumab has a statistically significant but clinically small detriment in global QoL but no HRQoL data are presented for the relevant subgroups for the ICON7*." On the contrary, by modelling QoL for the health states PFS and progressive disease, in combination with a longer PFS if bevacizumab is administered, an improvement in QoL is modelled by:

- Modelling a worse QoL value after disease progression. The mean utility was 0.7248, although the authors mention that in ICON7, QoL data was not routinely available for patients whose disease had progressed, and thus this estimate is based on relatively few observations.
- Modelling an increase in QoL following an initial diagnosis. The manufacturer argues that "*it is not uncommon for patients' quality of life to improve over time following an initial diagnosis as they become more able to cope with the symptoms of the disease, the effects of chemotherapy and other treatments become more apparent to her and the fear of disease progression or recurrence lessens.*"[49]

The manufacturer did thus not model directly the QoL data from the two treatment arms in the ICON7 study, as is usually the case. In contrast, an improvement in QoL was modelled indirectly through the progression-free health state.

From the other economic evaluations relying on the ICON7 trial, one study[40] did not include QoL (Table 22). Barnett et al. include an equal QoL for both treatment arms with and without bevacizumab. They mention that "*in ICON7, both treatment arms experienced improvement in global QOL over time. Because it was determined that the small QOL differences observed between arms in the trial were clinically insignificant, we assumed no differences in QOL for purposes of the model.*"[39] In their discussion they add that "*even though QOL scores did not differ significantly between groups in the ICON7 trial, there was a small but statistically significant decrease in QOL in the bevacizumab-containing arms before cycle 4 of therapy ... However, a transient change in QOL during treatment would be unlikely to have any impact on the cost effectiveness of each regimen, so this difference was not included in the base case analysis.*"[39]

The study of Lesnock et al.[45] adjusts the utilities not only for recurrence, but also for adverse events (Table 22). They also refer to the lack of published utility estimates: "*As there are no published utility estimates for patients with epithelial ovarian cancer (EOC) undergoing the regimens described in this model, a panel of three gynecological oncology experts … provided consensus judgments for utility values.*"[45]

Also Duong et al.[51] do not model a decreased utility by adding bevacizumab. An increasing ulility value over time is applied in combination with a utility value of 0.64 after disease progression (Table 22). Reference is made to an abstract[54] to justify the latter value. However, in this abstract, no such information could be retrieved.

[f] We remark that the initial protocol did mention to measure QoL with the EQ-5D instrument, but only as part of the economic evaluation. In the QoL-related peer-reviewed publication it was not reported. The authors state that "quality of life was assessed with the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-OV28 questionnaires."[31]

Similarly, the last study relying on the ICON7 trial from Hinde et al.[44] presented a figure from the ICON7 trial with the HRQOL scores, increasing over time, and assumed to be treatment independent (Table 22). They also apply a lower utility value of 0.74 when the disease progresses. For the latter value, they mention that "*there was a small difference in postprogression HRQOL between the two arms, being slightly higher in the chemotherapy-alone arm (0.75; SE 0.016) when compared with the bevacizumab arm (0.71; SE 0.020). However, as with progression-free HRQOL, there was no evidence that this difference was statistically significant (P=0.095).*" The value of 0.74 was therefore also assumed to be treatment independent.

The study of Chappell et al, relying on the AURELIA trial assumed perfect quality of life (QOL) in both arms (utility score = 1) in the base case (Table 23).[41] This was varied during sensitivity analysis by changing QOL in the arm without bevacizumab as a percentage of perfect QOL and keeping the 'perfect health' utility (value=1) in the bevacizumab group. Assuming perfect QoL in a population with ovarian cancer is of course overoptimistic.

Finally, the NICE TA285 study, relying on the OCEANS trial, faced the same major problem: utility values were not estimated in the trial. Utilities from a previous technology appraisal in recurrent ovarian cancer (TA222) were applied to the PFS and PD health states.[48] The ERG noticed however that "*the utilities used within the model were not identified from the literature search, and the manufacturer did not describe how these utilities were identified*." Furthermore, the manufacturer remarks that "*the use of utility data from OVA-301 presented in TA222 should be interpreted with caution due to little overlap in the types of adverse event between OVA-301 and OCEANS*." The ERG also investigated the impact of applying disutilities associated with adverse events in an exploratory analysis (Table 23).[50]

Table 21 – Quality of life in the identified economic evaluations (part 1/3)

Reference	Quality of life			
NICE TA284, 2012 (UK)	State	Utility value	Standard error	
	PFS			
	Weeks 0-2	0.6571	0.0133	
	3-5	0.7153	0.0118	
	6-8	0.7443	0.0110	
	9-11	0.7683	0.0100	
	12-14	0.7643	0.0112	
	15-20	0.7444	0.0121	
	21-26	0.7638	0.0131	
	27-32	0.7718	0.0129	
	33-38	0.7638	0.0136	
	39-44	0.7785	0.0155	
	45-50	0.7533	0.0165	
	51-53	0.7760	0.0170	
	54 +	0.8129	0.0113	
	PD	0.7248	-	
Cohn et al., 2011 (US)	QoL not included (CEA)			
Cohn et al., 2015 (US)		mean value (standard deviation)		
		CP	CPB	CPB + mB
	Baseline	0.79 (0.118)	0.79 (0.116)	0.79 (0.119)
	Cycle 4	0.82 (0.115)	0.80 (0.115)	0.79 (0.058)
	Cycle 7	0.83 (0.057)	0.81 (0.111)	0.81 (0.114)
	Cycle 13	0.86 (0.108)	0.85 (0.106)	0.85 (0.109)
	Cycle 21	0.85 (0.152)	0.86 (0.098)	0.85 (0.052)
	6 months following completion of treatment	0.84 (0.095)	0.85 (0.094)	0.85 (0.147)
Mehta et al., 2014 (US)	utility weights			
	GOG 218 trial:		CP arm	CPB arm
	Stable state chemotherapy cycles 1–6		0.67	0.59
	Stable state: 12 months post-chemo		0.78	–
	Stable state: post 12 months		0.85	0.85
	Progression phase — throughout		0.63	0.63
	ICON7 trial			
	Stable state chemotherapy cycles 1–6		0.81	0.79
	Stable state: 12 months post-chemo		0.83	–
	Stable state: post 12 months		0.85	0.85
	Progression phase — throughout		0.63	0.63
Lesnock et al., 2011 (US)	Three experts provided consensus judgments for utility values			
	Quality of Life Utility Index	Estimate	Range	
	Chemotherapy			
	CP Cycles	0.77	0.64 – 0.85	
	CPB Cycles	0.77	0.64 – 0.85	
	P Maintenance Cycles	0.80	0.66 – 0.88	
	B Maintenance Cycles	0.82	0.68 – 0.90	
	Months 1–6 Recovery	0.84	0.70 – 0.93	
	PFS	0.85	0.75 – 1.00	
	Cancer recurrence	0.65	0.50 – 0.85	
	Neuropathy	0.94	0.80 – 1.00	
	Bowel perforation	0.85	0.50 – 0.95	

Table 22 – Quality of life in the identified economic evaluations (part 2/3)

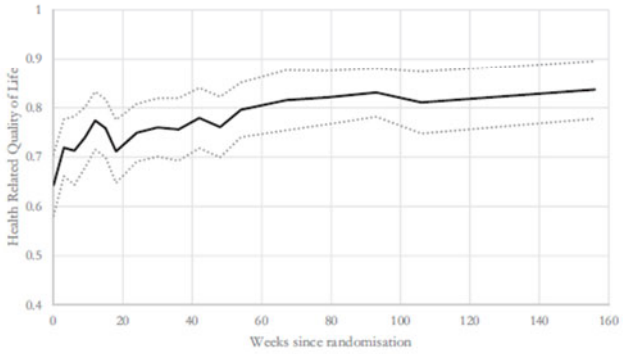
Reference	Quality of life			
Barnett et al., 2013 (US)	No differences in QoL (base case)			
Chan et al., 2014 (US)	QoL not included (CEA)			
Duong et al., 2016 (Canada)	PFS: EQ-5D from ICON7 trial			
		observations (n)	mean	standard error
	cycle 1	340	0.7252	0.0081
	cycle 2	383	0.767	0.0074
	cycle 3	380	0.7798	0.0074
	cycle 4	365	0.7971	0.0069
	cycle 5	367	0.7968	0.0077
	cycle 6	360	0.7835	0.0081
	cycle 8	308	0.7969	0.0092
	cycle 10	299	0.8059	0.0092
	cycle 12	287	0.804	0.0095
	cycle 14	226	0.8136	0.011
	cycle 16	206	0.7985	0.0109
	cycle 18	181	0.815	0.0119
	follow-up	395	0.8438	0.0078
	Progression: 0.64			
Hinde et al., 2016 (UK)	HRQOL scores over time while patients are in the preprogression state (means and 95% confidence intervals), in which HRQOL is assumed to be treatment independent.  Postprogression HRQOL: 0.74 (SE 0.013) (assumed to be independent of time since randomization and assumed to be treatment independent).			

Table 23 – Quality of life in the identified economic evaluations (part 3/3)

Reference	Quality of life		
Chappell et al., 2016 (US)	Base case: perfect QOL in both arms (utility score = 1)		
NICE TA285, 2012 (UK)		Utility value	95% CI
	PFS	0.718	0.699 to 0.737
	progressed disease	0.649	0.611 to 0.686
	Disutilities used by the ERG to estimate the impact of adverse events		
	Adverse event	Estimate of disutility	95% CI
	Anaemia	–0.12	–0.16 to –0.09
	Diarrhoea	–0.10	–0.13 to –0.08
	Dyspnoea	–0.12	–0.16 to –0.09
	Fatigue	–0.12	–0.14 to –0.09
	Febrile neutropenia	–0.15	–0.19 to –0.11
	Hypertension	–0.12	–0.16 to –0.09
	Neuropathy peripheral	–0.12	–0.16 to –0.09
	Neutropenia	–0.12	–0.16 to –0.09
	Thrombocytopenia	–0.12	–0.16 to –0.09

6.3.6 *Treatment effect*

An overview of the treatment effect applied in the models is provided in the following tables (Table 24 - Table 27).

In the NICE TA284 study, data from both GOG-0218 and ICON7 are modelled. For the GOG-0218 scenario, Kaplan-Meier survival curves for PFS are used until the convergence of survival functions for the intervention and comparator at month 28. Extrapolation beyond month 28 is based on a parametric survival model (log-logistic).[49] The ERG considers that "*the GOG-0218 model results are consistent with the clinical trial results for PFS. For OS, the ERG notes that there is a similar OS in both the chemotherapy and bevacizumab trial arms, whereas in the model the OS for bevacizumab is 2 months longer than for the chemotherapy arm*"[49] (see Table 24). For the ICON7 model, the manufacturer mentions that for PFS "*none of the parametric functions provided a satisfactory fit to the data and therefore it was determined that Kaplan Meier data from ICON7 should be used until*

convergence at 24 months followed by extrapolation using a Log Logistic parametric function."[47] For overall survival, the Gamma function provided the best fit to the observed survival times. Nevertheless, the manufacturer mentions to apply a Log Logistic function in the base case analysis. According to experts consulted by the manufacturer, "*a small but significant percentage of Stage III and IV patients (typically 5-10%) experience long term survival (in excess of 10 years)*",[47] and the Log Logistic function would provide the best fit for this.

Cohn et al. refer to initial results from the GOG-0218 trial presented in oral and abstract form for their 2011 analysis[42] and to the primary event data for PFS and OS for their 2015 analysis.[43]

Mehta et al. mention that "*For the base case analysis, only mortality risk due to ovarian cancer was considered. The base model was subsequently augmented in a sensitivity analysis to include patients' additional mortality risks*."[46] However, the time horizon in this model was "*until the death of 99% of the initial cohort of 1000 individuals.*" This would assume that total mortality should be modelled in the base case. In this model, transition probabilities were retrieved from the median PFS and OS from the clinical trials assuming a constant proportional hazard.

A limitation of the model of Lesnock et al.[45] is that the treatment effect of the three treatment arms is based on three separate and different clinical trials. The authors recognize that "*although the estimates are based on published literature and available data sets, the final value is based on judgment. For instance, survival estimates are based on published trials, but given the variation of the study populations and definitions of recurrence, it is difficult to define a single estimate that would be globally applicable*."[45]

The four studies mentioned in Table 26 all refer to the ICON7 trial. Only Barnett et al.[39] also model the treatment effect for the whole ICON7 population, while the other studies only model the high-risk subgroup. The difference in treatment effect between these two populations is as follows:

- Full trial population: a restricted mean time difference of 1.6 (-0.6 to 3.7) months in progression-free survival (PFS) between the arms and a restricted mean survival time difference in overall survival of 0.9 (-0.8 to 2.6) months.[31]
- Predefined high-risk subgroup: a restricted mean time difference of 4.1 (1.4 to 6.7) months in PFS and a restricted mean survival time difference of 4.8 (1.5 to 8.1) months in overall survival.[31]

Different extrapolation approaches are applied. For example, Duong et al.[51] mention to use the parametric function with the best overall fit to the patient-level data in the base-case analysis and test other functions in sensitivity analyses. However, it is not clear how well these parametric functions reflect the original data. Hinde et al.[44] extrapolate by assuming that the rate of mortality in those patients surviving at 5 years is the same as that found in a large observational study of epithelial ovarian cancer.[55] They also assume that the rate of progression in those women who were progression free at 5 years is the same as in patients subject to long-term follow-up in the ICON3 trial.[56]

Chappell et al.[41] model both for the whole AURELIA population, as well as a subgroup. They support this by arguing that a hypothesis-generating exploratory analysis of this trial revealed that the only subgroup to approach a statistically significant improvement in OS was bevacizumab plus paclitaxel once per week.[38]

In the NICE TA285 study, data from an initial analysis in 2010 were used by the manufacturer, while updated results from analyses in 2011 and 2012 were available.[g] The ERG stated that "*the manufacturer used data from*

[g] The ERG provides the following information related to these three analyses: "*In September 2010 approximately 29% patients had died; the median OS for bevacizumab was estimated to be 35.5 months compared with 29.9 months in the placebo group (hazard ratio versus placebo 0.751 [0.537 to 1.052]). In August 2011 approximately 49% patients had died; the median OS for bevacizumab was estimated to be 33.3 months compared with 35.2 months in the placebo group (hazard ratio versus placebo 1.027 [0.792 to 1.331]). In March 2012 approximately 59% patients had died; the median OS for bevacizumab was estimated to be 33.4 months compared with 33.7 months in the placebo group (hazard ratio versus bevacizumab 0.960 [0.760 to 1.214])*."

September 2010 to inform a number of model parameters including PFS, OS, adverse events, and post-progression treatments. The ERG considers that use of data from March 2012 would have been more appropriate for data that was collected at that time point, in particular OS data. The ERG considers the use of less mature data in the model, where more recent data were available, to be a major weakness of the analysis."[50] They add that "*The direction of effect in the first interim analysis favoured bevacizumab (25% reduction in risk of mortality; HR 0.75; 95% CI: 0.53 to 1.05). The mean effect size generated from the second and third interim analyses approached 1, that is, there was no difference between bevacizumab and placebo in the duration of OS.*"[50] The manufacturer extrapolated the less mature PFS and OS data by selecting the log-logistic distribution, which had the best statistical fit. In the end, the ERG believes that "*the use of September 2010 data to inform OS within the model may have resulted in an overestimate of the effectiveness of bevacizumab*."

Table 24 – Treatment effect in the identified economic evaluations (part 1/4)

Reference	Treatment effect		
NICE TA284, 2012 (UK)		Clinical trial (median months)	Model result
	Model results compared with clinical data (GOG 218):		
	Chemotherapy arm		
	PFS	12.12	12.00
	Post-progression survival	27.27	33.00
	OS	39.39	45.00
	Bevacizumab arm		
	PFS	18.79	19.00
	Post-progression survival	20.96	28.00
	OS	39.75	47.00
	Model results compared with clinical data (ICON7):		
	Chemotherapy arm		
	PFS	10.12	10.15
	Post-progression survival	17.64	18.69
	OS	27.76	28.85
	Bevacizumab arm		
	PFS	15.80	15.69
	Post-progression survival	19.32	21.23
	OS	35.12	36.92
Cohn et al., 2011 (US)	GOG 218 Median PFS (months): - PC: 10.3 - PCB: 11.2 - PCB + B: 14.1		
Cohn et al., 2015 (US)	GOG 218 Median PFS (months): - PC: 10.3 - PCB: 11.2 - PCB + B: 14.1 Median OS (months): - PC: 39.3 - PCB: 38.7 - PCB + B: 39.7		

Table 25 – Treatment effect in the identified economic evaluations (part 2/4)

Reference	Treatment effect		
Mehta et al., 2014 (US)	Transition probabilities		
	GOG 218 trial:	CPB arm	CP arm
	Stable to progressive	0.0334	0.0455
	Stable to death	0.0120	0.0121
	Stable to stable	0.9521	0.9399
	Progressive to death	0.0525	0.0525
	Progressive to progressive	0.9449	0.9449
	ICON7 trial		
	Stable to progressive	0.0295	0.0446
	Stable to death	0.130	0.0165
	Stable to stable	0.9550	0.9364
	Progressive to death	0.0525	0.0525
	Progressive to progressive	0.9449	0.9449
Lesnock et al., 2011 (US)	GOG 158, GOG 178 & GOG 218:	Estimate	Range
	Progression Free Survival (months):		
	CP (Optimal):	24	reference
	CP (Suboptimal):	14	reference
	CP+P (Optimal):	35	17.5 – 105
	CP+P (Suboptimal):	20	10 – 60
	CPB+B (Optimal):	35	17.5 – 105
	CPB+B (Suboptimal):	20	10 – 60
	Overall Survival (months):		
	CP (Optimal):	48	reference
	CP (Suboptimal):	35	reference
	CP+P (Optimal):	70	35 – 210
	CP+P (Suboptimal):	42	21 – 126
	CPB+B (Optimal):	70	35 – 210
	CPB+B (Suboptimal):	42	21 – 126

Table 26 – Treatment effect in the identified economic evaluations (part 3/4)

Reference	Treatment effect
Barnett et al., 2013 (US)	ICON7 - HR overall survival: 0.65 (the Hoyle and Henley method) - HR overall survival: 0.64 (95% CI: 0.48-0.85)
Chan et al., 2014 (US)	ICON7 subgroup Median PFS (months): - PC: 10.5 - PCB + mB: 15.9 Median overall survival (months): - PC: 28.8 - PCB + mB: 36.6 Hazard ratio: - PFS: 0.68 (95% CI: 0.55–0.85) - Overall survival: 0.64 (95% CI: 0.48–0.85)
Duong et al., 2016 (Canada)	ICON7 subgroup: Transition probabilities (PFS to Progressed, PFS to Death, and Progressed to Death) were based on the ICON7 trial and extrapolated applying log logistic parametric functions.
Hinde et al., 2016 (UK)	ICON7 subgroup: - PFS: mean difference of 3.5 months ($P < 0.001$) - OS: mean difference of 4.8 months ($P = 0.03$)

Table 27 – Treatment effect in the identified economic evaluations (part 4/4)

Reference	Treatment effect		
Chappell et al., 2016 (US)	AURELIA median PFS (months): - chemo: 3.4 - chemo + B: 6.7 median OS (months): - chemo: 13.3 - chemo + B: 16.6 Subgroups: (chemo vs. chemo + B, months) - Weekly paclitaxel (PFS): 3.9 versus 10.4 - Weekly paclitaxel (OS): 13.2 versus 22.4 - PLD (PFS): 3.5 versus 5.4 - Weekly topotecan (PFS): 2.1 versus 5.8 Hazard ratio: - PFS: 0.48 (95% CI, 0.38 to 0.60) - OS: 0.85 (95% CI, 0.66 to 1.08)		
NICE TA285, 2012 (UK)	OCEANS trial Median duration of PFS: - CGB: 12.4 months - CG: 8.4 months HR: 0.484 (95% CI: 0.388 to 0.605; p <0.0001). median OS: - CGB: 35.5 months - CG: 29.9 months HR: 0.751 (95% CI: 0.537 to 1.052).		
	Model results compared with clinical data (OCEANS):	Clinical trial (median months)	Model result
	Chemotherapy arm		
	PFS	8.4	8.77
	Post-progression survival	21.53	21.92
	OS	29.93	30.69
	Bevacizumab arm		
	PFS	12.4	12.46
	Post-progression survival	23.12	23.54
	OS	35.52	36.00

6.3.7 Uncertainty

Most input parameters are surrounded by uncertainty and can be described by a probability distribution, rather than a point estimate. For parameter uncertainty, most guidelines recommend probabilistic sensitivity analysis (PSA).[57] All but three of the identified economic evaluations apply PSA (Table 28). Variables changed in sensitivity analysis were a.o. drug costs, extrapolation scenarios, mortality and PFS, QoL, vial sharing, costs for complications, time horizon, etc. Duong et al.[51] also performed a threshold analysis calculating the price at which the lower dose of bevacizumab could be considered cost-effective for the English NHS.

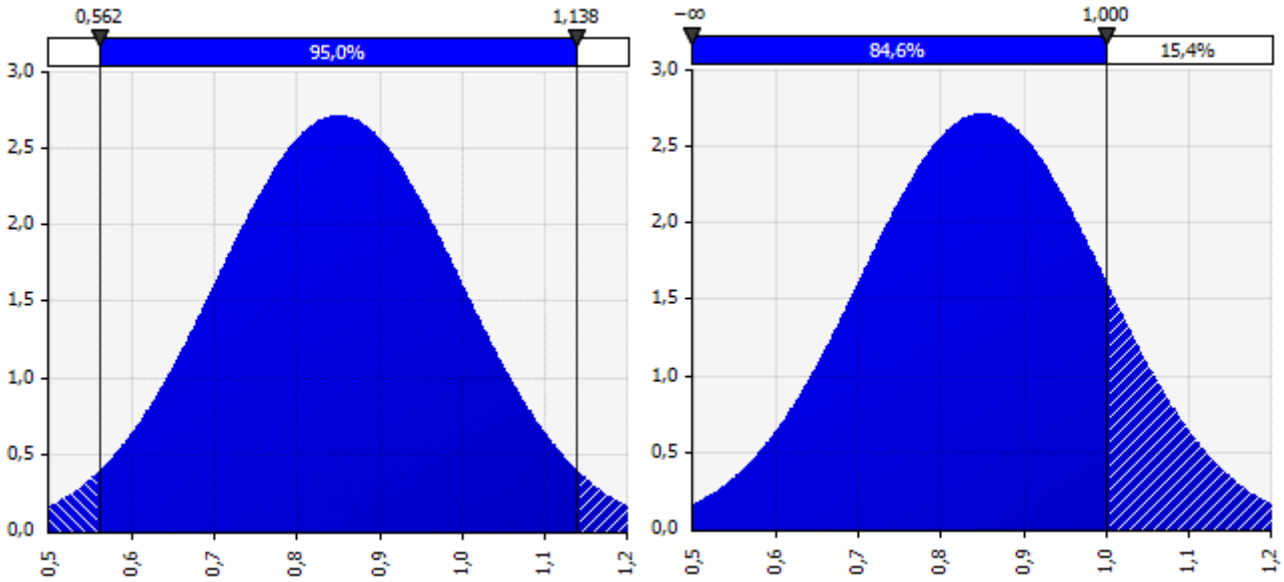
In TA284, the ERG group noticed that a lot of variables were subjected to sensitivity analyses: PFS extrapolation, post-progression survival, utility values, administration, AE and chemotherapy costs, time horizon and discounting rates. However, "*some key input parameters (such as the cost of bevacizumab, treatment duration and variation in effectiveness) which might be expected to be highly influential on the cost effectiveness results have been omitted from the sensitivity analysis*."[49] Therefore, the ERG conducted some additional analyses. For an overview of the most influential variables we refer to the results section (part 7.2.1).

Variables were not always varied according to the 95% confidence intervals. For example, Chappell et al.[41] varied costs and rates between 50% and 200% of the base case estimates. Mehta et al.[46] increased or decreased values by 25%. When performing PSA, details of the probability distribution were not always provided. In one case, inappropriate probability distributions were applied: Cohn et al.[43] mentioned to use a Normal distribution to model utilities with a mean of 0.85 and a standard deviation of 0.147. However, in this normal distribution, about 15% of simulated utilities would be bigger than 1, which is the maximum value for utilities (see Figure 10). For utilities, a Beta distribution is more appropriate.

Table 28 – Sensitivity analysis in the identified economic evaluations

Reference	Uncertainty
NICE TA284, 2012 (UK)	PSA + one-way sensitivity analyses.
Cohn et al., 2011 (US)	One-way sensitivity analyses.
Cohn et al., 2015 (US)	PSA + one-way sensitivity analyses.
Mehta et al., 2014 (US)	PSA + one-way sensitivity analyses.
Lesnock et al., 2011 (US)	One-way and two-way sensitivity analyses.
Barnett et al., 2013 (US)	PSA + one-way sensitivity analyses.
Chan et al., 2014 (US)	PSA + one-way sensitivity analyses.
Duong et al., 2016 (Canada)	PSA + one-way sensitivity analyses.
Hinde et al., 2016 (UK)	PSA + one-way sensitivity analyses.
Chappell et al., 2016 (US)	One-way sensitivity analyses.
NICE TA285, 2012 (UK)	PSA + one-way sensitivity analyses.

Figure 10 – Problems when applying an inappropriate probability distribution



6.3.8 Results

In this part, we provide an overview of the results as published by the several studies, together with an overview of the identified most determining variables (at the end of this part).

NICE TA284 (UK)

According to the calculations of the manufacturer, the deterministic study results relying on the GOG-0218 trial provide an incremental cost per QALY gained of £144 066. For the ICON7 high-risk subgroup, an ICER of £31 592/QALY is reported. In the probabilistic analyses, this becomes on average £144 682/QALY and £32 683/QALY (Table 29). In the PSA for the GOG-0218 trial, at a threshold willingness to pay of £30 000 per QALY gained, there is a 0% probability of CPB being cost-effective, relative to treatment with CP. Applying the ICON7 trial results, this becomes 42.3%. At a £20 000 per QALY threshold, the latter probability becomes 2.1%.[47]

The ERG remarks a.o. for the GOG-0218 study results that "*the treatment duration used within the model has been underestimated by using a maximum of one year, rather than 15 months as stated in the SPC for bevacizumab and for the GOG-0218 trial, and therefore the cost of bevacizumab has been underestimated. … a relatively favourable hazard ratio for PFS was used in the model … [based on an analysis that censored progression events defined by rising CA-125], … which might have produced a more favourable cost effectiveness estimate.*"[49]

For the economic evaluation based on the ICON7 trial, the ERG mentions that "*overall, the ICON7 model is built using appropriate data, with appropriate outcomes and is generally well described and justified in the MS.*

The data used in the model do however represent a subgroup of a clinical trial and consequently estimates based on this subgroup may not be very precise, simply because of the relatively small sample size."[49] Related to this, the manufacturer's PSA indicates that "*there is limited uncertainty in the degree of cost-effectiveness of the GOG-0218 trial … whilst there is much more uncertainty in the cost-effectiveness of the ICON7 study*."[47]

Cohn et al. 2011, 2015 (US)

The PC strategy is the least expensive ($2.5 million). The PCB strategy (without maintenance bevacizumab) costs $21.4 million. The PCB+mB strategy was the most expensive ($78.3 million) (Table 30). PCB was dominated and PCB+mB had an ICER of $401 088 per PF-LYS. When the cost of bevacizumab was reduced with 75%, this disease-specific ICER decreased to less than $100 000 per PF-LYS.[42] In the updated analysis, PCB was still dominated by a combination of PC and PCB+mB. The latter had an ICER of $792 380/QA-PFY compared to PC. In a model not incorporating QOL, this ICER became $632,571/PFY in comparison with PC. A reduction of the bevacizumab cost with 50%, 67%, and 75%, improved the ICER for PCB+mB compared to PC to $405 898, $281 395, and $216 635/QA-PFY, respectively.[43]

In the probabilistic analysis, with a WTP threshold of $100 000/QA-PFY, "*PC was the treatment of choice in 100% of simulations. PC remained the treatment of choice in 100% of simulations unless the WTP threshold exceeded $360 000/QA-PFY*."[43] Only when the cost of bevacizumab was less than 10% of the baseline, the ICER was less than $100 000 per QA-PFY.[43]

Mehta et al., 2014 (US)

Mehta et al. provide results for both the GOG-0218 study and subgroup of the ICON7 trial. "*The base case results for both the clinical trials resulted in the CPB strategy being cost-ineffective at a cost-effectiveness willingness-to-pay threshold of $150 000/QALY. The base case ICER for GOG-218 trial is $2 420 691/QALY and $225 515/QALY for ICON-7 trial. Considering the different patient populations for both the clinical trials, the strategy is cost-ineffective in the universal pool of patients of GOG-218 trial and in the high-risk subset of individuals of the ICON-7 trial*."[46] Applying a lower cost for bevacizumab did improve the ICER, but it remained relatively high: "*biosimilar bevacizumab didn't reduce cost sufficiently to change conclusions.*"[46]

Lesnock et al., 2011 (US)

The model of Lesnock et al., based on the GOG 158, GOG 178 and GOG-0218 trials, was the only model also including consolidated P to sustain a remission. This treatment option resulted in a cost of $23,886 per patient with an effectiveness of 3.36 QALYs. For consolidation B, the cost was $122 899 per patient with a similar effectiveness of 3.31 QALY's (Table 30). "*When compared to the reference arm, the ICER for CP+P is $13 402/QALY and is $326 530/QALY for CPB +B. When all three strategies are compared simultaneously, CPB+B is dominated by CP+P. In other words, CPB+B is more costly and less effective than CP+P*."[45] The authors calculated that the total cost of CPB+mB would have to drop to less than 12% of the current cost before it would become a cost-effective alternative to CP+P.[45]

Barnett et al., 2013 (US)

The economic evaluation of Barnett et al. was the only study including the ICON7 study results for all included patients, next to the high-risk subgroup. Giving bevacizumab to all patients was extendedly dominated by a combination of chemotherapy without bevacizumab treatment and providing bevacizumab to high-risk patients. The latter had an ICER of $168 000 per QALY gained compared with chemotherapy alone (Table 31). The scenario including a predictive test had an ICER of $129 000 per QALY compared with chemotherapy alone and dominated other bevacizumab treatment strategies.[39] However, the authors remark that there is currently not a predictive biomarker test for bevacizumab responsiveness.[39] Based on the PSA, "*at a willingness-to-pay threshold of $100 000 per QALY, [chemotherapy] for all is the strategy of choice. At willingness-to-pay thresholds of $150 000 per QALY and $200 000 per QALY, [CPB+mB] for high risk is the strategy of choice in 24% and 82% of simulations, respectively.*"[39]

Chan et al., 2014 (US)

The study of Chan et al. calculated an 8-month improvement in OS and presented an ICER for CPB+mB versus CP of $167 771 per life-year saved. However, the cost-effectiveness acceptability curve showed that most estimated ICERs were higher than this ICER: "*In a willingness-to-pay threshold of $200 000, approximately 37% of samples suggested that the addition of B was cost-effective.*"[40] With a skewed distribution to the right, this should on average result in an ICER which is higher than $200 000/LYG. It is unclear how this difference between presented numbers and the figure can be explained.

Duong et al., 2016 (Canada)

This Canadian study calculated that "*ovarian cancer patients at high risk of progression receiving bevacizumab plus standard chemotherapy experienced a mean incremental QALY gain of 0.374 years. At an additional cost of $35 902, the ICER for the addition of bevacizumab to standard chemotherapy, relative to standard chemotherapy alone, was $95 942 per QALY.*"[51]

Hinde et al., 2016 (UK)

Similar as the previous study, Hinde et al. also calculated an incremental QALY gained of 0.381 QALYs, although based on higher total QALYs for both the intervention and comparator group. The bevacizumab treatment arm was associated with an incremental costs of £18 684 versus the chemotherapy arm. The largest part (£17 760) of this incremental cost was the additional drug-related cost for bevacizumab.[44] In the base-case analysis this study calculated that "*bevacizumab has an ICER of £48 975 per additional QALY, which is above NICE's standard cost-effectiveness threshold (£20 000–£30 000 per QALY). The official price of bevacizumab in 2013 was between £2.31 and £2.63 per milligram. A price reduction of between 46% and 67%, dependent on the NICE threshold, would be required for the product to be cost-effective in the high-risk subgroup.*"[44]

Chappell et al., 2016 (US)

The economic evaluation of Chappell et al. used a disease-specific outcome: extra costs per progression-free life-year saved (PFLYS). Based on the AURELIA trial, inclusion of bevacizumab in the treatment of platinum-resistant recurrent ovarian cancer resulted in an ICER of $100 000 per PFLYS for 15-mg/kg 3-weekly dosing and $160 000 per PFLYS for the 10-mg/kg bi-weekly dosing (Table 32). Exploratory analysis of different bevacizumab chemotherapy partners showed better or worse ICERs. However, the authors also notice that "*although this subgroup result is promising, it comes with the caveat that this exploratory analysis is underpowered.*"[41]

NICE TA285 (UK)

Referring to the results of the OCEANS trial, the manufacturer calculated a deterministic and probabilistic ICER of £149 050 and £221 750 per QALY, respectively, for bevacizumab treatment in comparison with the placebo group (Table 32). The ERG remarks that "*the probabilistic ICER is likely to provide a more reliable estimate of cost-effectiveness*."[50] Based on the PSA, the manufacturer states that "*there is a 0.0% chance of the addition of 15mg/kg bevacizumab to carboplatin/gemcitabine combination therapy being considered cost-effective at a willingness to pay threshold of £30 000 per QALY. At a willingness to pay threshold of £100 000 per QALY, this rises to 14.7%*."[48] In all of the scenario analyses, none of the deterministic ICERs had an ICER of less than £120 000 per QALY. The ERG considered the results even to be optimistic since the OS benefit associated with bevacizumab was likely to be overestimated in the manufacturer's base case. This would only worsen the results.[h] As stated by the manufacturer, "*it is clear that if later data-cuts were more complete and were incorporated*

[h] The ERG mentioned that a scenario with an equivalent OS would result in a deterministic ICER of £1,826,779 per QALY for bevacizumab in comparison with the placebo group (IC: £44,059; QALYs gained: 0.02).[50]

into the economic model, the ICER would be greater than the current estimate of £150 000 per QALY and therefore do not impact on the likelihood of meeting NICE's cost-effectiveness threshold."[50]

Influential variables

Table 33 gives an overview of the most influential variables for the cost-effectiveness of bevacizumab that were identified in the different economic evaluations. Not surprisingly, the cost of bevacizumab is most influential. Related to this are the dose and treatment duration with bevacizumab. Furthermore, also the treatment effect on overall survival and impact on QoL were most influential.

Table 29 – Results of the identified economic evaluations (part 1/4)

Reference	Results (I)C, (I)E, ICER				
NICE TA284, 2012 (UK)		GOG-0218:		ICON7:	
		CP	CPB + mB		
	Total costs	£17,166	£44,254	£16,111	£33,841
	Total LYG	3.985	4.212	3.066	3.809
	Total QALYs	2.973	3.161	2.278	2.839
	Inc. costs		£27,089		£17,729
	Inc. LYG		0.228		0.743
	Inc. QALYs		0.188		0.561
	ICER (£/LYG)		£118,876		£23,846
	ICER (£/QALY)		£144,066		£31,592
	Probabilistic results (2.5% and 97.5% percentiles between brackets)				
		GOG-0218		ICON7	
		CP	CPB + mB	CP	CPB + mB
	Total costs	£17,570	£44,704	£16,143	£33,891
		(16,302 - 19,087)	(43,300 - 46,343)	(15,367 - 17,068)	(32,899 - 34,978)
	Total LYG	3.987	4.214	3.058	3.813
		(3.76 - 4.21)	(4 - 4.43)	(2.731 - 3.409)	(3.411 - 4.237)
	Total QALYs	2.976	3.163	2.272	2.841
		(2.8 - 3.17)	(2.99 - 3.35)	(2.034 - 2.518)	(2.548 - 3.154)
	Inc. costs		£27,133		£17,748
			(25,243 - 29,072)		(16,770 - 18,821)
	Inc. LYG		0.227		0.755
			(0.215 - 0.24)		(0.342 - 1.23)
	Inc. QALYs		0.188		0.569
			(0.177 - 0.199)		(0.273 - 0.918)
	ICER (£/LYG)		£119,367		£25,844
			(108,879 - 130,318)		(15,005 - 49,341)
	ICER (£/QALY)		£144,682		£32,683
			(131,654 - 158,355)		(20,379 - 61,861)

Table 30 – Results of the identified economic evaluations (part 2/4)

Reference	Results (I)C, (I)E, ICER			
Cohn et al., 2011 (US)	GOG 218	Total Cost (600 patients)	PFS (months)	ICER ($/PF-LYS)
	PC	$2.5 million	10.3	Referent
	PCB	$21.4 million	11.2	479,712
	PCB + B	$78.3 million	14.1	401,088
Cohn et al., 2015 (US)	GOG 218	Mean Cost (95% CI)	mean QA-PFY (95% CI)	ICER ($/QA-PFY)
	Primary analysis			
	PC	$4044 (3823–4296)	1.1 (1.04–1.16)	Referent
	PCB	$43,703 (42,342–44,087)	1.13 (1.07–1.18)	Dominated
	PCB + B	$122,700 (120,572–124,784)	1.25 (1.19–1.30)	$792,380
	Secondary analysis	Mean Cost (95% CI)	mean QALY	ICER ($/QALY)
	PC	idem	not reported	Referent
	PCB	idem	not reported	Dominated
	PCB + B	idem	not reported	$2,523,405/QALY
Mehta et al., 2014 (US)	GOG 218 trial		CP arm	CPB arm
	Life expectancy (years)		1.78	1.97
	Incremental life expectancy (years)			0.19
	Total cost — base case (USD)		70,158	201,423
	Total cost — biosimilar bevacizumab (USD)		70,158	162,500
	Incremental cost (USD)			131,265
	Incremental cost — biosimilar (USD)			92,342
	QALY		1.252	1.306
	Incremental QALY			0.05
	ICER — base case			$2,420,691/QALY
	ICER — biosimilar bevacizumab			$1,702,968/QALY
	ICON7 trial		CP arm	CPB arm
	Life expectancy (years)		1.67	2.01
	Incremental life expectancy (years)			0.34
	Total cost — base case (USD)		63,311	125,114
	Total cost — biosimilar bevacizumab (USD)		63,311	107,598
	Incremental cost (USD)			61,803
	Incremental cost — biosimilar (USD)			44,286
	QALY		1.234	1.508
	Incremental QALY			0.27
	ICER — base case			$225,515/QALY
	ICER — biosimilar bevacizumab			$161,603/QALY
Lesnock et al., 2011 (US)	GOG 158, 178 & 218	Cost - (Incr. Cost)	QALYs - (Incr. QALYs)	ICER ($/QALY)
	CP	$18,877	2.99	
	CP + P	$23,886 ($4,909)	3.36 (0.37)	$13,402
	CPB + mB	$122,899 ($99,012)	3.31 (-0.05)	Dominated

Table 31 – Results of the identified economic evaluations (part 3/4)

Reference	Results (I)C, (I)E, ICER			
Barnett et al., 2013 (US)	ICON7	Mean Cost (95% CI)	QALYs (95% CI)	ICER
	- CP for all	$6220 (5800-6667)	2.80 (2.74-2.86)	Referent
	- CPB + mB for high risk	$20,751 (18,517-23,017)	2.89 (2.84-2.94)	$168,610/QALY
	- CPB + mB for all	$56,351 (56,052-56,682)	2.88 (2.84-2.93)	Dominated
	scenario: - test for bevacizumab responsiveness	$19,605 (17,507-21,776)	2.90 (2.85-2.95)	$128,928/QALY (CT+B for high risk → dominated)
Chan et al., 2014	ICON7 subgroup CP versus CPB + mB		LYG: +8 months	ICER: $167,771/LYS
Duong et al., 2016 (Canada)	ICON7 subgroup	Cost	QALY	ICER (CAD/QALY)
	PC	CAD18,495	2.287 QALYs	
	PCB + mB	CAD54,396	2.661 QALYs	
	Incremental	CAD35,902	0.374 QALYs	$95,942/QALY
Hinde et al., 2016 (UK)	ICON7 subgroup	Total costs	Total QALYs	ICER (£/QALY)
	PC	£12,876	2.820 QALYs	
	PCB + mB	£31,560	3.201 QALYs	
	Incremental	£18,684	0.381 QALYs	£48,975/QALY

Table 32 – Results of the identified economic evaluations (part 4/4)

Reference	Results (I)C, (I)E, ICER			
Chappell et al., 2016 (US)	AURELIA	Cost ($)	PFS (months)	ICER ($/PF-LYS)
	B (10 mg/kg bi-weekly):			
	- chemo	$21,611	3.4	
	- chemo + B	$66,511	6.7	$160000
	B (15 mg/kg 3-weekly):			
	- chemo	$18,857	3.4	
	- chemo + B	$48,861	6.7	$100000
	Subgroup analysis:			
	Weekly paclitaxel			
	- chemo	$18,056	3.9	
	- chemo + B	$59,263	10.4	$76000
	Weekly paclitaxel (OS)			
	- chemo	$18,056	13.2	
	- chemo + B	$59,263	22.4	$54000
	Pegylated liposomal doxorubicin (PFS)			
	- chemo	$27,776	3.5	
	- chemo + B	$79,117	5.4	$321000
	Weekly topotecan (PFS)			
	- chemo	$18,998	2.1	
	- chemo + B	$61,147	5.8	$140000
NICE TA285, 2012 (UK)	OCEANS			
	Deterministic results	CG	CGB	
	Total costs	£14,912	£59,340	
	Total LYG	2.96	3.38	
	Total QALYs	1.98	2.28	
	Inc. costs		£44,428	
	Inc. LYG		0.42	
	Inc. QALYs		0.298	
	ICER (£/LYG)		£105,707	
	ICER (£/QALY)		£149,050	
	Probabilistic results (2.5% and 97.5% percentiles between brackets)			
	Total costs	£14,937 (14,302 - 15,646)	£59,368 (58,305 - 60,669)	
	Total LYG	2.96 (2.63 - 3.31)	3.38 (2.97 - 3.78)	
	Total QALYs	1.98 (1.75 - 2.21)	2.28 (2.01 - 2.55)	
	Inc. costs		£44,431 (43,882 - 45,105)	
	Inc. LYG		0.42 (–0.01 - 0.84)	
	Inc. QALYs		0.30 (0.02 - 0.57)	
	ICER (£/LYG)		£140,124 (–163,277 - 725,369)	
	ICER (£/QALY)		£221,750 (69,979 - 857,367)	

Table 33 – Most influential variables in the identified economic evaluations

Reference	Most influential variables
NICE TA284, 2012 (UK)	- dose and cost of bevacizumab - duration of the treatment
Cohn et al., 2011 (US)	- cost of bevacizumab.
Cohn et al., 2015 (US)	- cost of bevacizumab.
Mehta et al., 2014 (US)	- QoL - PFS - cost of bevacizumab
Lesnock et al., 2011 (US)	- cost of bevacizumab. - overall survival
Barnett et al., 2013 (US)	- cost of bevacizumab.
Chan et al., 2014 (US)	- hazard ratio for difference in overall survival.
Duong et al., 2016 (Canada)	- time horizon, health state utilities, and the parametric function used to extrapolate overal survival.
Hinde et al., 2016 (UK)	- cost of bevacizumab. - mortality and extrapolation.
Chappell et al., 2016 (US)	- cost of bevacizumab.
NICE TA285, 2012 (UK)	- OS - the duration of treatment - the utility of patients in PFS

6.3.9 Authors' conclusions

We provide an overview of the summary/conclusions of the authors. In general, the conclusions are not beneficial for bevacizumab, especially not for the licensed dose of 15mg/kg. Even for the unlicensed doses of 7.5mg/kg as administered in the ICON7 trial, the conclusions are not very optimistic. The most positive conclusions come from the study of Chappell et al. applying a difficult to interpret disease-specific outcome (PF-LYS), Chan et al. applying a very high WTP threshold, and the Canadian industry-sponsored study of Duong and colleagues. The best results are obtained by a combination of 1) administration of the lower doses of bevacizumab (and only 12 additional cycles as in the ICON7 trial instead of 16 as in the GOG-0218 trial), and 2) for a selection of high-risk patients, and 3) in combination with a price discount. Related to the selection of high-risk patients, Barnett et al. states that "*the subgroup analysis performed in ICON7 requires validation in future studies to strengthen the conclusions in our analysis.*"[39]

NICE TA284 (UK)

- GOG-0218: "The model results suggest that bevacizumab is not cost effective at the licensed dose for a willingness-to-pay threshold of £20 000-£30 000 per QALY."[49]
- ICON7: we remark that in the "Summary of cost effectiveness issues" of the ERG report,[49] no conclusions are made with respect to the modelled ICON7 trials results, which used a lower dose than was licensed.

Cohn et al. 2011 (US)

- GOG-0218: "*The addition of bevacizumab to standard chemotherapy in patients with advanced ovarian cancer is not cost effective. Treatment with maintenance bevacizumab leads to improved PFS but is associated with both direct and indirect costs. The cost effectiveness of bevacizumab in the adjuvant treatment of ovarian cancer is primarily dependent on drug costs.*"[42]

Cohn et al. 2015 (US)

- GOG-0218: "*In this analysis of patients with advanced ovarian cancer treated on GOG-0218, we demonstrate that the addition of bevacizumab to standard carboplatin and paclitaxel is not cost-effective. While the regimen of concurrent and maintenance bevacizumab (PCB + B) had the longest progression free survival (compared with PC or PCB), the decrement in quality of life and the additional cost of bevacizumab led to a high incremental cost–effectiveness ratio (ICER) compared to PC, far exceeding usual willingness to pay thresholds.*"[43]

Mehta et al., 2014 (US)

- GOG-0218 & ICON7: "*Addition of bevacizumab, by in large, is cost-ineffective. It can become cost-effective with the ICON-7 protocol, in patients at high risk of progression using biosimilar bevacizumab.*"[46]

Lesnock et al., 2011 (US)

- GOG 158, 178 & 218: "*Consolidation for advanced epithelial ovarian cancer was associated with a modest improvement in effectiveness that is less than that with P consolidation and more costly. A statistically significant improvement in survival may improve the value of B consolidation.*"[45]

Barnett et al., 2013 (US)

- ICON7 (All & high-risk subgroup): "*The selective treatment of women with suboptimal and/or stage IV ovarian cancer was a more cost-effective use of bevacizumab than universal treatment but still did not fall within the limits of common willingness-to-pay thresholds. Continued investigation of potentially cost-effective strategies, such as a predictive test, is necessary to optimize the use of this expensive treatment.*"[39]

Chan et al., 2014 (US)

- ICON7 high-risk subgroup: "*In this clinically relevant subset of women with high-risk advanced ovarian cancer with overall survival benefit after bevacizumab, our economic model suggests that the incremental cost of bevacizumab was approximately $170 000 [per LYG]. … In this economic analysis in a subset of high-risk advanced ovarian cancer patients with survival benefit, we showed that adding bevacizumab was near cost-effective based on current benchmarks.*"[40]

Duong et al., 2016 (Canada)

- ICON7 high-risk subgroup: "*No formal health technology assessment willingness-to-pay threshold exists in Canada. However, at a threshold of CAD100 000 per qaly, bevacizumab in addition to chemotherapy is a cost-effective alternative for ovarian cancer patients who are at high risk of progression (stage III suboptimally debulked, and stage III or IV with unresectable disease). Using the CAD100 000 per qaly threshold in a probabilistic sensitivity analysis, it was determined that, compared with standard chemotherapy, the addition of bevacizumab to chemotherapy is cost-effective in 56% of tested scenarios.*"[51]

Hinde et al., 2016 (UK)

- ICON7 high-risk subgroup: "*The lower dose of bevacizumab for advanced ovarian cancer is not cost-effective based on the product's list price and using NICE's cost-effectiveness thresholds. Significant price discounts would be needed to make the drug affordable to the NHS.*"[44] "*Although the ICON7 trial found that there were gains from bevacizumab in both overall survival and PFS in this subgroup, the short duration of these gains and the significant acquisition cost associated with bevacizumab resulted in only small gains in expected QALYs but a high incremental cost.*"[44]

Chappell et al., 2016 (US)

- AURELIA: "*Using a willingness-to-pay threshold of $100 000 incremental cost-effectiveness ratio (ICER), the addition of bevacizumab to chemotherapy either demonstrates or approaches cost-effectiveness and net health benefit when added to the treatment of patients with platinum-resistant recurrent ovarian cancer. Additionally, exploratory subgroup analysis suggests that bevacizumab in combination with weekly paclitaxel is the most cost-effective use of bevacizumab to date.*"[41]

NICE TA285 (UK)

- OCEANS: "*The ERG's revised base case ICER for the addition of bevacizumab to gemcitabine and carboplatin was comparable to the manufacturer's estimate, and was calculated to be £148 360/QALY (deterministic) and £212 079/QALY (probabilistic). The ERG agrees with the manufacturer that the model was robust to changes in many of the model inputs; however, the ERG considers that the key driver of the cost-effectiveness results was the estimate of OS gain associated with bevacizumab. The manufacturer elected to use data from September 2010, rather than March 2012, in the economic analysis.*

  The ERG has concerns that the OS gain estimated for the bevacizumab group is associated with a large degree of uncertainty. Moreover, at the September 2010 time point, an OS benefit was found for the bevacizumab group that was not sustained at the March 2012 analysis; therefore, the ERG believes that the OS benefit associated with bevacizumab is likely to be overestimated."[50]

Key Points

- **No good QoL estimates, measured with a generic utility instrument, were identified for both the control arm and bevacizumab treatment arm in the economic evaluations. A lot of different assumptions were made related to the impact of bevacizumab treatment on QoL, both in favour and disfavour of the drug.**
- **Based on the identified economic literature, the health gains with bevacizumab for the treatment of ovarian cancer seem to be relatively small. In contrast, the extra costs associated with bevacizumab treatment are significant. The combination of relatively small health gains with high extra costs leads to very high ICERs.**
- **The majority of results and conclusions of the authors are not in favour of bevacizumab. Even the manufacturer's submission to NICE demonstrate the intervention is not cost-effective, both in first and second line, at the licensed doses and applying NICE's ICER threshold.**
  These results were critically assessed by an Evidence Review Group. Outcomes of both manufacturer's submission would even be worse if the observed treatment duration would have been applied (TA284) or if the most up-to-date results would have been taken into account (TA285).
- **Even for a selected high-risk subgroup from the ICON7 trial, in combination with a lower doses (7.5mg/kg instead of 15mg/kg) and a shorter treatment duration (maximum 18 3-weekly cycles), most analyses still provide unfavourable results.**
- **The price of bevacizumab is one of the most influential variables. According to several sensitivity analyses, very large price discounts (up to 90%) are needed to consider the bevacizumab treatment being cost-effective, which of course highly depends on the stated willingness-to-pay (see discussion in part 8.8).**

7 COST-EFFECTIVENESS OF BEVACIZUMAB IN OVARIAN CANCER IN BELGIUM

HTA CORE MODEL DOMAIN: ECO

In this chapter the cost-effectiveness of bevacizumab versus relevant comparators for the first and second-line treatment of ovarian cancer is calculated for Belgium. We provide a transparent overview of all input variables. The Belgian guidelines for economic evaluations are followed,[58] and the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist[59] for transparently reporting all relevant information is provided in Appendix.

7.1 Input

7.1.1 Perspective of the evaluation

In accordance with the Belgian guidelines, the analysis is performed from the health care payer's perspective and includes direct health care costs. Payments out of the government's health care budget as well as patients' co-payments are included. No extension to a societal perspective was modelled since there is no evidence for relevant differences in employment rate, transport or other costs. An incremental impact seems negligible and would thus not influence the results.

7.1.2 Population

The guidelines recommend that "*the patient population to which the economic evaluation applies should be consistent with the patient population defined in the clinical part of the reimbursement request submission.*"[58] In this economic evaluation, we include the evidence of the published selected trials in the medical part of this report (see part 5.2.1). Results of the GOG-0213 trial were not modelled since results were not published at the moment of writing of this report. The description of the eligible population in the selected studies is as follows:

- **GOG-0218**: "previously untreated, incompletely resectable stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian-tube cancer histologically confirmed by the Gynecologic Oncology Group (GOG) Pathology Committee after standard abdominal surgery with maximal debulking effort within 12 weeks before study entry; a GOG performance status score … of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about more than 50% of waking hours); and no history of clinically significant vascular events or evidence of intestinal obstruction. Owing to competing trials, patients with stage III disease and no residual lesions greater than 1 cm in maximal diameter were initially excluded, but after a protocol modification they were permitted."[28]
- **GOG-0218 stage IV**: subgroup of GOG-0218 eligible patients with stage IV cancer.
- **ICON7 all**: "Eligible patients were aged 18 years or older; with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; FIGO 1988 stage IIb–IV or high-risk (grade 3 or clear cell histology) stage I–IIa disease; had undergone debulking cytoreductive surgery or, in advanced disease, had a biopsy with no further surgery planned; and had adequate coagulation parameters and liver, renal, and bone marrow function. The exclusion criteria were having other tumour types, previous systemic therapy, planned surgery, and uncontrolled hypertension."[31]
- **ICON7 high-risk subgroup**: "High risk of progression was defined as stage IV disease, inoperable stage III disease, or suboptimally debulked (>1 cm) stage III disease … ."[31]
- **OCEANS**: "histologically confirmed platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer and disease progression > 6 months after completion of front-line platinum-based chemotherapy."[34]
- **AURELIA**: "histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer … that had progressed within 6 months of completing > four cycles of platinum-based therapy."[26]

Table 34 gives an overview of age and body weight in the GOG-0218 and ICON7 (high-risk) populations. Information on averages and standard deviation was retrieved from the manufacturer's submission to NICE (TA284 and TA285). Both of these studies refer to a UK retrospective study to calculate the body weight. However, in one study, an average body weight of 60.49kg was included in the base case, while the other study, referring to the same source, included a mean body weight of 69.35kg.

Table 34 – Population characteristics – Age and weight

	Age (years)	Weight
GOG-0218[28]	Median: 60	Mean: 70.68kg[a]; SD: 18.6kg[a]
ICON7[31]	Median: 57	Mean: 66.69kg[a]; SD: 14.08kg[a]
ICON7 high-risk[31]	Median: 60	Mean: 66.07kg[a]; SD: 13.16kg[a]
Manufacturer submission TA284[47]		
Sacco et al.[52]	Mean: 56.34	Mean: 60.49kg[a, b]; SD: 13.08kg[a]
Manufacturer submission TA285[48 c]		
Sacco et al.[52]	Mean: 61.37	Mean: 69.35kg[d]; SD: 17.52kg
OCEANS[34]	Mean: 61.02	Mean: 75.68kg; SD: 18.47kg
AURELIA[26]	Median: 61-62	Not available

a: information retrieved from table 50 in NICE TA284[47];
b: the manufacturer's submission mentions that mean body weight = 68.15 x (mean BSA / mean population BSA)^(1/0.425) = 60.49, with 68.15kg being the body weight from an overall survey female population. However, the ERG[50] was unable to locate the overall survey population weight of 68.15 kg in the referred study of Sacco et al.[52];
c: This study was based on the OCEANS trial. However, body weight from a UK multicentre retrospective study were taken into account – data retrieved from table 28 in the report of Edwards et al.[50] and table 38 in TA285;[48]
d: Body weight was calculated from BSA, which was on average 1.71 in a population on 321 ovarian cancer patients in a study of Sacco et al.[52]

In our model, we included a population of on average 60 years. Setting this value somewhat higher or lower in both the intervention and comparator group did not have a meaningful incremental influence on results and is not further taken into account. The body weight, on the other hand, is of more importance since this influences the treatment cost with bevacizumab.

We don't have information on body weight for our Belgian population. However, we have information on the cost of bevacizumab per cycle and thus number of vials used per cycle. Also for the above weights, we can calculate the theoretical average cost per cycle. This is done in four steps: 1) sample a population (1000 patients) with the same weight characteristics; 2) calculate the dosage of bevacizumab (15mg/kg, 10mg/kg or 7.5mg/kg body weight); 3) determine the number of needed vials (of 100mg or 400mg); 4) calculate the total cost applying the Belgian cost per vial (see further). Applying this approach, the average waste of bevacizumab without vial sharing can be calculated (see Table 35). The cost of a treatment with bevacizumab 7.5mg/kg is 52.9% of the cost with 15mg/kg body weight. This is somewhat higher than 50% due to an increase in waste (see Table 35). In case of 10mg/kg this is 68.7%.

Based on our Belgian sample of ovarian cancer patients treated with bevacizumab, we calculated the cost per cycle. In the IMA–AIMreimbursement data, a cycle was defined as all reimbursements of bevacizumab on the same day. In 3.82% of the identified cycles, bevacizumab cost was registered as a supplement to the patient without NIHDI reimbursement. These cycles were not used for calculating the cost per cycle since, based on expert opinion, it is possible that a lower dose is administered when the treatment is not reimbursed.

The Belgian cost per cycle was on average €3169 (SD: €977, based on 806 treatment cycles, see also Figure 11). In Belgium, the price of a 100mg vial and 400mg vial is €333.67 and €1240.65, respectively. If 15mg/kg body weight bevacizumab is administered, the average cost of €3169 corresponds to an average population weight of about 64kg.

Figure 11 – Distribution of Belgian bevacizumab cost per cycle

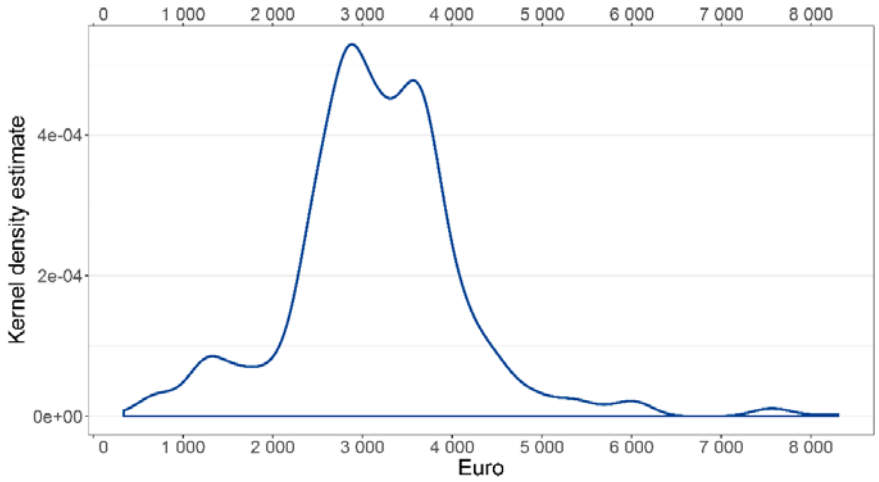


Table 35 – Percentage of waste and cost per cycle depending on body weight and doses

Source*	Weight	Average waste			Average cost		
		15mg/kg	10mg/kg	7.5mg/kg	15mg/kg	10mg/kg	7.5mg/kg
Sacco - TA285:	Mean: 69.35kg; SD: 17.52kg	4.81%	7.02%	9.02%	€3417	€2342	€1804
Sacco - TA284:	Mean: 60.49kg; SD: 13.08kg	5.37%	7.78%	10.00%	€3005	€2070	€1591
GOG-0218:	Mean: 70.68kg; SD: 18.60kg	4.82%	6.99%	8.98%	€3478	€2382	€1835
ICON7:	Mean: 66.69kg; SD: 14.08kg	4.92%	7.13%	9.23%	€3294	€2260	€1742
ICON7 high-risk:	Mean: 66.07kg; SD: 13.16kg	4.94%	7.14%	9.24%	€3265	€2241	€1727
OCEANS:	Mean: 75.68kg; SD: 18.47kg	4.46%	6.47%	8.38%	€3712	€2537	€1954

** See Table 34.*

7.1.3 Intervention and comparator

In our economic model, in agreement with the underlying research questions, both first and second-line treatment bevacizumab are modelled. In first line, results of the GOG-0218 and ICON7 trials are modelled. In second line, results of the OCEANS and AURELIA studies are applied.

GOG-0218 & GOG-0218 high risk

"*Each of the three study regimens comprised 22 3-week cycles with intravenous infusions on day 1, with the first 6 cycles consisting of standard chemotherapy with carboplatin at an area under the curve of 6 and paclitaxel at a dose of 175 mg per square meter of body-surface area. Control treatment was chemotherapy with placebo added in cycles 2 through 22; bevacizumab-initiation treatment was chemotherapy with bevacizumab (15 mg per kilogram of body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Bevacizumab-throughout treatment was chemotherapy with bevacizumab added in cycles 2 through 22. Bevacizumab or placebo was initiated at cycle 2, rather than cycle 1, to reduce the risk of wound-healing complications. Treatment was discontinued at the onset of disease progression, unacceptable toxic effects, completion of all 22 cycles, or withdrawal — whichever came first.*"[28]

The bevacizumab-initiation treatment was not modelled since the HR for OS was 1.078 (95% CI, 0.919 to 1.270), making the treatment on average more expensive and less effective expressed in LYG. There are also no good arguments to select this treatment arm if expressed in QALYs. The only treatment arm included from the GOG-0218 study is thus the bevacizumab-throughout treatment which is compared with the standard chemotherapy arm.

- Bevacizumab-throughout treatment:

Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
drug treatment	C	C	C	C	C	C																
	P	P	P	P	P	P																
	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B

B: bevacizumab 15mg/kg; C: carboplatin AUC 6; P: paclitaxel 175mg/m².

ICON7 & ICON7 high risk

"*Patients received either six 3-weekly cycles of intravenous carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m² of body surface area), or the same regimen with intravenous bevacizumab (7.5 mg/kg of bodyweight) given concurrently and continued for 12 further 3-weekly cycles (with a duration of bevacizumab exposure of about 1 year), or until disease progression. To avoid delayed wound healing, bevacizumab was omitted at cycle 1 if chemotherapy was started within 4 weeks of surgery. Bevacizumab cycles omitted for any reason were not replaced.*"[31]

- Bevacizumab treatment arm

Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
drug treatment	C	C	C	C	C	C												
	P	P	P	P	P	P												
	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B

B: bevacizumab 7.5mg/kg; C: carboplatin AUC 5 or 6; P: paclitaxel 175mg/m².

OCEANS

"*Patients received G 1,000mg/m2 on days 1 and 8 and C area under the curve 4 mg/mL/min on day 1 … . Cycles were repeated every 21 days. The trial was designed so that patients would receive six cycles of GC but would be allowed to receive up to 10 cycles if continued response was documented. bevacizumab or placebo 15 mg/kg was administered intravenously on day 1 of each cycle, before GC. After completion of GC, either bevacizumab or placebo, respectively, was continued until progressive disease or unacceptable toxicity.*"[34]

- Bevacizumab treatment arm

Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
drug treatment	G	G	G	G	G	G	G	G	G	G												
	C	C	C	C	C	C	C	C	C	C												
	B	B	B	B	B	B	B	B	B	B	B	→ until PD or unacceptable toxicity										

B: bevacizumab: 15mg/kg; C: carboplatin AUC 4; G: gemcitabine: 1,000mg/m2; PD: progressive disease.

AURELIA

"*Investigators selected single-agent chemotherapy on an individual patient basis from the following options, with appropriate premedication according to local standards: paclitaxel 80mg/m2 intravenously (IV) on days 1, 8, 15, and 22 every 4 weeks; PLD 40 mg/m2 IV on day 1 every 4 weeks; or topotecan 4 mg/m2 IV on days 1, 8, and 15 every 4 weeks or 1.25 mg/m2 on days 1 to 5 every 3 weeks. Patients were then randomly assigned to receive the selected chemotherapy either alone (CT) or with bevacizumab 10 mg/kg every 2 weeks (or 15 mg/kg every 3 weeks in patients receiving topotecan in a schedule repeated every 3 weeks; BEV-CT). … Chemotherapy and bevacizumab were continued until disease progression, unacceptable toxicity, or consent withdrawal.*"[26]

- Bevacizumab treatment arm

Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	…
drug treatment	Chemotherapy → until PD or unacceptable toxicity															
	Bevacizumab → until PD or unacceptable toxicity															

Chemotherapy: liposomal doxorubicin (40mg/m2 iv every 4 weeks), or paclitaxel (80mg/m2 iv on days 1, 8, 15 and 22 of each 4-week cycle), or topotecan (4mg/m2 iv on days 1, 8 and 15 of each 4-week cycle, or 1.25 mg/kg on days 1-5 of each 3-week cycle); Bevacizumab: 10m/kg iv every 2 weeks or 15mg/kg iv every 3 weeks; PD: progressive disease.

7.1.4 Analytical technique

Quality of life is of major importance to patients with cancer and can be influenced by both the disease as well as by the treatments. Therefore, a cost-utility analysis (CUA) is performed. Results of the cost-effectiveness analysis (CEA) in which the years of life are not adjusted for quality of life are also presented. Both incremental costs (IC), incremental effects (IE) in life years gained and QALYs gained, and incremental cost-effectiveness ratios (ICER) will be presented separately in the results section.

7.1.5 Time horizon and discount rate

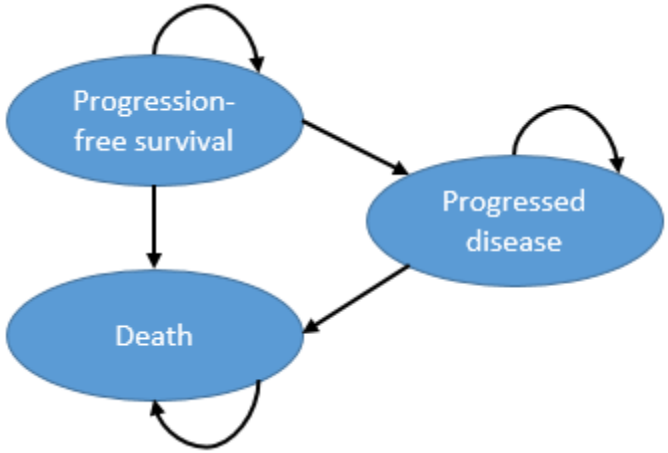
Bevacizumab treatment might have an impact on mortality. Trials have a limited follow-up that only partly reflects the total impact on gained life years. Adopting a lifetime time horizon is necessary to capture the full possible impact on all relevant incremental costs and effects. Therefore, results are extrapolated after the trial follow-up period until all patients in the theoretical cohort are deceased. In alternative scenarios, this time horizon is limited to 10 and 5 years.

Costs and effects are discounted on a 3-weekly basis in the Markov model. The choice for 3-weekly cycles is determined by the QoL scenarios (see part 7.1.8). According to the Belgian guidelines for economic evaluations,[58] a yearly discount rate of 3% and 1.5% for costs and effects, respectively, should be applied (or 0.1702% and 0.0857% 3-weekly). Following the Belgian guidelines for economic evaluations,[58] this is changed in scenario analyses to 0%, 3% and 5% for both costs and effects. To avoid complexity, extra costs for bevacizumab treatment were all allocated at the start of the model (and not spread over the first cycles). Similarly, costs for AEs were assigned to the second cycle (see part 0). Adjusting with a discount rate over such a short period will not influence results. Therefore, no discount rate adjustments were made for the costs assigned to the start and second 3-weekly cycle of the model.

7.1.6 Markov model

A hypothetical cohort of 1000 patients was modelled in Microsoft Excel 2010, using @Risk software (Palisade Corporation) to incorporate uncertainty around the input variables. This cohort reflects the population from the underlying trials. Figure 12 reflects the structure of the model in which there are three health states: progression-free survival, progressed disease and death. For all included scenarios, this was modelled by extracting survival and PFS from the trials (see part 7.1.7). The number of patients with progressed disease is derived from the difference between the number of survivors and progression-free survivors. Both in the intervention and comparator arm, half-cycle correction is applied to reflect that the patients do not all die at the beginning or at the end of a 3-weekly cycle, but on average halfway this cycle.

Figure 12 – Schema of the Markov model



7.1.7 Treatment effect

This economic evaluation estimates the cost-utility of bevacizumab for the first- or second-line treatment of ovarian cancer. Several RCTs are identified including the relevant intervention, comparator, and population. We don't have access to individual patient data and rely on published information. Trials with sufficient information to model the cost-utility are included in this modelling exercise.

The same approach was used for all trials. To be able to model the cost-utility, published KM-curves for both OS and PFS were identified and hazard ratios for these outcomes were selected. In cases were different analyses were available, the most up-to-date results were used. The OS and PFS were extracted at fixed points in time for all trials. This was done separately by two persons using a different software. The first person used Datathief, while the second person used R-Digitize. In Datathief, the KM was enlarged (160%-500% in the pdf-file and another 200%-400% in the software) to be able to extract data with sufficient precision. The data of the second person were used to validate the results. The difference was more than 1% in five

cases of the 84 point estimates. Because of these differences, a second check was performed and an incorrect measurement was excluded. Finally, the values presented in Table 36 are used in the model. The incremental difference between the control and bevacizumab group between the two persons was always lower than 1%.

For OS

- Yearly (or 6-monthly) mortality rates extracted from the published KM-curves were transformed to 3-weekly mortality rates.
- The mortality in the control group was modelled.
- The mortality in the bevacizumab group was modelled by applying the following formula: probability of death intervention = 1 - [probability of survival control therapy ^ (hazard ratio)]
- Having no access to individual patient data from the RCTs, a constant hazard was assumed and the result was visually checked to see whether the modelled survival curves were in agreement with the extracted data from the published KM-curves.
- In the ICON7 high-risk, this fit was not satisfying (see further description of validation). In this case, both survival curves were based on the extracted observations from the published KM-curves (and thus not applying the published HR)

For PFS:

- The same approach as for OS was initially applied. However, the visual check showed that applying the approach with the published hazard ratios was not satisfying. Therefore, in all cases, it was preferred to work with the extracted information from the published KM-curves for PFS.
- A second check was performed to see whether the PFS lines crossed each other. If this was the case, we conservatively decided to coincide the curves. This assumption was always in the advantage of the bevacizumab group (since in these cases the KM-curves showed a somewhat worse PFS after some time for the bevacizumab group).
- A third check was performed to see whether the PFS lines didn't cross the OS-curves in the extrapolation period. If this was the case, the extrapolation of the PFS curves followed the same trend as the OS-curves. This did not have an incremental impact since this was only the case were PFS-curves crossed and the incremental impact was erased (see previous bullet).

For transparency, for all modelled trials, a figure is presented in the result section to show the modelled OS and PFS curves and observed OS and PFS at fixed points in time from the published KM-curves.

We remark that for the stage IV subgroup in the GOG-0218 trial the manufacturer made us aware of the poster presentation[37] with OS data for this subgroup. This poster also presented the KM-curve for OS in the stage IV subgroup. No such figure was available for PFS in this subgroup. As a result, the model for this subgroup will only include the base case QoL scenario (see further in part 7.1.8).

The identified hazard ratios are mentioned in Table 37. These were modelled applying a lognormal probability distribution with the same confidence interval and mean values. In the end, the fit of modelled curves and original data was not satisfying for PFS (in all cases) and OS in the ICON7 high-risk population. As mentioned above, the observations at fixed points in time from the KM-curves were used in these cases.

Table 36 – OS and PFS at fixed points in time, extracted from published KM-curves

Source*	GOG-0218	GOG-0218 st.IV	ICON7	ICON7 HR		OCEANS		AURELIA
OS Control								
12 months:	90.9%	84.8%	92.5%	84.4%		93.4%	6 months:	74.8%
24 months:	73.6%	63.0%	80.1%	64.1%		68.7%	12 months:	57.4%
36 months:	55.2%	42.7%	66.1%	41.6%		48.1%	18 months:	38.8%
48 months:	41.2%	30.4%	57.4%	35.4%		35.0%	24 months:	*26.1%*
60 months:	/	/	49.4%	27.1%		/	30 months:	17.6%
OS bevacizumab arm								
12 months:	91.2%	89.3%	94.9%	91.5%		94.4%	6 months:	84.9%
24 months:	76.8%	73.2%	83.4%	74.5%		72.2%	12 months:	62.7%
36 months:	58.1%	55.3%	68.7%	56.7%		44.4%	18 months:	45.5%
48 months:	46.5%	42.7%	57.4%	40.9%		34.1%	24 months:	29.6%
60 months:	/	/	48.3%	30.8%			30 months:	19.8%
PFS Control								
12 months:	46.0%	/	67.4%	46.8%	6 months:	79.0%	6 months:	22.0%
24 months:	22.3%	/	43.6%	22.1%	12 months:	25.1%	12 months:	6.7%
36 months:	16.4%	/	36.7%	14.9%	18 months:	7.5%		
48 months:	/	/	33.3%	13.1%	24 months:	3.3%		
60 months:	/	/	31.7%	12.2%				
PFS bevacizumab arm								
12 months:	62.8%	/	82.1%	73.6%	6 months:	93.6%	6 months:	53.7%
24 months:	26.9%	/	45.3%	26.3%	12 months:	54.0%	12 months:	19.0%
36 months:	18.4%	/	34.6%	18.2%	18 months:	24.7%		
48 months:	/	/	30.2%	14.7%	24 months:	12.9%		
60 months:	/	/	28.7%	12.2%				

** Sources: .*
GOG-0218: Burger (2011):[28] OS – Figure 3B; PFS – Figure 2B.
GOG-0218 st.IV: Randall (2013):[37] OS – Figure 6.
ICON7: Oza (2015):[31] OS – Figure 2A; PFS – Supplementary Figure 2A.
ICON7 High-risk: Oza (2015):[31] OS – Figure 2C; PFS – Supplementary Figure 2C.
OCEANS: NICE TA285 (2012):[48] OS – Figure 8; PFS – Figure 12.
AURELIA: Pujade-Lauraine (2014):[26] OS – Figure 3; PFS – Figure 2

Table 37 – OS and PFS hazard ratios

	OS: mean (95%CI)	PFS: mean (95%CI)
GOG-0218*[28]	0.885 (0.750 - 1.040)	0.770 (0.681 - 0.870)
GOG-0218 st.IV[37]	0.72 (0.53 - 0.97)	0.64 (0.49 - 0.82)
ICON7[31]	0.990 (0.850 - 1.140)	0.930 (0.830 - 1.050)
ICON7 HR[31]	0.780 (0.630 - 0.970)	0.730 (0.610 - 0.880)
OCEANS**[48]	0.960 (0.760 - 1.214)	0.484 (0.388 - 0.605)
AURELIA[26]	0.850 (0.660 - 1.080)	0.480 (0.380 - 0.600)

** GOG-0218: results of the updated analysis of August 26, 2011. ** OCEANS: results of the third interim analysis of March 30, 2012.*

Life-time extrapolation

KM-curves were published with a time window of 30 months (AURELIA) up to 60 months (ICON7) for OS and 12 months (AURELIA) up to 60 months (ICON7) for PFS. The possible differences in OS and PFS do not disappear at once after this follow-up period. Therefore, extrapolation of results to a longer time horizon is more appropriate. The 3-weekly mortality during the last year in the trial is used to extrapolate.i Three possible extrapolation scenarios are applied: 1) the 3-weekly risk of death remains constant over time (exponential survival); 2) the 3-weekly mortality risk increases with the absolute increase in mortality risk of the general Belgian female population with the same age; 3) the 3-weekly mortality risk increases with the relative increase in this mortality risk of the general Belgian female population with the same age. A first view on results showed that the first two options do not differ much. The third option is very probably too pessimistic. Therefore, in the base case scenario, the first extrapolation approach was applied (not making much difference with the second one, but being more conservative). The other two options were modelled in scenario analyses.

7.1.8 Quality of life

The effect of first-line bevacizumab on QoL was reported in the GOG-0218 trial (measured with the FACT-O TOI instrument) and ICON7 trial (measured with the EORTC QLQ-C30 and QLQ-OV28 instruments). Lower QoL scores were reported in the bevacizumab arms (see part 5.2.2.4). The pooled results showed a significant better QoL for the standard chemotherapy group at 18 weeks and no further significant difference at 54-60 weeks. Unfortunately, no utility values were reported. Good QoL estimates measured with a generic utility instrument are unfortunately lacking.

In the NICE TA284 manufacturer submission, QoL data from the ICON7 trial, measured with the generic EQ-5D questionnaire were presented. We remark that no such information was presented in the original publication of the ICON7 trial. The publication of Oza et al. just mentions that "*quality of life was assessed with the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-OV28 questionnaires.*"[31] The manufacturer's submission does not model the QoL results per treatment arm. In contrast, they transfer these results to utility values for the PFS and PD health states (see Table 38). As such, an improvement in QoL is modelled indirectly. In contrast with the available evidence, no decrease in QoL during the first cycles with bevacizumab was modelled. Further, we remark that the QoL values from the TA284 manufacturer submission come from the ICON7 study. As previously mentioned by the ERG, this trial "*employed a lower dose of bevacizumab than in the NICE scope. Any AEs caused by the higher dose of bevacizumab as specified in the NICE scope would not be captured using the utility data from the ICON7 trial.*"[49]

In the AURELIA trial, no generic utility instrument was used to enable the generation of utility values. However, the EORTC QLQ-C30 global health QoL subscale showed no significant difference between treatment groups (see part 5.2.3.4).

i In the AURELIA trial, for overall survival, only 12 and 13 patients were at risk in the placebo and bevacizumab treatment arm, respectively, at 30 months follow-up. This might result in great uncertainty, which is then also used in the extrapolation phase. However, the 3-weekly mortality over a six-month period did not vary much when modelling up to 18, 24 or 30 months (between 4.41% and 4.46%). In the GOG, ICON7, and OCEANS trial, at least 56, 117, and 23 patients were at risk, respectively, at the last follow-up moment.

In case of the TA285 study, the values were retrieved from other studies and the manufacturer noticed that “the use of utility data from OVA-301 presented in TA222 should be interpreted with caution due to little overlap in the types of adverse event between OVA-301 and OCEANS.”[48]

In our base case scenario, we conservatively assume no decrease in QoL due to bevacizumab treatment and model an equal QoL through all cycles. We assume a utility value of 0.72 (as in PFS in TA285 and PD in TA284) with an uncertainty ranging from 0.62 to 0.82 (minimum and maximum values in the NICE submissions, modelled with a beta-distribution). In two scenario analyses, we model the input from the two manufacturer’s submissions to see in how far this influences our results (Table 38).

Table 38 – QoL values

3-weekly cycles	Base case	TA28548	TA284*47
Progression-free survival			
Cycle 1	Mean 0.72 (beta-distribution, min: 0.62; max: 0.82) for all PFS cycles.	Mean 0.718 (beta-distribution, 2.5%: 0.699 – 97.5%: 0.737) for all PFS cycles.	Mean: 0.6571 (SD: 0.0133)**
Cycle 2			Mean: 0.7153 (SD: 0.0118)
Cycle 3			Mean: 0.7443 (SD: 0.0110)
Cycle 4			Mean: 0.7683 (SD: 0.0100)
Cycle 5			Mean: 0.7643 (SD: 0.0112)
Cycle 6			Mean: 0.7444 (SD: 0.0121)
Cycle 7			Mean: 0.7444 (SD: 0.0121)
Cycle 8			Mean: 0.7638 (SD: 0.0131)
Cycle 9			Mean: 0.7638 (SD: 0.0131)
Cycle 10			Mean: 0.7718 (SD: 0.0129)
Cycle 11			Mean: 0.7718 (SD: 0.0129)
Cycle 12			Mean: 0.7638 (SD: 0.0136)
Cycle 13			Mean: 0.7638 (SD: 0.0136)
Cycle 14			Mean: 0.7785 (SD: 0.0155)
Cycle 15			Mean: 0.7785 (SD: 0.0155)
Cycle 16			Mean: 0.7533 (SD: 0.0165)
Cycle 17			Mean: 0.7533 (SD: 0.0165)
Cycle 18			Mean: 0.7760 (SD: 0.0170)
Cycle 19 and further			Mean: 0.8129 (SD: 0.0113)
Progressed disease	Idem as PFS	Mean 0.649 (beta-distribution, 2.5%: 0.611 – 97.5%: 0.686)	0.7248 (fixed)

** QoL values from a study with a lower dose of bevacizumab administered (7.5mg/kg).** these values are also modelled with a beta probability distribution.*

7.1.9 Costs

Bevacizumab treatment costs

In our Belgian sample of ovarian cancer patients receiving bevacizumab, the average cost per cycle was €3169 (SD: €977, based on 806 treatment cycles). The year of costs is mainly 2014 since the majority of the patients (82.2%) received their first session in 2014. No adjustments were made to transfer the costs of another year to the year 2014. We remark that only the patients with reimbursed bevacizumab treatment were selected for this estimate since, based on expert opinion, it is possible that a lower dose is administered when the treatment is not reimbursed. In our model, applying the central limit theorem, a normal distribution is applied to include the average cost per bevacizumab treatment cycle (mean: €3169, SD mean: 977/√N = 34.4). For the cost of a bevacizumab 7.5mg/kg or 10mg/kg body weight administration, taking into account the small differences in drug waste, respectively 52.9% and 68.7% of the cost of a 15mg/kg administration is applied (see above in Table 35): on average €1676.2 (7.5mg/kg) and €2176.8 (10mg/kg) for the ICON7 and AURELIA model, respectively.

The bevacizumab cost per cycle is multiplied with the number of treatment cycles (total drug cost in Table 39). For the GOG-0218, ICON7 and OCEANS trial, the average number of treatment cycles are provided in the NICE manufacturer submissions (see Table 39). For the high-risk subgroup of the ICON7 trial no separate information on the mean treatment duration could be retrieved. In case of the AURELIA trial, median treatment duration is published: median duration of therapy was three cycles (range, one to 17 cycles) in the CT arm versus six cycles (range, one to 24 cycles) in the bevacizumab arm.[26] Treatment exposure was also published in figure 4 of this original publication. With the data extraction software Datathief, an average treatment duration of 6.6 cycles of 4 weeks was extracted for the bevacizumab group and 4.2 cycles for the chemotherapy treatment arm. With a 4-weekly treatment cycle, an average treatment duration of 26.2 and 16.7 weeks was included. These data were validated with information retrieved from the manufacturer's submission to NIHDI, in which an average treatment duration of 27.6 weeks was mentioned for the bevacizumab arm, i.e. very close to our 26.2 weeks estimate. We included the information retrieved from the published figure which also includes information on the chemotherapy duration. This enables us to include the extra number of treatment cycles. Including the shortest treatment duration of 26.2 weeks is conservatively in favour of bevacizumab.

In case of the stage IV subgroup of the GOG-0218 trial, the manufacturer's submission to NIHDI mentions an average treatment duration of 11.9 cycles in this subgroup, which is two cycles less than in the overall GOG-0218 population. It is not clear whether the average chemotherapy treatment duration was also shorter. Conservatively in favour of bevacizumab treatment, the extra number of administrations was also reduced with two cycles.

One remark related to the retrieval of information from the manufacturer's submission to NIHDI: in case of the OCEANS trial, an average of 13.6 cycles is mentioned, which equals 40.8 weeks. This contrast with the 50.74 weeks for the same trial mentioned in the manufacturer's submission to NICE.

Next to the drug cost, all extra costs on the day of administration are also taken into account. These costs are based on IMA–AIMreimbursement data. These costs were almost the same when comparing chemotherapy with and without bevacizumab administration: €555 (N=415) and €528 (N=43418), respectively (see Figure 13). This small difference was not taken into account. When bevacizumab was administered without other chemotherapy, this average cost on the day of treatment was €339 (N=423, SD: 204.25). Applying the central limit theorem, a normal distribution with the same mean and a standard deviation of the mean of 9.93 (204.25/√N) was taken into account. This extra cost on the day of administration was only counted for the extra treatment duration after chemotherapy (Table 39). To avoid complexity, these bevacizumab treatment costs are allocated to all patients at the start of the model.

No differences in chemotherapy costs were included for the bevacizumab treatment arm versus the chemotherapy arm.

Figure 13 – Distribution of the extra costs on the day of administration.

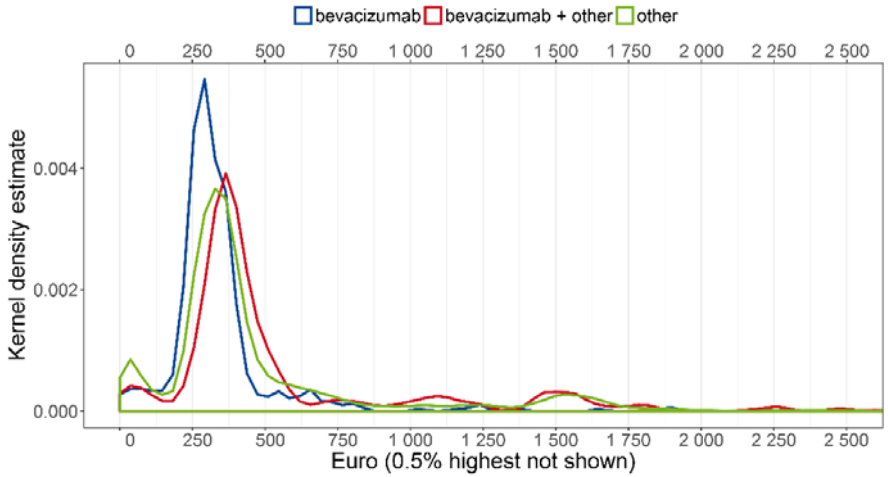


Table 39 – mean treatment duration and bevacizumab treatment costs

	GOG-0218[47]	GOG-0218 st.IV*	ICON7[47]	OCEANS[48]	AURELIA**[26]
Mean treatment duration					
Bevacizumab	41.93 weeks	35.7 weeks	42.99 weeks	50.74 weeks	6.55 cycles of 4 weeks
Chemotherapy	16.55 weeks	NA	15.96 weeks	22.50 weeks	4.16 cycles of 4 weeks
Bevacizumab treatment costs					
Total drug costs	€44 286	€37 706	€24 020	€53 591	€28 529
Extra administration costs	€2870***	€2165	€3057	€3193	€1622****

** Source: INAMI - Service des Soins de Santé, Rapport jour 60, AVASTIN 25 mg/ml solution à diluer pour perfusion.*
*** Numbers were extracted from figure 4 in the original publication of Pujade et al.[26]*
**** €2870 = €339.24 x (41.93 weeks – 16.55 weeks)/3-weekly cycle.*
***** €1622 = €339.24 x 2.39 cycles of 4 weeks x 2 (i.e. 2-weekly bevacizumab administration).*

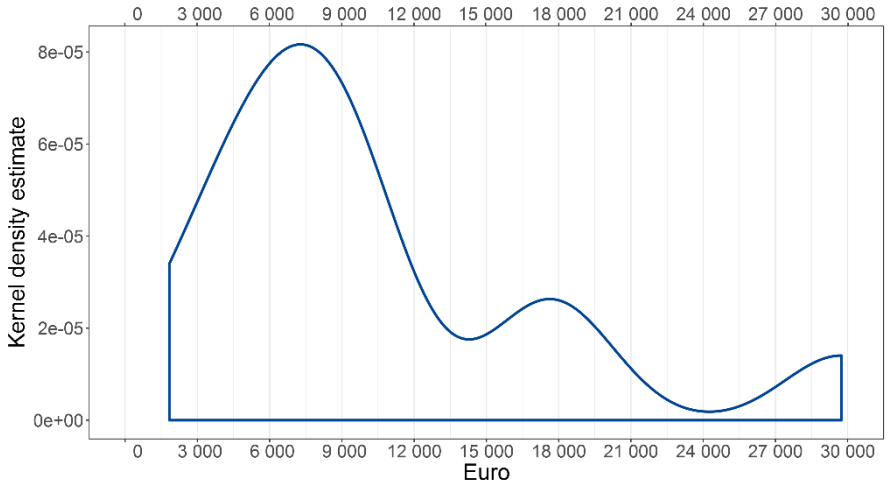
Adverse events and follow-up costs

The medical review showed an increase in AEs in the bevacizumab treatment arm. We tried to include the AEs with a possible significant impact on costs. Four AEs were selected from the meta-analyses in the medical part of this report because the absolute difference in incidence was relatively large or because the cost of treating the AE was potentially high.

- Perforations: In TCT data of our sample (2008-2013), twelve inpatient hospital stays were identified with ID-9-CM codes 569.83 (perforation of the intestine) or 569.81 (fistula of intestine, excluding rectum and anus) as the principal diagnosis of the stay. All NIHDI reimbursements associated with a particular stay were summed. The per diem price in the TCT data only contains the hospital specific lump sum price per day and per admission. However, a large part of the hospital budget is covered by the BFM–BMF (approximately 80%).[60] To include all parts of the per diem price, the lump sums are replaced by the 100% per diem price.[58] The distribution of the costs per stay for perforations are shown in Figure 14. Because the costs are based on a very small sample and costs for AEs are usually skewed to the right, they are best represented by a gamma-distribution. The parameters of the function are determined to reflect exactly the same mean, standard deviation and minimum of our small sample. The probability of occurrence was modelled with a beta distribution.
- Hypertension: Hypertension was identified in IMA–AIMdata based on the reimbursement of the following pharmaceutical products: ATC C02 (antihypertensives), ATC C03 (diuretics), ATC C07 (beta blocking agents), ATC C08 (calcium channel blockers), or ATC C09 (agents acting on the renin-angiotensin system). Of bevacizumab patients, 92.1% had at least one of these products reimbursed following their diagnosis of ovarian cancer. However, only 4.6% of bevacizumab patients started with any of these products after their first bevacizumab session. For this reason and the fact that it is difficult to differentiate the hypertension grades in the available data, no cost was retained for hypertension. This is a conservative approach not disfavouring bevacizumab.
- Thrombosis: Identifying patients with thrombosis was done using two approaches:
  - In the IMA–AIMdata, 98.7% of bevacizumab patients had reimbursements for ATC B01A (antithrombotic agents) pharmaceutical products. All of these patients started with antithrombotic agents prior to their bevacizumab treatment.
  - In the TCT data, hospital stays with principal diagnosis ICD-9-CM codes 444 (arterial embolism and thrombosis), 451 (phlebitis and thrombophlebitis), or 453 (other venous embolism and thrombosis) occurred only in 5.3% of bevacizumab patients, with half of the stays occurring prior to the start of bevacizumab treatment. However, because 2014 TCT data was not available at the time of the study, these figures are most likely underestimating the occurrence in bevacizumab patients as most started bevacizumab treatment in 2014.

Because most treatments of thrombosis started before bevacizumab treatment, no cost was retained for thrombosis. This is also a conservative approach not disfavouring bevacizumab.

Figure 14 – Distribution of hospital stay costs for perforation



In TA284, the ERG noticed that all AEs were assumed to occur in the first cycle of the model. This was considered unlikely to reflect the clinical situation since bevacizumab would not be administered until the second cycle. On the other hand, the ERG stated this would not alter the overall costs included in the model.[49] In our model, the AEs costs are all modelled during the second cycle of the model. Changing this to the first or a later cycle would not have a significant impact on results.

No differences in follow-up were modelled since it is not expected these costs are very different between patients with and without bevacizumab treatment.

Sensitivity and scenario analyses

Probabilistic sensitivity analyses (PSA) and one-way scenario analyses were performed in Microsoft Excel 2010, using @Risk software (Palisade Corporation). An overview of the variables and their probability distribution is provided in Table 41. Table 42 gives an overview of the modelled scenarios. In all of these scenarios, the same probability distributions are applied. Results are presented in table format (mean and 95% credibility intervals) and figures. Both cost-effectiveness planes, cost-effectiveness acceptability curves, and tornado graphs are provided.

Table 40 – Adverse events (not) included in the model

	Total events/population	Cost
Hypertension grade 2+	Control: 61/1535 Bevacizumab: 288/1532	/
GI perforation grade 2+	Control: 13/2095 Bevacizumab: 36/2109	Mean: €10 458, SD: 7778; min. €1836 Gamma distribution: alpha: 1.23; beta: 7016.81; shift: 1836.
Venous thromboembolism grade 3+	Control: 23/1313 Bevacizumab: 55/1322	/
Arterial thromboembolism any grade	Control: 20/2095 Bevacizumab: 50/2109	/

GI: gastrointestinal perforation.

Table 41 – Variables included in the model with their probability distribution

Description	Probability distribution	Part in the report
Hazard ratios OS and PFS (GOG-0218, ICON7, ICON7 high-risk, OCEANS, and AURELIA)	Lognormal distributions	Part 7.1.7
QoL - utilities	Beta distributions	Part 7.1.8
Bevacizumab cost per cycle (15mg/kg)	Normal distribution: mean 3168.6; SD mean 34.4.	Part 0
Extra costs on day of B administration	Normal distribution: mean 339.24; SD mean 9.93.	Part 0
GI perforation grade 2+	% control group: beta distribution: alpha 13; beta (2095-13). % bevacizumab group: beta distribution: alpha 36; beta (2109-36). Cost: Gamma distribution: alpha: 0.9; beta: 5536.2; shift: 5049.	Part 0

B: bevacizumab; GI: gastrointestinal perforation.

Table 42 – Variables included in scenario analyses

Description	Scenarios	Part in the report
Population	1) GOG-0218; 2) ICON7; 3) ICON7 high-risk; 4) OCEANS, and 5) AURELIA	Part 7.1.2
For all of the above populations, the following scenarios are modelled		
Time horizon	1) Lifetime (base case); 2) 10 years; 3) 5 years.	Part 7.1.5
Discount rate	1) 3% for costs and 1.5% for effects (base case); 2) 0% for C&E; 3) 3% for C&E; 4) 5% for C&E.	Part 7.1.5
Extrapolation	1) Constant mortality (base case); 2) absolute increase according to the Belgian female population of the same age; 3) relative increase according to the Belgian female population of the same age.	Part 7.1.7
QoL	1) equal QoL in the two treatment arms (base case); 2) QoL as in manufacturer submission TA285; 3) QoL as in manufacturer submission TA284.	Part 7.1.8
Price of bevacizumab	1) no discount (base case); 2 → 11) price discount of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%.	Part 0

B: bevacizumab; C&E: costs and effects; GI: gastrointestinal perforation.

7.1.10 Validation of the model

The modelling approach and outcomes are validated in different ways. In the first place, a visual inspection of the model is performed by comparing the modelled OS and PFS curves with the extracted data at fixed points in time from the published KM-curves. Also the position of the OS and PFS-curves in the long-term extrapolation is checked.

In the ICON7 trial, a restricted mean survival time is published for all patients and the high-risk subgroup. The published mean OS difference between the bevacizumab group and the control group is compared with our modelled incremental impact on overall survival.

Finally, our incremental impact on life-years and QALYs is compared with the outcomes of previously published economic evaluations.

7.2 Results

7.2.1 Base case results and scenario analyses

In Table 43, the base case results are provided for all modelled trials: GOG-0218, GOG-0218 stage IV subgroup, ICON7, ICON7 high-risk subgroup, OCEANS, and AURELIA. For an overview of the base case assumptions we refer to Table 42. In the following tables (Table 44 - Table 49), an overview of the most important results are provided per trial. Both the cost-effectiveness plane, cost-effectiveness acceptability curve, tornado graph, and figure with influence of price discounts are presented.

Table 43 – IC, IE & ICERs for the base case scenario (GOG-0218, ICON7, ICON7 HR, OCEANS, and AURELIA)a

	GOG-0218	GOG-0218 st.IV	ICON7	ICON7 HR*	OCEANS	AURELIA
	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)
Life expectancy (years)						
Control	4,06	3,27	6,24	3,66	3,66	1,46
	(4,06 - 4,06)	(3,27 - 3,27)	(6,24 - 6,24)	(3,66 - 3,66)	(3,66 - 3,66)	(1,46 - 1,46)
Bevacizumab	4,48	4,34	6,33	4,12	3,80	1,70
	(3,94 - 5,07)	(3,36 - 5,53)	(5,61 - 7,08)	(4,12 - 4,12)	(3,17 - 4,53)	(1,37 - 2,10)
QALYs (years)						
Control	2,93	2,36	4,49	2,63	2,64	1,05
	(2,60 - 3,25)	(2,09 - 2,62)	(3,99 - 5,00)	(2,34 - 2,93)	(2,34 - 2,94)	(0,93 - 1,17)
Bevacizumab	3,22	3,13	4,56	2,97	2,74	1,23
	(2,71 - 3,82)	(2,36 - 4,04)	(3,81 - 5,32)	(2,63 - 3,30)	(2,20 - 3,37)	(0,95 - 1,56)
IC	€ 47.268	€ 39.984	€ 27.188	€ 27.189	€ 56.897	€ 30.259
	(€46.309 - €48.209)	(€39.149 - €40.786)	(€26.611 - €27.743)	(€26.611 - €27.743)	(€55.750 - €58.022)	(€29.611 - €30.880)
IE (LYG)	0,42	1,07	0,09	0,46	0,13	0,24
	(-0,12 - 1,01)	(0,09 - 2,25)	(-0,63 - 0,84)	(0,46 - 0,46)	(-0,50 - 0,87)	(-0,09 - 0,64)
IE (QALY gained)	0,30	0,77	0,06	0,33	0,10	0,18
	(-0,09 - 0,73)	(0,07 - 1,62)	(-0,45 - 0,60)	(0,29 - 0,37)	(-0,37 - 0,63)	(-0,07 - 0,47)
ICER (€/LYG)**	*€ 113.523*	*€ 37.299*	*€ 314.963*	€ 59.008 (€57.755 - €60.212)	*€ 424.318*	*€ 124.317*
ICER (€/QALY gained)**	*€ 157.816*	*€ 51.931*	*€ 443.027*	€ 82.277 (€73.597 - €92.577)	*€ 587.182*	*€ 172.370*

The text in grey shows that there is no difference with another number in the table. E.g. the life expectancy in the control arm was modelled deterministically. The confidence interval is thus mentioned in grey.

** we remark that the modelling of the ICON7 high-risk subgroup, making use of the hazard ratios, did not provide a good fit with the point estimates of the published KM-curve (see validation). Therefore, it was decided to model survival through the fixed points in time extracted from the published KM-curves. This is rather a deterministic approach to model overall survival and results in a too narrow credibility interval around the ICERs.*

*** Calculation of the average ICER based on the 1000 simulations is not reliable if the outcomes are situated in different quadrants. In these cases, the presented ICERs are calculated by dividing the mean incremental cost by the mean incremental benefit.*

7.2.1.1 First-line bevacizumab

GOG-0218

- Average ICER: €158 000/QALY.
- Up to €50 000/QALY there is a 0% probability that bevacizumab is considered a cost-effective intervention (Table 44).
- A price discount of 80% is needed to reach an ICER of about €40 000/QALY. Even 90% to reach an average ICER of about €25 000/QALY (Table 44).

GOG-0218 stage IV subgroup

- Average ICER: €52 000/QALY.
- Based on a lifetime extrapolation, the incremental QALYs amount to 0.77. Results are very sensitive to the extrapolation time horizon. Limiting this horizon to ten and five years increases the ICER to 68 000/QALY and 136 000/QALY, respectively (Table 45).
- In the most optimistic scenario, a price discount of about 25% is needed to reach an ICER of about €40 000/QALY. The price discount needs to be more than 50% to reach an average ICER of about €25 000/QALY (Table 45).

ICON7

- Average ICER: €443 000/QALY.
- This ICER is very high due to the limited gain in QALYs (0.06).
- Even providing the treatment for free results in an ICER of more than €50 000/QALY (Table 46).

ICON7 high-risk subgroup

- Average ICER: €82 000/QALY
- The average number of QALYs gained is about the same as in the GOG-0218 trial (0.33 versus 0.30 QALYs). However, due to the lower dose (7.5mg/kg vs 15mg/kg) and less cycles (maximum 12 cycles of maintenance bevacizumab instead of 16 cycles), the incremental costs are much lower and provide better ICERs.
- A price discount of 60% is needed to reach an ICER of less than €40 000/QALY. This is 80% to reach an average ICER of less than €25 000/QALY (Table 47).
- Remark: no information on the average treatment duration could be retrieved for this high-risk subgroup. Incremental costs are probably overestimated.
- Remark: in this scenario, modelling through the hazard ratios did not provide a good fit with the published evidence (see validation of modelling outcomes). Therefore, a deterministic approach was modelled which results in an underestimation of modelled uncertainty (i.e. the cloud of simulated dots on the cost-effectiveness plane is too narrow).

7.2.1.2 Second-line bevacizumab

OCEANS

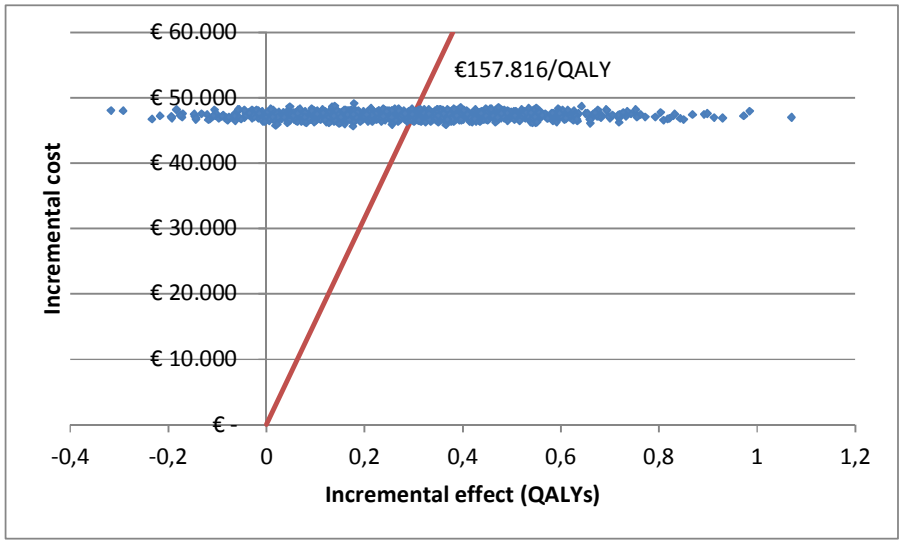
- Average ICER: €587 000/QALY.
- The added value is relatively small. Even with a price discount of 90%, the average ICER remains almost €90 000/QALY (Table 48).

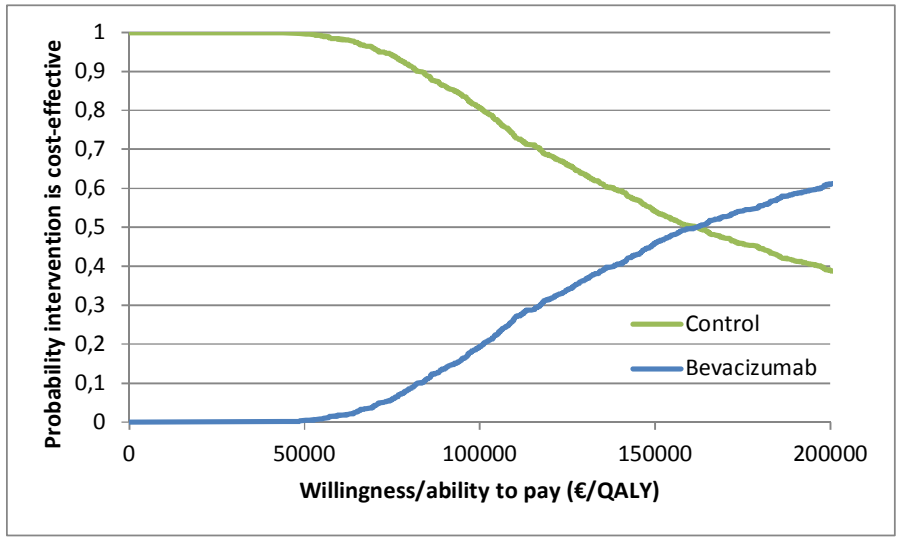
AURELIA

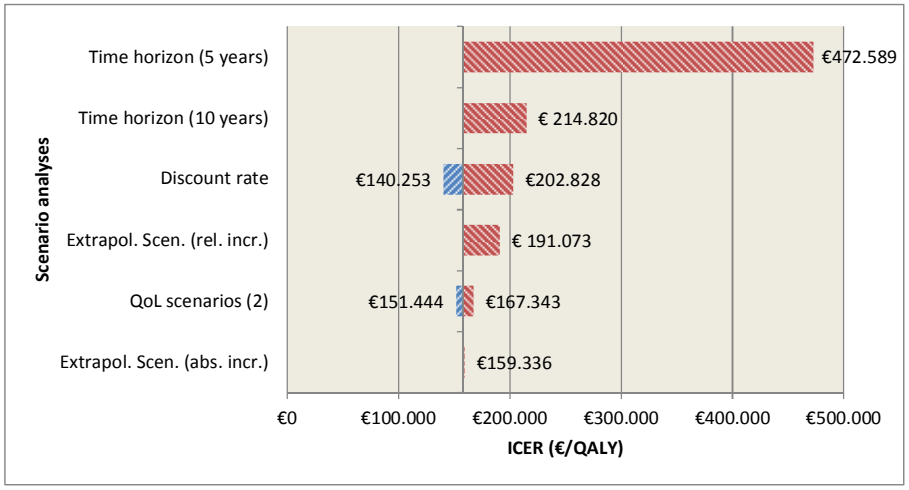
- Average ICER: €172 000/QALY.
- A price discount of more than 80% is needed to reach an ICER of less than €40 000/QALY. This needs to be more than 90% to reach an average ICER of less than €25 000/QALY (Table 49).

In general, we notice the high uncertainty around the treatment effect, as seen by the wide confidence interval around the incremental effects and part of the simulations situated in the fourth quadrant of the cost-effectiveness plane. The results are most sensitive to both the price of bevacizumab and the time horizon. The alternative QoL scenarios do not have a major impact on results.

Table 44 – Results of the economic evaluation for the GOG-0218 trial







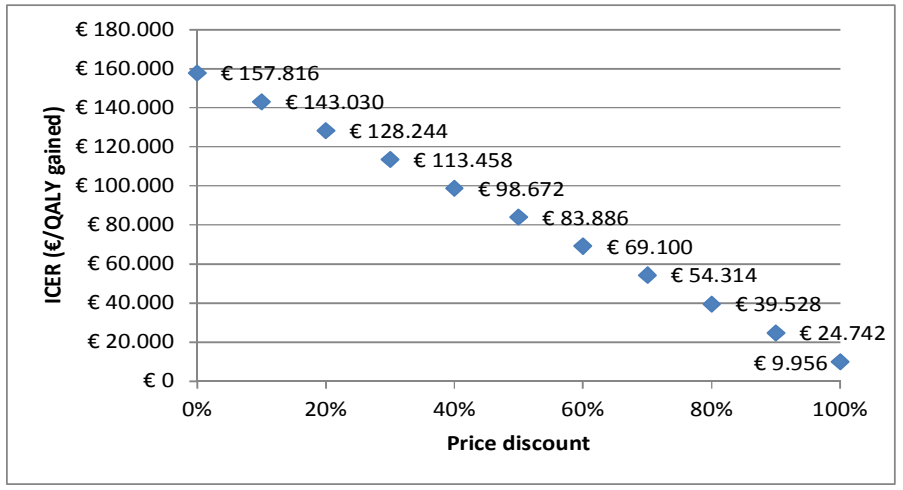


Table 45 – Results of the economic evaluation for the GOG-0218 trial (stage IV subgroup)

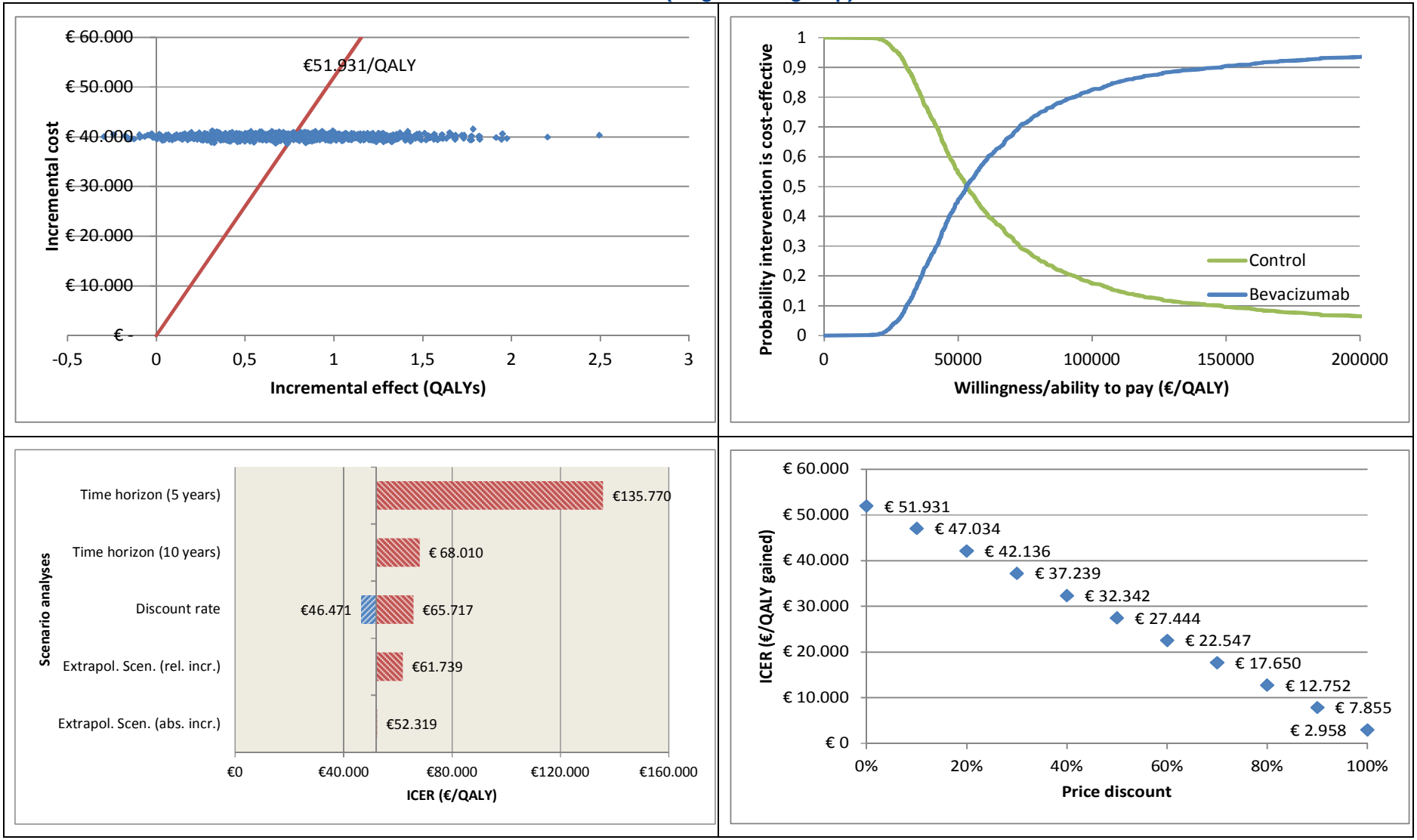
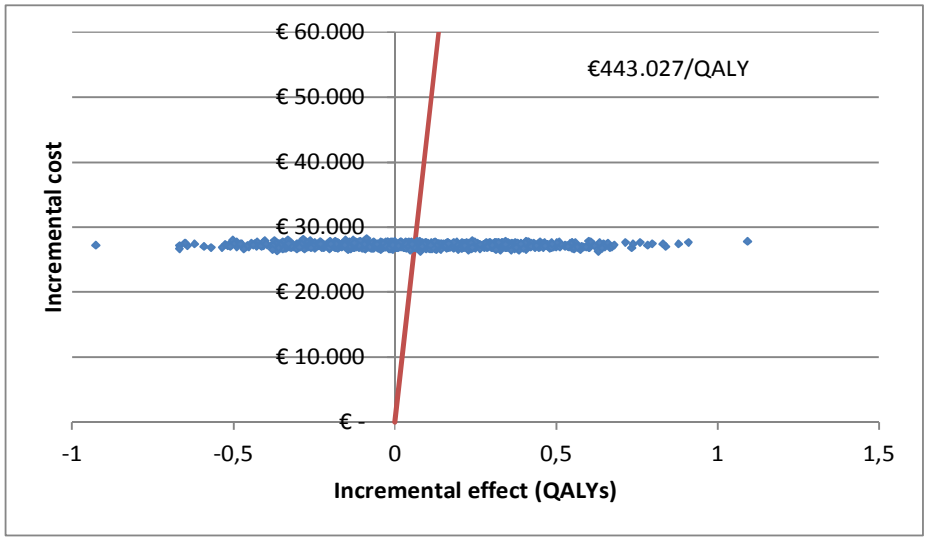
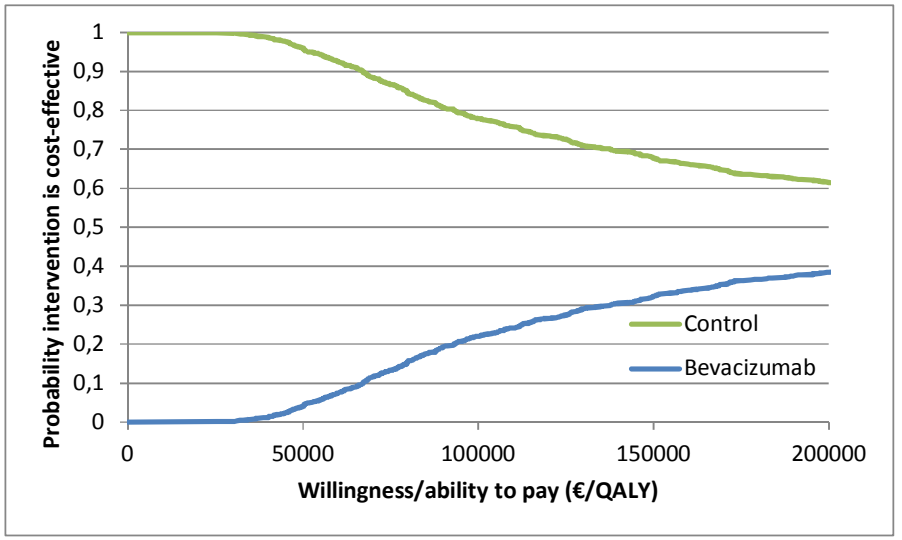
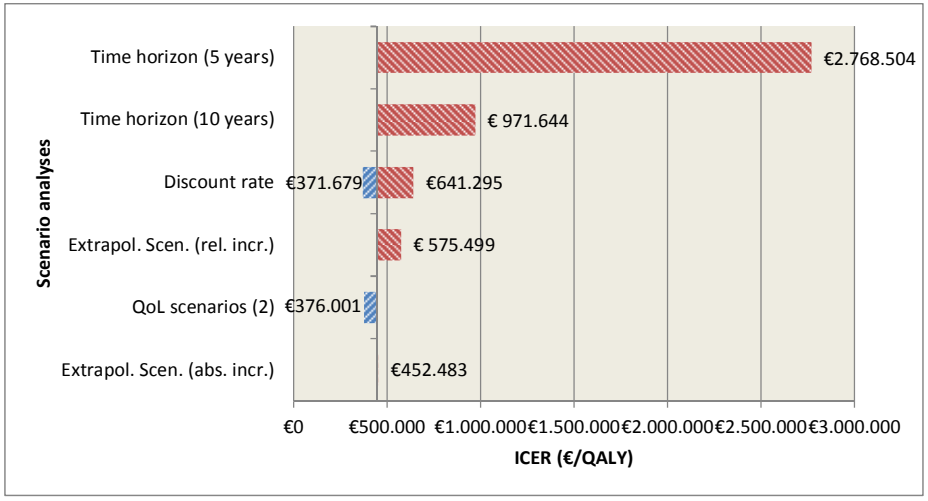


Table 46 – Results of the economic evaluation for the ICON7 trial







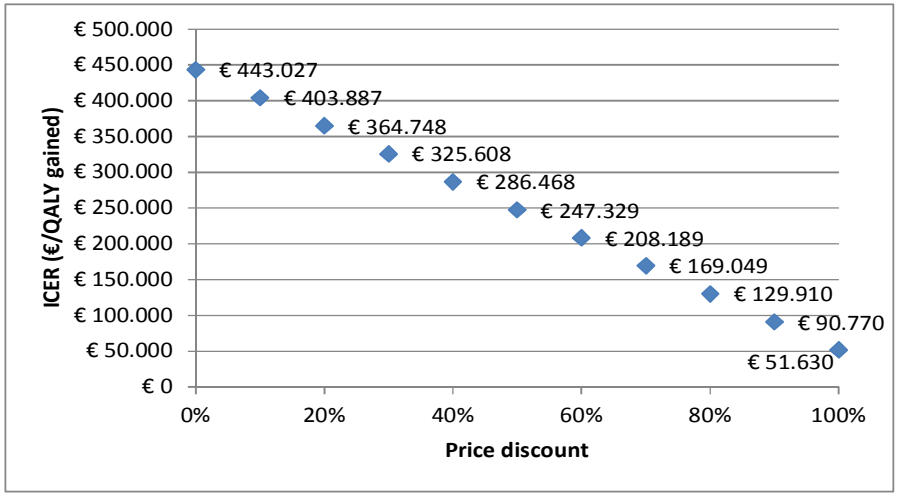


Table 47 – Results of the economic evaluation for the ICON7 trial (high-risk subgroup)

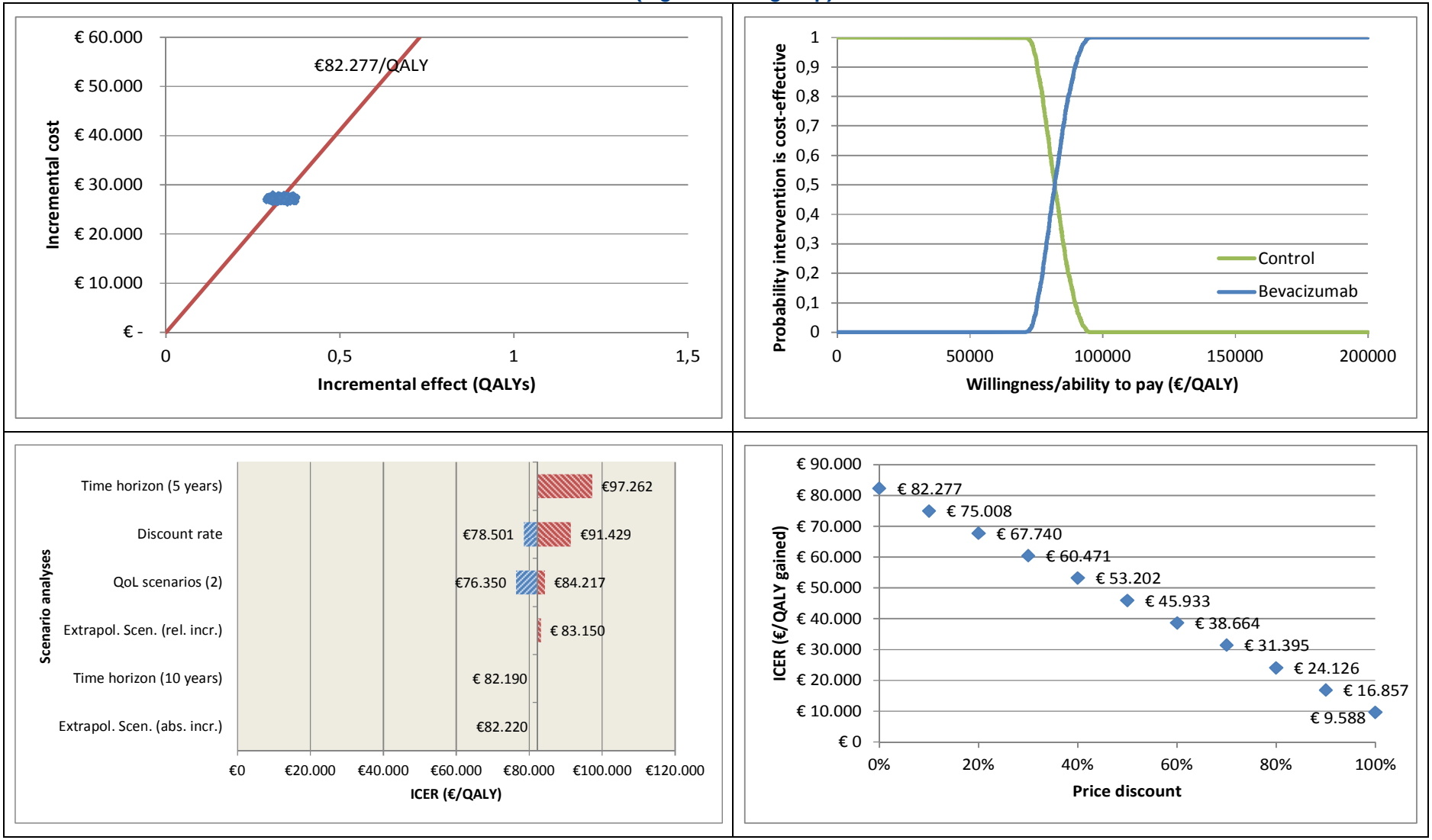
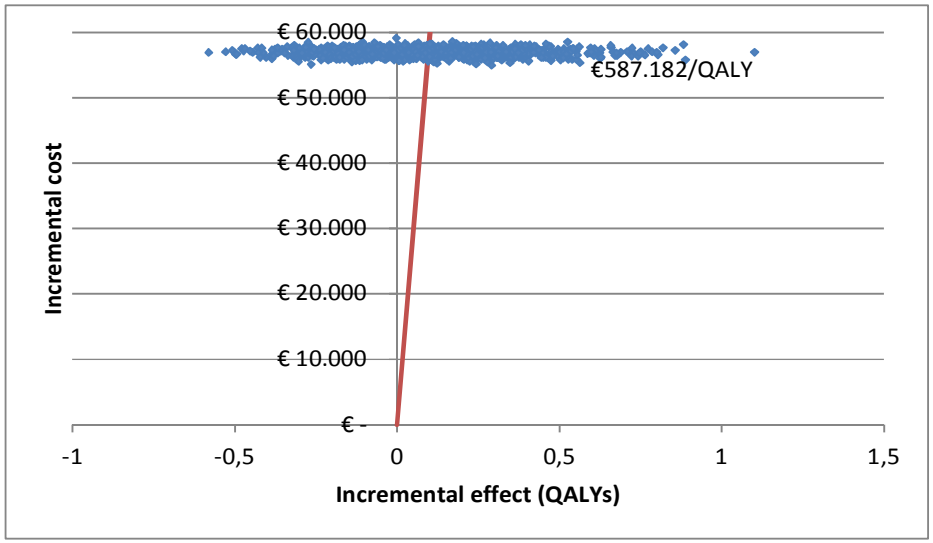
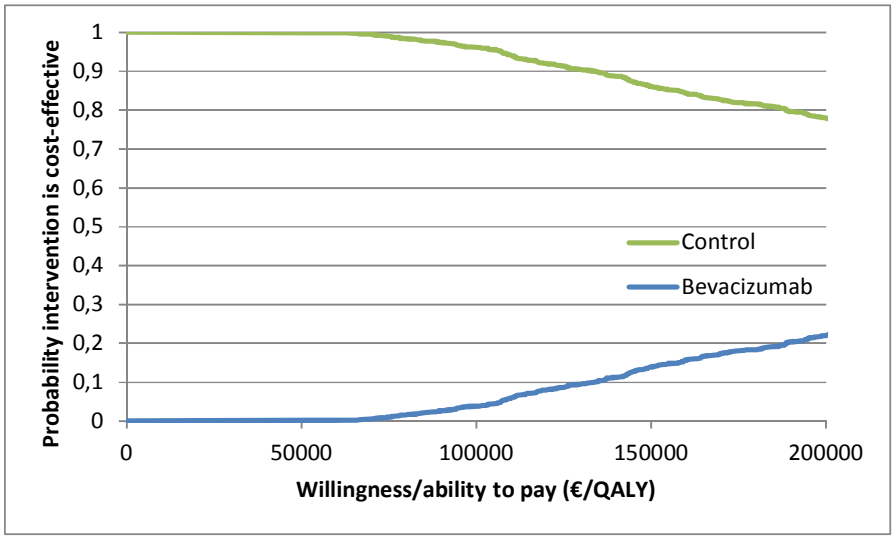
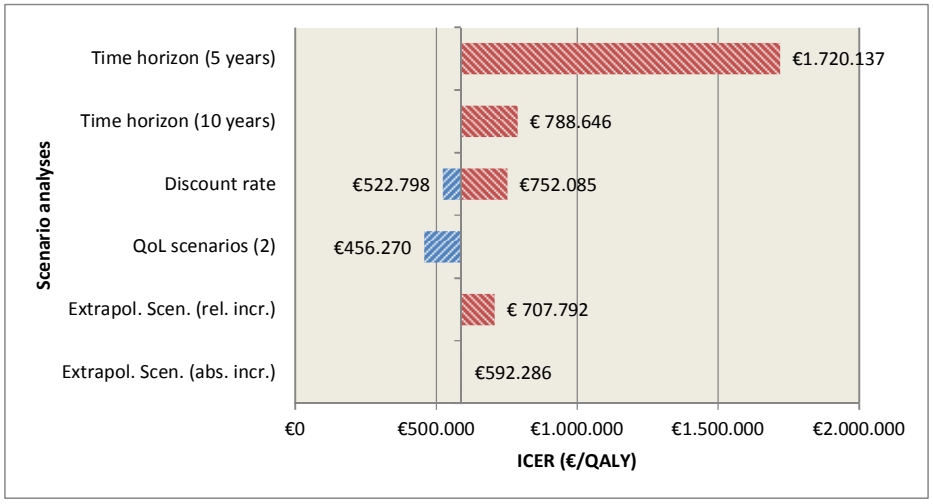


Table 48 – Results of the economic evaluation for the OCEANS trial







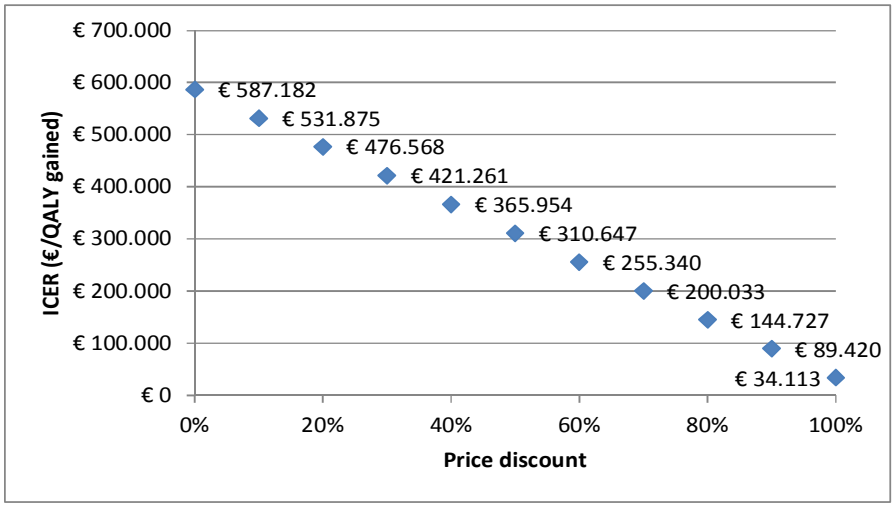
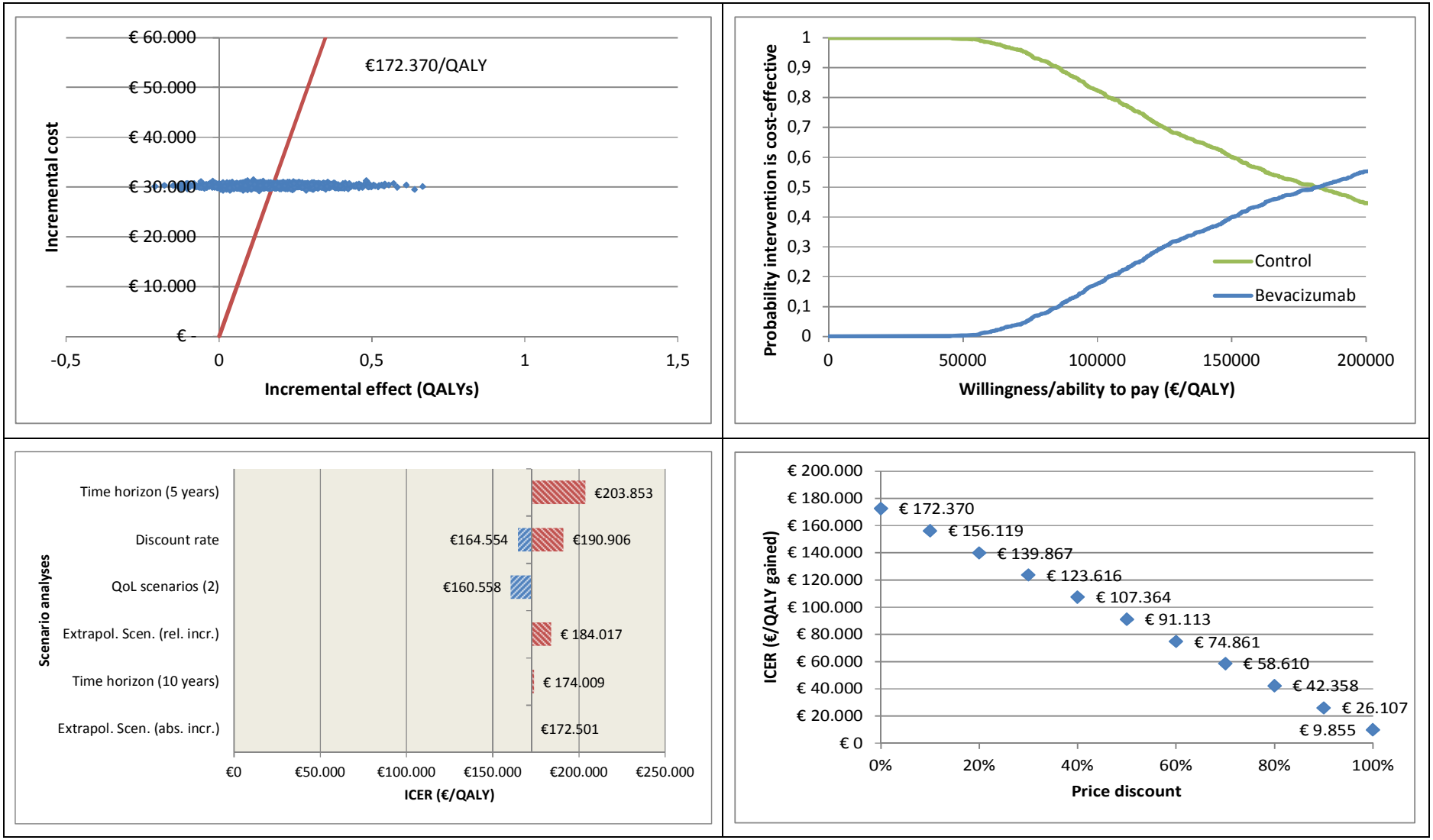


Table 49 – Results of the economic evaluation for the AURELIA trial



7.2.2 Validation of modelling outcomes

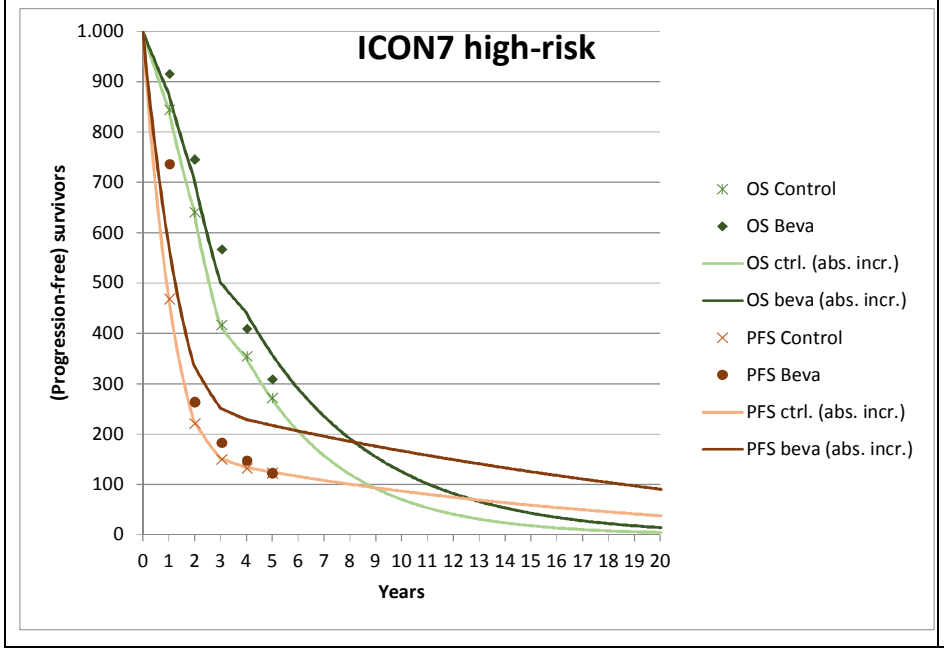
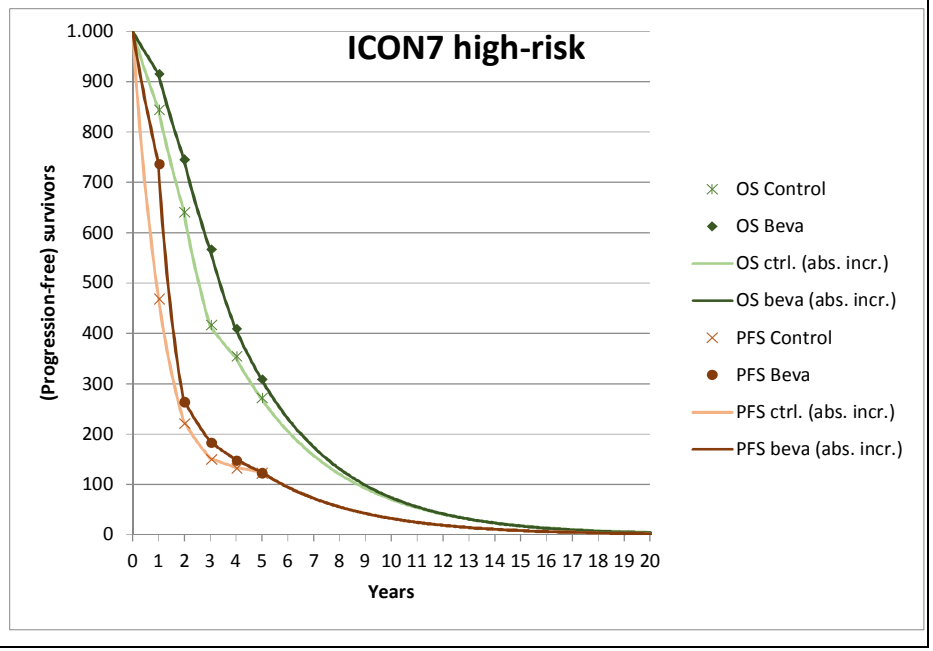
Visual check of the modelled OS and PFS curves

The two figures in Table 50 are an example of the importance of performing a visual check of what is modelled. Setting up the Markov model starts with modelling OS and PFS in the control group. Both figures show that the modelled curves coincide with the extracted point estimates for the control group. Secondly, the OS and PFS curves for the bevacizumab group were modelled using the published hazard ratios. A visual check shows that the modelled curves do not fit well with the underlying point estimates. For OS: during the first three years, the modelled OS-curve is situated too low; during the last two years (also influencing the extrapolation), the model is too optimistic. For PFS we see the same problem: the curve is too pessimistic in the beginning, and much more optimistic thereafter (and influencing the extrapolation). Furthermore, separately modelling OS and PFS shows that these curves cross during the extrapolation phase, which is of course not possible.

In case of the ICON7 high-risk subgroup model, corrections were incorporated to better fit with the observed evidence. First, instead of modelling through the hazard ratios, the extracted points from the published KM-curves were used. Second, were PFS-curves crossed, the curves further coincide and follow the same trend during extrapolation as the OS-curves (Table 50, right panel).

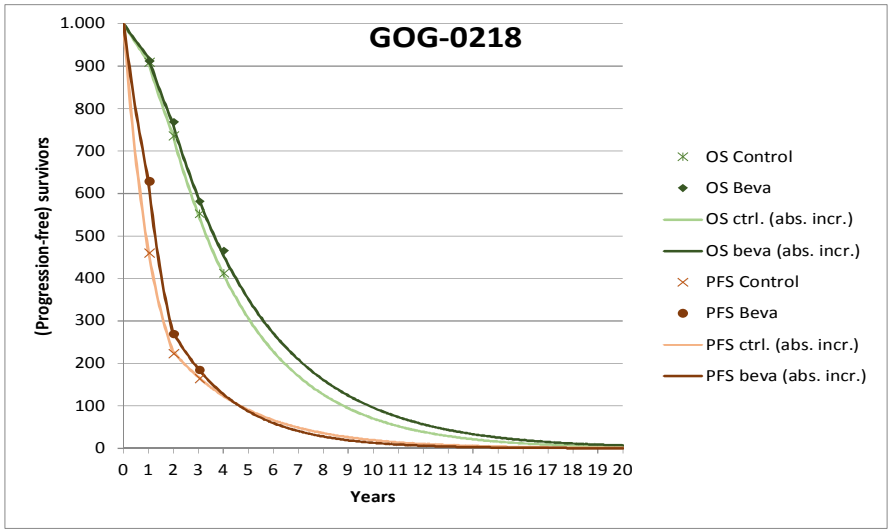
Table 51 presents these figures for the other four modelled trials. In these cases, the fit of the bevacizumab OS through the hazard ratios was interpreted as being sufficiently satisfying. For the bevacizumab PFS-curves, a similar correction as for the ICON7 high-risk subgroup model was needed.

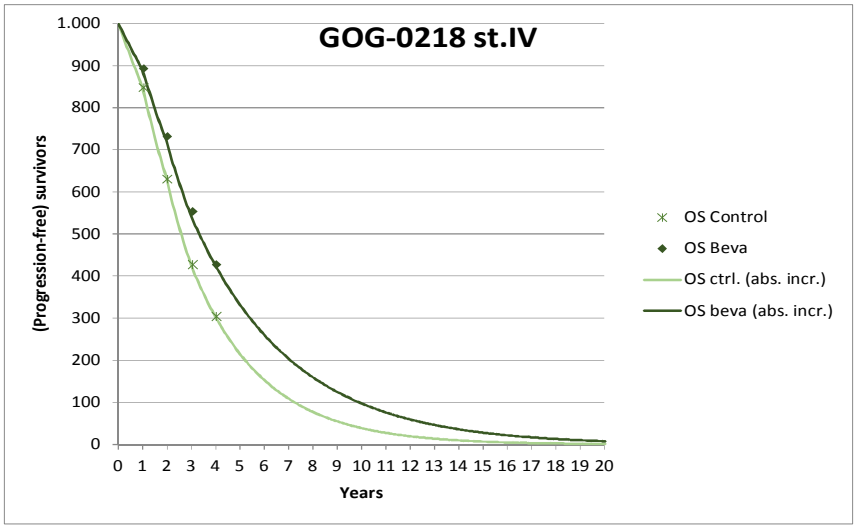
Table 50 – Visual validation of modelled outcomes: unsatisfactory fit/mistakes and corrections (case of ICON7 high-risk population)

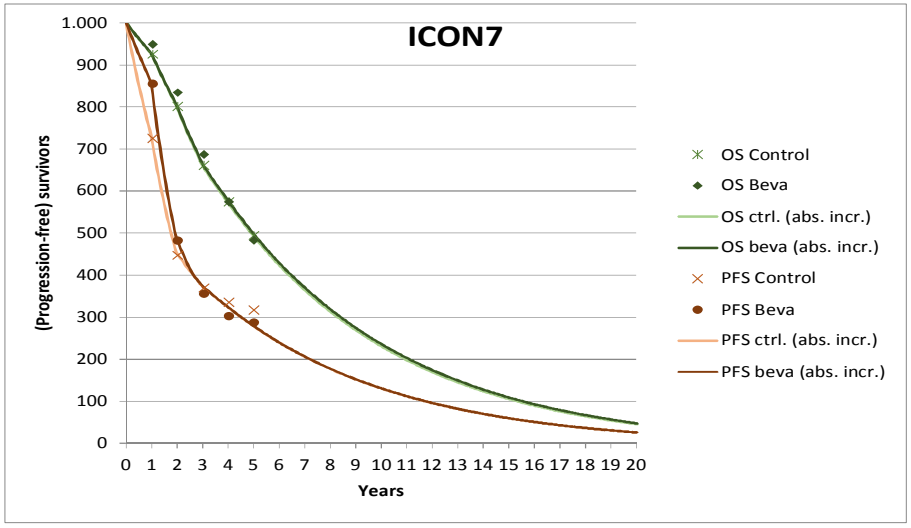
Uncorrected (wrong) approach	Corrected approach
	

Left: the uncorrected approach, which was not used anymore. Right: the corrected approach which was used to calculate results.
The lines represent the modelled OS and PFS. The indicated points represent the extracted data at fixed points in time from the published KM-curves.

Table 51 – Presentation of modelled OS and PFS curves and extracted KM point estimates allowing visual validation of the models







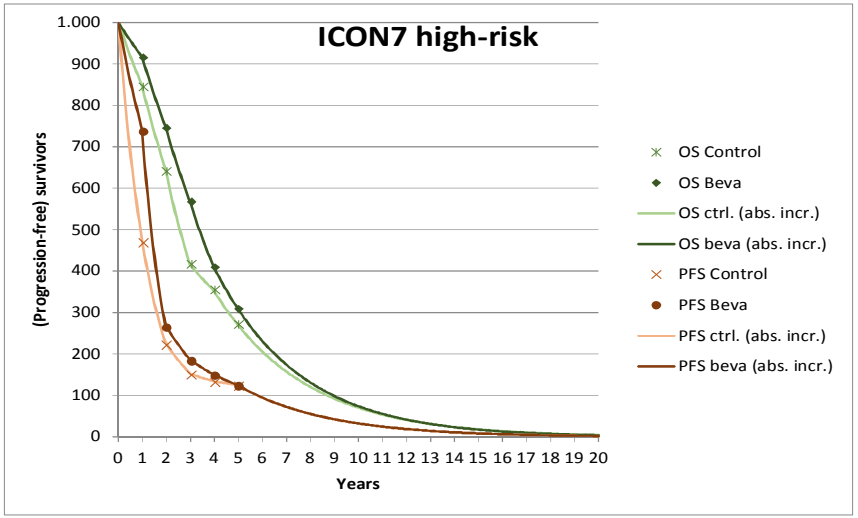
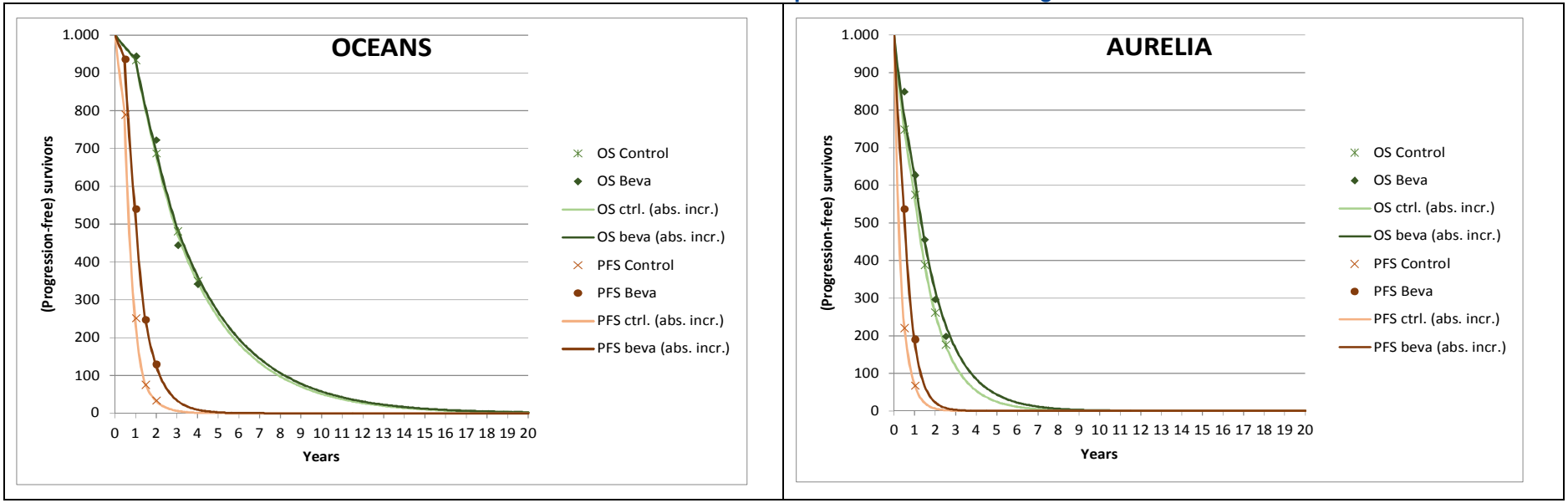


Table 52 – Presentation of modelled OS and PFS curves and extracted KM point estimates allowing visual validation of the models



Comparison of modelled IE (LYG & QALYs) with previous economic evaluations

The comparison shows that in the majority of cases, our modelling approach was not providing an underestimation of the incremental impact on LYG or QALYs gained. The largest differences were noticed for the OCEANS study. However, as noticed by the ERG, the manufacturer submission in TA285 modelled a positive impact on OS based on the September 2010 results, which was not sustained in the March 2012 analysis, which explains the different incremental impact.

Also for the ICON7 high-risk subgroup population some differences are noticed. However, comparing with the published trial results, it seems that our model fits well and does not underestimate the incremental impact on life-years gained. Applying a 0% discount rate as in the trial results, our model provides 0.48 LYG in comparison with a published restricted mean OS difference of about 0.4 LYG. Our incremental impact is also relatively close to the results of Mehta[46] and the industry-sponsored study of Duong.[51] In the ICON7 model, the undiscounted LYG equals 0.1 LYG, also showing our results are close to the published restricted mean survival difference from the original trial.

For the AURELIA study, no comparison could be made since Chappell et al.[41] express their results in PF-LYS (progression-free life-year saved). Results of Cohn[42, 43] and Lesnock[45] also did not publish LYG or QALYs gained and are not included in Table 53.

The GOG-0218 stage IV subgroup is not included in Table 53 since none of the other studies modelled this subgroup.

Table 53 – modelled outcomes versus previously published results

Trial	Model (3% discount rate scenario)	TA284	TA285	Mehta	Oza*	Barnett	Chan	Duong
GOG-0218	0.37 LYG 0.27 QALYs gained	0.23 LYG 0.19 QALY	/	0.19 LYG 0.05 QALY	/	/	/	/
ICON7	0.07 LYG** 0.05 QALYs gained	/	/	/	0.9 months* (~0.075 LYG))	0.08 LYG	/	/
ICON7 high-risk	0.44 LYG*** 0.32 QALYs gained	*0.74 LYG* *0.56 QALY*	/	0.34 LYG 0.27 QALY	4.8 months* (~0.4 LYG)	0.09 QALY	*8 months* *(~0.67 LYG)*	0.374 QALY
OCEANS	0.12 LYG 0.09 QALYs gained	/	*0.42 LYG* *0.298 QALY*	/	/	/	/	/
AURELIA	0.23 LYG 0.17 QALYs gained	/	/	/	/	/	/	/

Numbers in red and in italics indicate the studies with a much more optimistic impact on life-years gained (LYG) or quality-adjusted life years (QALYs) gained in comparison with our study results.
** reference Oza (2015),[31] no discount rate applied.*
*** the results from the ICON7 trial (i.e. mentioned in the column 'Oza') are undiscounted results. The undiscounted life-years gained in our model is 0.1 for the ICON7 and 0.48 for the high-risk subgroup.*

7.3 Conclusion

In general, from a health economic point of view, the results for second-line bevacizumab treatment are not favourable. The average ICER based on the OCEANS and AURELIA trials amount to €587 000/QALY and €172 000/QALY, respectively. For both models, there is a 0% probability that bevacizumab is a cost-effective treatment up to a willingness-to-pay value of more than €50 000/QALY.

In the first-line setting, results are not favourable when results for the whole population of the GOG-0218 or ICON7 trials are modelled, with ICERs of on average 158 000/QALY and 443 000/QALY, respectively. The most optimistic results are based on the stage IV subgroup of the GOG-0218 trial. However, even in this subgroup analysis, average ICERs amount to €52 000/QALY in a rather optimistic scenario (e.g. no decrease of QoL with bevacizumab treatment, extrapolation of results to lifetime time horizon with constant mortality, not taking into account costs for all AEs). Results are most sensitive to the price of bevacizumab and the extrapolation period. Scenarios including the QoL assumptions according to the manufacturer's submissions to NICE do not have a major impact on our results.

8 DISCUSSION

8.1 Unproven effectiveness of first-line bevacizumab on overall survival and quality of life, but subgroups may benefit

Two published RCTs provided evidence about the effect of bevacizumab on progression-free survival in patients with previously untreated advanced stage epithelial ovarian, primary peritoneal, or fallopian-tube cancer.[28, 31] When both trials were pooled, important heterogeneity was identified (I^2 80%). This can in part be explained by the difference in dosage and treatment duration that was used in both trials (GOG-0218, bevacizumab-throughout: 15 mg/kg every 3 weeks for 21 cycles; ICON7: 7.5 mg/kg every 3 weeks for 5-6 cycles and continued for 12 additional cycles or until disease progression). An additional explanation could be that a different definition was used by both trials. In the GOG-0218 trial disease progression was based on RECIST criteria, global clinical deterioration or CA-125, while in the ICON7 trial disease progression was based on RECIST, clinical or symptomatic progression. In the ICON7 trial, CA-125 measurements alone were not used to determine disease progression. Finally, the two trials showed differences in disease stage and residual disease post-surgery. All patients in the GOG-0218 trial had stage III and IV disease, while 81% of ICON7 patients had stage III or IV disease. Resected stage IV patients and stage III with >1cm residual disease comprised 54% of the population in the GOG-0218 study, but only 31% of the ICON7 study population. For all these reasons, pooling was considered inappropriate. If only the GOG-0218 trial were considered, a significant effect on progression-free survival would be noted (according to GRADE, our confidence in this estimate is moderate). The ICON7 trial did not find a significant effect.

Both trials also provided evidence of moderate quality that first-line bevacizumab has no effect on overall survival and is associated with a transient worsening in quality of life. It is important to mention that in both RCTs, overall survival was a secondary outcome and the studies were not powered for this.

Both trials published predefined subgroup analyses.[28, 31] The GOG-0218 trial found significant effects on progression-free survival in the bevacizumab-throughout group for the three predefined strata (stage III cancer with a maximal residual lesion diameter ≤1 cm, stage III cancer with a maximal residual lesion diameter >1 cm, and stage IV cancer), but only a positive effect on overall survival for stage IV cancer patients. The ICON7 trial found significant effects on progression-free survival for two of the three predefined strata (FIGO stages I-III and >1 cm of residual disease, and FIGO stage III (inoperable) or IV), but no results for overall survival were reported for these strata. In addition, based on a Cox regression analysis and predefined in the statistical plan, the ICON7 trial found a significantly better progression-free and overall survival for patients with a high risk for progression (FIGO stage IV disease, or FIGO stage III disease and >1 cm of residual disease after debulking surgery), the subgroup of patients defined as closest to the GOG-0218 population. However, although the subgroup analysis was predefined, randomization was not stratified for this high-risk subgroup, so there is still a risk of prognostic imbalance between the ICON7 treatment groups.

Finally, remarkably, in the assessment report of NICE (TA284) EQ-5D scores are also reported for quality of life.[24] However, these were never published in a peer-reviewed article. No clear reason was found for this. Unfortunately, in the NICE submission, the EQ-5D scores were not published per treatment arm, but immediately pooled per non-progressed or progressed health state.

8.2 Positive effect of second-line bevacizumab on progression-free survival and one item of quality of life, but not on overall survival

Two published RCTs[26, 34] and one unpublished RCT[36] provided evidence of moderate quality that bevacizumab has a positive effect on progression-free survival, but no effect on overall survival in patients with recurrent epithelial ovarian, primary peritoneal, or fallopian-tube cancer. Also in this case, the studies were not powered for this secondary outcome. The studies also provide evidence of very low quality that second-line bevacizumab increases the proportion of patients achieving a 15% improvement in patient-reported abdominal/gastrointestinal symptoms (measured with EORTC QLQ-OV28) during chemotherapy, but no differences in quality of life were found with other instruments (FOSI, EORTC QLQ-C30 and FACT-O-TOI). In absolute terms, the gain in (median) progression-free survival is limited to a minimum of 3.3 months (AURELIA trial) and a maximum of 4.0 months (OCEANS trial).

Our pooled results for progression-free and overall survival confirm those reported by other identified systematic reviews.[18, 21, 22, 25]

The overall effect on (progression-free and overall) survival is also true for specific subgroups, i.e. platinum-sensitive patients (OCEANS and GOG-0213 trials), platinum-resistant patients (AURELIA trial), and patients receiving different types of concurrent chemotherapy (predefined strata of the AURELIA trial).

8.3 Is bevacizumab a safe treatment?

Bevacizumab is associated with typical adverse events, such as hypertension, bleeding, thromboembolism and bowel perforation, of which some are potentially life-threatening. Meta-analyses for the present report (including the results from the four most relevant RCTs) have clearly confirmed these observations. However, in absolute terms the impact of the more serious adverse events is rather limited. For example, a relative risk of 2.9 (95%CI 1.44-5.82) for grade ≥2 gastrointestinal perforation translates in an absolute effect of 11 more events per 1000 patients (95%CI 2-27) (see GRADE tables in appendix). Another example is the arterial thromboembolism, where a relative risk of 2.15 (95%CI 1.08-4.30) translates in an absolute effect of 12 more events per 1000 patients (95%CI 1-34).

In general, toxicity can therefore be considered acceptable.

8.4 Which outcomes do matter?

Crucial in decisions about the added value of an intervention is the relative importance of the different outcomes on which the intervention has an effect or not. Importance of outcomes is likely to vary within and across cultures or when considered from the perspective of patients, clinicians, or policy makers.[61]

In 2014, the Society of Gynecologic Oncology published a white paper on clinical trial endpoints in ovarian cancer.[62] Both overall and progression-free survival were considered to be clinically important, although the authors acknowledge the fact that overall survival remains the most objective and accepted endpoint, because it is least vulnerable to bias. Nevertheless, according to the authors, the feasibility of overall survival in ovarian cancer is compromised by the requirement for large trial size, prolonged time-line for final analysis, and potential for unintended loss of treatment effect from active post-progression therapies. These reasons are often used to justify the choice of progression-free survival over overall survival as primary endpoint, both in clinical trials and regulatory approvals. Unfortunately, little evidence is available on the relationship between progression-free and overall survival specifically for ovarian cancer. Statistical modelling by Broglio et al. has shown that for clinical trials with a significant effect on

progression-free survival, lack of a statistically significant overall survival benefit does not imply a lack of improvement in overall survival, especially for diseases with more than 12 months between progression and death (such as ovarian cancer).[63] They found that, for a trial with an observed p-value for improvement in progression-free survival of 0.001, there was a greater than 90% probability for statistical significance in overall survival if median survival post-progression was 2 months, but less than 20% if median survival post-progression was 24 months. This has prompted some researchers to recommend the addition of intermediate clinical endpoints, such as time to second disease progression or death and time to second subsequent therapy or death, to the evaluation with progression-free and overall survival.[64]

As a preparation of the KCE clinical practice guideline on ovarian cancer,[1] the involved guideline development group was asked to formally score a list of outcomes on their importance for 11 research questions. For most questions about advanced cancer, overall survival and quality of life were valued higher than progression-free survival.

Havrilesky et al. surveyed 95 women with advanced or recurrent ovarian cancer about their preferences for symptoms, treatment-related side effects, and progression-free survival relevant to choosing a treatment regimen.[65] Progression-free survival was found to be the predominant driver of patient preferences for chemotherapy regimens, but overall survival and quality of life were not included in the experiment. Furthermore, patients' choices indicated that they were willing to accept a shorter progression-free survival to avoid severe side effects: a reduction of 6.7 months to reduce nausea and vomiting from severe to mild, 5.0 months to reduce neuropathy from severe to mild, and 3.7 months to reduce abdominal symptoms from severe to moderate. In a larger study, 1413 women with ovarian cancer were surveyed about their preference regarding side effects and therapy endpoints.[66] 77% and 85% of the participants, respectively, reported that for a new agent to be meaningful, the minimum extension of progression-free survival and overall survival should be five or more months. Most subjects (55%, N=612) were interested in an agent that would keep tumour growth relatively static without change in overall survival. There was significant migration ($p<0.0001$) to acceptance of greater toxicity (three-fold higher neurotoxicity) and cost under the scenario of a 5-6 months overall survival gain as compared to a progression-free survival gain of 3-4 months / no overall survival gain without toxicity. Response patterns weren't altered by recurrence status.

8.5 Results and limitation of current model

In an economic evaluation, we try to combine the best available information in a model, including the impact of the uncertainties around the input variables. For example, the trials show no significant impact on overall survival (or were not able to detect an impact). However, this does not mean that no impact on overall survival is modelled. Instead, the model includes the impact as shown by the trials, taking into account exactly the same mean and confidence interval for this outcome.

Based on the results of the GOG-0218, ICON7, OCEANS and AURELIA trials, ICERs expressed as extra costs per QALY gained were calculated. With average ICERs of more than €172 000/QALY in second line and €158 000/QALY in the first-line setting, results for the entire population in these trials are not very favourable. Best results are achieved for the stage IV ovarian cancer patients from the GOG-0218 trial, with an average ICER of €52 000/QALY. Although the analysis of this subgroup coincides with inevitable uncertainty.

Modelling is almost always associated with some limitations, for which we try to assess whether the assumptions made are justified and/or whether changing assumptions might have a major impact on results.

One of the determining variables in models like ours is *treatment duration*. Information on treatment duration was published explicitly in the manufacturer's submissions for the GOG-0218[47], ICON7[47], and OCEANS[48] trials, and was used as such in our model. For the AURELIA trial, treatment duration was deducted from a published figure (see part 0). Validation with a submission from the manufacturer to NIHDI shows that this deduction was in agreement with the manufacturer's numbers. Subgroup analyses were also performed as part of our model for the ICON7 high-risk group and GOG-0218 stage IV ovarian cancer patients. However, no information on the average treatment duration was available for these subgroups. For the ICON7 high-risk subgroup the same treatment duration as for the whole population was taken into account, while the survival curve for the ICON7

high-risk patients is worse than for the whole population. It is thus possible that the average treatment duration is also shorter. Further information is needed to be able to improve the estimates for this subgroup. For the GOG-0218 stage IV subgroup, the manufacturer's report to NIHDI[67] mentioned an average treatment duration of 11.9 cycles, and these data were used in our model. However, we note that the dossier also referred to a 13.6 cycle duration for the OCEANS trial, which equals 40.8 weeks, while the manufacturer's submission to NICE makes reference of 50.7 weeks for the same trial. The reason for this difference is unclear.

A second limitation of our model is the *exclusion of some adverse event (AE) treatment costs*. The assessment of safety showed an increase for several AEs. Equal costs are to be excluded in the model and we tried to include the most important toxicities. However, based on our sample of real-life data, no good estimate of specific AE-related treatment costs could be extracted. Furthermore, it did not seem to be justified to award specific costs to bevacizumab treatment, since some drugs for treating AEs were already administered to the patient before receiving bevacizumab (e.g. antihypertensive treatment). Therefore, only costs for perforations were included in the model, which is a rather conservative assumption in favour of bevacizumab. On the other hand, the relatively small absolute difference in AEs between the two treatment arms would probably result in only a minor increase of the ICERs. Similarly, *differences in follow-up* were also disregarded, since we assume that such costs apply to patients in both treatment arms and the incremental impact is thus probably negligible.

Costs of post-progression treatment were also disregarded in our model. The manufacturer's submission for the GOG-0218 trial mentions that "*the type and duration of treatments received by patients after their tumour had progressed are not available in sufficient detail for either the effect on overall survival or the appropriate costs incurred to be estimated. Therefore, post-progression costs are not included in this model and we recommend caution when interpreting the results of the model based on the GOG-0218 study.*"[47] The manufacturer also notes that OS may be confounded by the use of bevacizumab in the placebo group following progression. In the GOG-0218 trial, up to 40% of placebo patients received bevacizumab post progression.[47] Also in the second-line OCEANS trial, cross-over has been mentioned as a confounding factor: 18.1% of patients within the bevacizumab group received bevacizumab post-progression (37/204) compared with 34.7% (74/213) within the placebo group.[50] However, with respect to the possible impact on OS, we should not forget that no significant impact has been shown in second line. Using the second-line cross-over argument to justify a higher impact on OS in first line seems somewhat problematic. Furthermore, post-progression bevacizumab administration is a very expensive strategy without supporting evidence to significantly improve survival. Modelling an approach in which bevacizumab is provided post-progression to the placebo group would thus mainly increase the costs of the control arm. Improving bevacizumab's cost-effectiveness, by adding relatively high bevacizumab treatment costs to the control arm, seems not to be justified.

8.6 Limitations of subgroup analyses

When the overall results in trials are not convincingly positive, it might be tempting to focus on a specific subgroup. Researchers have already pointed at the danger of such analyses. A systematic review of Sun et al.[68] found that "*about a third of a representative sample of recent randomised trials published in core clinical journals report subgroup analyses. After judging these reports of subgroup analyses using 10 carefully developed predefined criteria, the authors conclude that only in very few instances can we be confident that subgroup analyses provide a better estimate of effect than the overall results of trials*".[69]

Another study mentions that, on the other hand, subgroup analyses may sometimes be entirely appropriate.[70] This study summarizes several proposed guidelines[71-75] for deciding when subgroup analyses are reasonable, how to carry them out, and how to report them. Some of the criteria are fulfilled in the GOG-0218 trial; e.g. the factors that determine the subgroups and the rationale for the subgroup analysis were formally prespecified in the protocol, and the factors that determine the subgroups were assessed before randomisation. However, the last two criteria in their overview are the following:

- "Subgroup findings should be exploratory, and only exceptionally should they affect the trial's conclusions. Editors and referees need to correct any inappropriate, overenthusiastic uses of subgroup analyses.[71] Avoid over interpretation of subgroup differences. Unless there is strong supporting evidence, the results are best viewed as hypothesis-generating.
- The overall 'average' result of a randomised clinical trial is usually a more reliable estimate of treatment effect in the various subgroups examined than are the observed effects in individual subgroups. Therefore, put emphasis on overall results, which may be considered better estimates of treatment effects than the subgroup effects."[70]

In 2016, NICE also evaluated whether their original analyses (TA284 and TA285) needed an update. Regarding the subgroup analyses of the GOG-0218 trial they considered that "*the results from GOG-0218 (Randall 2013) represent an exploratory subgroup analysis of people with stage IV disease; confirmatory studies are required to strengthen Randall et al.'s conclusion that bevacizumab is more effective in people with stage IV disease. In addition, this analysis may not address the uncertainty in the survival benefit of bevacizumab. Considering these limitations, and the high incremental cost effectiveness ratio (ICER) for bevacizumab in the overall patient population, this exploratory subgroup analysis does not warrant a review of the guidance*".[76]

Currently, bevacizumab is reimbursed in first line for this stage IV subgroup. Therefore, not forgetting to stress the danger of such analyses, we decided to perform an economic evaluation for this subgroup. As mentioned by NICE, confirmatory studies are required to strengthen the conclusion of this subgroup analysis. At least three studies are ongoing in first line that included stage IV patients.

The least policy makers can ask is that longer follow-up results are provided for the already published trials, e.g. to see whether the positive OS impact remains in the long-term, especially because the extrapolated survival curve in our model seems to be rather optimistic with a 10% survival for stage IV ovarian cancer patients after 10 years. As shown in our sensitivity analyses, the impact on the ICER of restricting the extrapolation period from life-time to ten or five years is substantial for this most optimistic subgroup analysis of stage IV ovarian cancer patients.

Next to the danger of being a subgroup analysis and the uncertainty around the extrapolation, the cost-effectiveness estimates for the GOG-0218 stage IV subgroup are probably rather optimistic since e.g. not all AEs costs are included, no decrease in QoL due to bevacizumab treatment are included and no extra chemotherapy costs are included.

8.7 Budget impact for stage IV subgroup in first line

Both economic evaluations and budget impact analyses are important elements for the decision maker, as they give clues about the efficient allocation of scarce resources and the affordability of specific interventions.[77] A major difference between both elements is that economic evaluations take into account the health gains by calculating incremental cost-effectiveness ratios (ICERs), while budget impact focusses on the monetary impact of a reimbursement decision.

The budget impact depends on both the number of patients and the incremental costs per patient. The outcomes of our economic evaluation show these incremental costs for all trials (see Table 43). For the subgroup of stage IV ovarian cancer patients of the GOG-0218 trial, the incremental costs are about €40 000. This is almost completely due to the extra drug costs of about €37 700 for this subgroup of patients (see Table 39). During the period 2008-2013, an average of about 150 patients per year were diagnosed with stage IV ovarian cancer (see Figure 1[j]). Reimbursing bevacizumab for this group, disregarding possible price discounts, would lead to a yearly budget impact of about €6 million.

[j] We remark that in the referred Figure 1 only a distinction between stage I, II, III and IV ovarian cancer could be made. No information on percentage of second-line treatments is available.

8.8 QoL

As shown in our literature review of economic evaluations, all studies made assumptions regarding the impact of bevacizumab treatment on QoL. Lesnock et al. noted that there are no utility values that have been validated for patients specifically with epithelial ovarian cancer, nor for the therapies included in their model.[45] Some authors modelled a decrease in QoL due to more AEs, others modelled an improvement trough prolonged PFS. Cohn et al.[43] converted QOL scores from the FACT-O instrument to a utility and admitted this has not been extensively validated. They noted that future prospectively collected studies will address this issue by including both the FACT and a more standard instrument for measuring utilities such as the EQ-5D.[78] However, as also recommended in the EUnetHTA guideline on HRQoL,[79] in order to avoid mapping, which is always entailed with an extra level of uncertainty, it is better to directly include a generic utility instrument in the clinical trials.

The ICON7 protocol incorporated the EQ-5D questionnaire to measure patients' HRQoL: "*Quality of life will be assessed using the EORTC QLQ C-30+OV-28 and EQ-5D questionnaires at the start of every chemotherapy cycle, every six weeks until the end of the first year and then every three months until treatment for progression commences, or to the end of year two. An additional QoL form will be completed by all patients still alive three years after randomisation.*"[80] In the part 'ancillary studies' of the protocol, the EQ-5D instrument is not mentioned under 'Quality Of Life', but only referred to in the part on 'Health Economics': "*patients' health-related quality of life (HRQL) will be assessed at baseline and throughout follow-up using the EQ-5D instrument*[81]*as part of the QoL forms that all patients will complete. This will facilitate the expression of HRQL in terms of 'utilities' which are used to estimate patients' quality-adjusted survival duration.*"[80] As a result, EQ-5D information was not reported in the article entitled: "*Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial*".[33]

EQ-5D results were published in the manufacturer's submission to NICE. The manufacturer states that, given the overlap of patient recruitment in the GOG-0218 and ICON7 trials, the results from EQ-5D are used in the economic models for both studies.[47] Unfortunately, results are not provided per treatment arm. The manufacturer justified this by arguing that "a log-rank test confirmed that there was no difference in utility values whilst patients were progression-free across the intervention and control arms, therefore it was assumed that utility estimates from both treatment arms at each time-point could be combined."[47] The manufacturer's submission also provides the argument that "cancer survivors whose disease recurs have a worse HRQoL in most indices than those who remain disease-free[82] and the factor causing most distress among cancer patients (and therefore impacting on HRQoL) has been found to be the fear of disease progression[83]."[47] Nevertheless, EQ-5D outcomes should have been published transparently per treatment arm, without any aggregation, so researchers can also model the crude QoL impact per treatment arm, including the confidence intervals around these values. With the current presentation of results per health state (progression-free or progressed disease), the size of the possible negative (non-significant) impact on QoL is not clear. In contrast, only an improvement in QoL is modelled, while the evidence rather shows an opposite effect in the short term.

Cohn et al. also note that "with respect to abdominal discomfort, all arms of the trial improved over time. While no QOL differences were observed between bevacizumab-containing and control arms on this outcome measure, study-associated placebo treatments may have negatively influenced QOL in the PC arm and contributed to the lack of difference in QOL observed during the maintenance phase."[43]

Furthermore, as previously mentioned by the Evidence Review Group, the ICON7 trial "employed a lower dose of bevacizumab than in the NICE scope. Any AEs caused by the higher dose of bevacizumab as specified in the NICE scope would not be captured using the utility data from the ICON7 trial."[49] Applying utility estimates from the ICON7 trial to the GOG-0218 trial might thus be too optimistic. In our base case, we did not model an improvement, nor a deterioration of QoL. Scenario analyses showed that including QoL values from the manufacturer's submission did not generate much better ICER values. A short-term reduction in QOL due to bevacizumab treatment would for sure not have a positive impact on our results. Therefore, our modelled results are rather conservative.

8.9 Dose

In the overview of economic evaluations, most analyses were based on the GOG-0218 or ICON7 trial. A major difference between the two treatment regimens is the dose and treatment duration. In the ICON7 trial, the bevacizumab dose was half the dose used in the GOG-0218 trial (7.5mg/kg every 3 weeks versus 15mg/kg every 3 weeks), and patients received 4 fewer maintenance cycles (12 versus 16 cycles).[39] The registered dose is the 3-weekly 15mg/kg dose. NICE restricts their recommendation to licensed indications. However, "*it is argued by the manufacturer (and agreed by the clinical expert consulted by the ERG) that the lower dose is representative of current clinical practice*".[49] According to experts, the non-registered lower dose is often used when the patient pays herself for the treatment. We refer to another KCE report[84] on off-label use for more information on the possibility to perform research with off-label use of drugs and the possible inclusion in treatment guidelines and/or reimbursement mechanism if evidence supports the safety, efficacy and cost-effectiveness of off-label intervention.

8.10 Confidential contracts and changing reimbursement conditions

The reimbursement of bevacizumab for the treatment of ovarian cancer is based on a confidential contract (article 81 of the Royal Decree of 21 December 2001[12]). A first 3-year contract was concluded on 1 March 2014 for the first-line treatment of stage IV and the treatment of first recurrence in platinum-sensitive patients. A second 3-year contract was concluded on 1 July 2015 for the treatment of platinum-resistant patients. We have no access to the content of the appendices in which the conditions of the contract are specified. It is thus not clear whether the contract only includes e.g. price-volume agreements or if also scientific information was requested. However, in accordance with the Declaration of Helsinki, information from clinical trials requested in confidential contracts should be registered and results should afterwards be published. Since no clinical trial related to the confidential reimbursement agreement was registered, we assume that no such scientific information was requested.

Concerning the confidential price agreements, sensitivity analyses were performed with price discounts between 0% and 100%. As such, policy makers can link e.g. the necessary price discounts to reach a specific willingness/ability-to-pay value.

At the end of a confidential contract, possible changes in reimbursement criteria should not immediately have an influence on patients already under treatment with bevacizumab. These should only apply to patients for which treatment has not yet been started.

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