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SUMMARY

BEVACIZUMAB IN THE TREATMENT OF OVARIAN CANCER

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

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■ FOREWORD

You can hear it more often: with this treatment or this preventive measure we can save at least this many lives. We too, at KCE, have certainly been guilty of these kinds of statements. For, honesty implies: until further notice, a so-called 'saved' life is nothing else than postponing the inevitable end. So, at best we can add years to life and, if we are lucky, give a push to make it 'livable' years.

For patients whose ovarian cancer is detected in an advanced stage, we do not always speak about years but months. Even not always about life extension, but about a few months of more respite until the disease takes the upper hand again without mercy.

What develops then is a fundamental discussion between the clinician and his patient, the health economist, the epidemiologist and the policy maker – let's say the health insurance. Each with their own values, starting from their own objectives or purposes in life, from their own ethical framework as well. It is about giving all the chances to the patient who is in front of us ... or trying to help the maximum number of patients with the limited resources of the health insurance. Are we going for maximum life extension, or for maximum quality of life? Or just the maximally achievable, how limited this might be.

It is not a comfortable discussion, because choosing is always loosing. Certainly when a high price has to be paid for a limited profit. Money that could have been spent, for example, on strengthening the palliative offer, or on support to caregivers. But this is not the place to reopen the debate on the drug price. In this report, we restrict ourselves to reporting the scientific data on efficacy and safety, as well as the economic consequences of the various options. Because, since choices always have to be made in health insurance, these are preferably based on as complete and transparent information as possible. The patient, the citizen is entitled to this.

Christian LÉONARD

Deputy general director

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General director

■ SUMMARY

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1. INTRODUCTION

In Belgium, ovarian cancer is the eight most frequent female cancer and the fifth one in terms of female cancer mortality. In 2014, 848 women were diagnosed with ovarian cancer (ICD-O C56). Because symptoms occur rather late, 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).

In 2016, KCE published a clinical practice guideline on the diagnosis, first-line treatment and follow-up of ovarian cancer. In advanced stage, cytoreductive surgery and chemotherapy are used. Standard first-line chemotherapy combination is carboplatin-paclitaxel. 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 (PLDH), topotecan or gemcitabine represent possible options.

During the elaboration of the 2016 guideline, it was decided to investigate the role of bevacizumab in ovarian cancer treatment in a separate HTA project. Currently, in Belgium, bevacizumab is reimbursed for ovarian cancer patients in three situations:

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.

The present HTA report aims to evaluate the safety, clinical effectiveness and cost-effectiveness of bevacizumab in the following situations: (1) in addition to first-line chemotherapy; (2) in the treatment of recurrent ovarian cancer (platinum-sensitive or platinum-resistant).

When the term 'ovarian cancer' is used in this synthesis, fallopian and primitive peritoneal cancer are also referred to from here onwards.

Box 1 – What is a Health Technology Assessment (HTA)?

The aim of an HTA is to inform policymakers in making decisions on the development of an accessible, qualitative and sustainable healthcare system. An HTA is a multidisciplinary scientific research process in which the safety and efficacy, but also the economic, social and ethical acceptability, of a technology or product are examined. These various aspects are not necessarily discussed (in the same depth) in every HTA. In practice, the focus is primarily on the medical aspects of safety and efficacy. In function of these medical results the cost effectiveness is also examined: what added value is offered, at what price? This can be useful in striving towards the most efficient possible use of the available resources.

2. METHODS

2.1. Clinical effectiveness and safety

The clinical effectiveness and safety of bevacizumab in ovarian cancer was evaluated based on a systematic review of the medical literature. The Cochrane Library, Medline and Embase were searched for (systematic reviews and meta-analyses of) randomized controlled trials (RCTs). In addition, HTA websites were searched, and the reference lists of included articles were checked for relevant publications. Clinical experts and manufacturers were asked to provide any information about unpublished trials and/or results. Furthermore, the FDA website (Food and Drug Administration, US) and clinical trial registers were searched.

Study selection and quality appraisal were performed by one researcher. The quality of systematic reviews was assessed by the use of AMSTAR (http://amstar.ca/Amstar_Checklist.php). For RCTs the Cochrane Collaboration's tool for assessing risk of bias was used.

Meta-analyses were performed according to the guidelines described in the Cochrane Handbook and by the use of Review Manager software (RevMan 5.3).

For each critical and important outcome, GRADE (for systematic reviews) was used to grade the quality of the supporting evidence (see Box 2).

A more detailed description of the general methodology can be found in the KCE process book.

2.2. Cost-effectiveness

2.2.1. Literature review

A systematic search for economic literature about the cost-effectiveness of bevacizumab for the treatment of ovarian cancer was performed by consulting the following databases and sources: the CRD[a] HTA database, websites of HTA institutes, the POP database (Planned and Ongoing Projects) of the EUnetHTA partners[b], NHS EED[c], Medline (OVID), and EMBASE.

2.2.2. Economic model

A health economic model has been developed for the Belgian situation, drawn up according to the KCE guidelines for economic evaluations[d].

The model calculated the incremental cost-effectiveness ratio (ICER) for both first- and second-line bevacizumab treatment, expressed as the extra costs per quality-adjusted life year (QALY) (see Box 3). These calculations were based on the results of four international trials, including two subgroup analyses for which the most optimistic effects were presented. With sensitivity analyses the influence of uncertainty around the input variables was taken into account, the robustness of results was checked, and the impact of changing specific assumptions (e.g. price discounts, extrapolation and QoL scenarios) was evaluated. Results of the economic model were validated by a visual check of the modelled survival curves with the original Kaplan Meier-curves and by comparing results of the model with previous economic evaluations.

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[a]   Centre for Reviews and Dissemination

[b]   European Network for Health Technology Assessment

[c]   CRD's Economic Evaluation Database

[d]   KCE report 183

3. CLINICAL EFFICACY AND SAFETY OF BEVACIZUMAB

3.1. Unproven effect of first-line bevacizumab on overall survival and quality of life, but subgroups may benefit

For the first-line treatment with bevacizumab we identified two international RCTs: the GOG-0218 and ICON7 trials.

Progression-free survival

Only the GOG-0218 trial showed a significant effect **on progression-free survival in patients with treatment-naive and advanced ovarian cancer**, the ICON7 trial didn't. The increase in progression-free survival was 2.4 months in the ICON7 trial, but was not reported in the most recent analysis of the GOG-0218 trial. Based on the primary analysis of the GOG-0218 trial the increase in progression-free survival was estimated to be 3.8 months. Due to methodological constraints, there is a moderate confidence in these effect estimates according to GRADE (see Box 3).

Pooling of the two studies was considered inappropriate for several reasons. There were differences in dosage and treatment duration, but also in the disease stage and residual disease-post-surgery. Both trials also used a different definition of progression-free survival.

Box 2 – Differences between the GOG-0218 and ICON7 trials

GOG-0218

Used doses and duration of maintenance treatment: bevacizumab 15 mg/kg every 3 weeks for up to 21 cycles.

Disease stages: all patients were in stage III or IV; 54% of patients were in stage IV after surgical resection or in stage III with a residual tumor > 1 cm.

Definition of progression-free survival: Based on the RECIST criteria, global clinical deterioration or the CA-125 Marker.

ICON 7

Used doses and duration of maintenance treatment: 7.5 mg/kg every 3 weeks for 5-6 cycles and possible continuation for 12 additional cycles.

Disease stages: 81% of patients were in stage III or IV and 31% of patients were in stage IV after surgical resection or in stage III with a residual tumor > 1 cm.

Definition of progression-free survival: Based on RECIST criteria or the clinical or symptomatic progression. The CA-125 marker was not used to check the progression of the disease.

Overall survival

Also for overall survival no significant effect was found. Due to methodological constraints, there is a moderate confidence in the effect estimate according to GRADE. It is important to note that both trials reported overall survival as a secondary outcome, and that they were not powered individually to detect a significant difference.

Quality of life

The results show an **early (18 weeks) worsening in quality of life. This negative effect disappeared in the long run in the GOG-0218 trial (60 weeks), but not in the ICON7 trial (54 weeks)**. Due to methodological constraints, there is a moderate confidence in the effect estimate according to GRADE.

Subgroup analyses in individual trials

The GOG-0218 trial found significant effects on progression-free survival in the bevacizumab-throughout group for the three predefined subgroups[e]. Only for **stage IV cancer patients also a positive effect on overall survival** was found.

The ICON7 trial only found significant effects on progression-free survival for two of the three predefined subgroups: FIGO stages I-III and >1 cm of residual disease, and FIGO stage III (inoperable) or IV. There was no significant effect on overall survival. 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[f] EQ-5D scores are also reported for quality of life. However, these were never published in a peer-reviewed article. Furthermore, the EQ-5D scores were not published per treatment arm, but immediately pooled per non-progressed or progressed health state. Still, these outcomes should be reported by treatment group in a transparent way, without any aggregation, to allow researchers to calculate the unadjusted impact on quality of life per treatment group.

Box 3 – What is GRADE?

GRADE (Grading of Recommendations Assessment Development and Evaluation) is a method to evaluate the quality of the scientific evidence, e.g. in systematic reviews. For further information, see the GRADE website (http://www.gradeworkinggroup.org/) and the KCE Process book (http://processbook.kce.fgov.be/node/51).

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

For second-line treatment with bevacizumab we identified two other published international trials, the AURELIA and OCEANS trials, and one unpublished international trial, the GOG-0213 trial.

Progression-free and overall survival

We found that bevacizumab has a **positive effect on progression-free survival, but not on overall survival**, in patients with recurrent ovarian cancer. Due to methodological constraints, there is a moderate confidence in the effect estimate according to GRADE. In absolute terms the gain in (median) progression-free survival is 3.3 months (AURELIA trial) and 4.0 months (OCEANS trial). Also here, it is important to note that both trials reported overall survival as a secondary outcome, and that they were not powered individually to detect a significant difference.

Subgroup analyses in individual studies

The above-mentioned results are 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).

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[e]   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

[f]   National Institute for Health and Care Excellence, UK, TA284

Quality of life

With second-line bevacizumab fewer patients reported abdominal/gastrointestinal symptoms (pain, ascites …) during chemotherapy, measured with EORTC QLQ-OV28. However, no differences in **quality of life** were found with other instruments (FOSI, EORTC QLQ-C30 and FACT-O-TOI). Mainly due to methodological constraints and imprecision, there is a very low confidence in the effect estimate according to GRADE.

3.3. Acceptable side effects

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)[g]. Toxicity of bevacizumab can therefore be considered acceptable.

3.4. Quality of life and overall survival versus progression-free survival?

Crucial in decisions about the (absence of) added value of an intervention is the relative importance of the different outcomes on which the intervention has an effect. Importance of outcomes is likely to vary within and across cultures and also depends from the perspective of the stakeholders (e.g. patients, clinicians, or policy makers).

The Society of Gynecologic Oncology, for example, considered both overall and progression-free survival to be clinically important. Nevertheless they acknowledge the fact that overall survival remains the most objective and accepted endpoint, because it is least vulnerable to bias.

As a preparation of the KCE clinical practice guideline on ovarian cancer, 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.

Patient surveys[h,i] showed that women with ovarian cancer are willing to accept a shorter progression-free survival to avoid severe side effects. For a longer overall survival they are prepared to accept a higher toxicity. For a new agent to be meaningful, the minimum extension of progression-free survival and overall survival should be five or more months according to patients with ovarian cancer.

In an HTA-report, results of a health economic analysis are expressed as extra costs per life year gained, with and without correction for quality of life. Also in this case preference is given to the two outcomes that are considered most important by patients: extra life years and quality of life. On the other hand, progression-free survival is difficult to interpret, because it is not always accompanied by an improvement in quality of life or a longer survival.

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[g]   see GRADE tables in appendix

[h]   Havrilesky LJ, Alvarez Secord A, Ehrisman JA, Berchuck A, Valea FA, Lee PS, et al. Patient preferences in advanced or recurrent ovarian cancer. Cancer. 2014;120(23):3651-9.

[i]   Minion LE, Coleman RL, Alvarez RD, Herzog TJ. Endpoints in clinical trials: What do patients consider important? A survey of the Ovarian Cancer National Alliance. Gynecol Oncol. 2016;140(2):193-8.

The example of a better progression-free survival in the GOG-0218 trial with a short-term worsening in quality of life is illustrative.

Also, the EUnetHTA guidelines on the use of clinical endpoints stress that an analysis for metastasised cancer that is limited to progression-free survival is insufficient, and that quality of life and survival need to be evaluated too. This approach is supported by a systematic review[j] of eight meta-analyses in metastasised cancer, which showed a low correlation between progression-free and overall survival in six studies.

Nevertheless, the feasibility of overall survival in ovarian cancer is compromised by the requirement for large trial size and prolonged time-line for final analysis. Furthermore, there is a potential for masking of the treatment effect by different 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. In health economic analyses this is covered by including the uncertainty about the impact on survival by modelling the confidence intervals published in the RCTs.

Finally, in 2016 KCE published a report about the use of multi-criteria decision analysis (MCDA) to define a list of unmet medical needs.[k] In this assessment the impact of a disease on quality of life and the discomfort of the current treatment are given a prominent place, because of the importance citizens attach to it, more than on the impact of the treatment on survival alone.

3.5. Comparison of the clinical evidence with the current reimbursement criteria

Currently, bevacizumab is reimbursed for the treatment of ovarian cancer in three circumstances (see introduction).

In Table 1 the clinical evidence is presented next to the current reimbursement criteria.

For the reimbursement of first-line bevacizumab for stage IV cancer, the subgroup analysis of the GOG-0218 trial showed a significant effect on overall and progression-free survival.

For the reimbursed indications in second-line the effect on overall survival was statistically not significant (both in the platinum-sensitive and –resistant patients). Still, a significant effect on progression-free survival was observed. This was not accompanied by an improvement in overall quality of life.

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[j] Prasad V, Kim C, Burotto M, Vandross A. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. JAMA Intern Med. 2015;175(8):1389-98.

[k] KCE report 272

Table 1 – Overview of clinical evidence and economic results for bevacizumab in the treatment of ovarian cancer

	Current reimbursement	Clinical results						Economic results	
		Progression-free survival (PFS)		Overall survival (OS)		Quality of life (QoL)		ICER	Budget impact
		Effect estimate	Conclusion	Effect estimate	Conclusion	Effect estimate	Conclusion		
First-line									
Overall population (patients with previously untreated advanced stage epithelial ovarian, primary peritoneal, or fallopian-tube cancer)									
Bevacizumab 15 mg, *'throughout'* group (GOG-0218)		Hazard Ratio 0.77 (CI: 0.68 to 0.87) Median PFS: not reported for updated analysis	Significant effect on PFS (Confidence [GRADE]: MODERATE)	Hazard Ratio 0.89 (CI: 0.75 to 1.04) Median OSI: not reported for updated analysis	No significant effect on OSI. NOTE: Both trials reported OS as a secondary outcome, and were not powered individually to detect a significant difference. (Confidence [GRADE]: MODERATE)	FACT-O TOI 18 weeks: Median -2.2 (CI: -3.75 to -0.65) 60 weeks: Median 1.0 (CI: -0.93 to 2.93)	Early worsening of QoL. In the GOG-0218 trial no effect was found at 60 weeks. In the ICON7 trial a persistently worse QoL was found at 54 weeks. (Confidence [GRADE]: MODERATE)	On average €158000 / QALY.	No results
Bevacizumab 7.5 mg (ICON7)		Hazard Ratio 0.93 (CI: 0.83 to 1.05) Median PFS: 19.9 months (CI: 19.1 to 22.0) vs. 17.5 months (CI: 15.7 to 18.7)	No significant effect on PFS. (Confidence [GRADE]: MODERATE)	Hazard Ratio 0.99 (CI: 0.85 to 1.14) Median OS: 58.0 months (CI: 52.4 to 66.9) vs. 58.6 months (CI: 53.5 to 67.5)		EORTC QLQ-C30 18 weeks: Median -5.2 (CI: -7.32 to -3.08) 54 weeks: Median -6.4 (CI: -8.86 to -3.94)		On average €443000 / QALY.	No results
Subgroups									
Bevacizumab 15 mg, *'throughout'* group, stadium IV (GOG-0218)	Stage FIGO IV, 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.	Hazard Ratio 0.64 (CI: 0.49 to 0.82) Median PFS: 12.8 months (CI: not reported) vs. 9.5 months (CI: not reported)	Significant effect on PFS (Confidence [GRADE]: LOW)	Hazard Ratio 0.72 (CI: 0.53 to 0.97) Median OSI: 40.6 months (CI: not reported) vs. 32.8 months (CI: not reported)	Significant effect on OS. (Confidence [GRADE]: LOW, published as abstract)	No results		This provides the best ICER of on average €52000/ QALY (in a rather optimistic scenario).	+/- €6 mio/ year
Bevacizumab 7.5 mg, high risk for		Hazard Ratio 0.73	Significant effect on PFS	Hazard Ratio 0.78	Significant effect on OS.	No results		On average	No results

progression (FIGO stage IV disease, or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery) (ICON7)		(CI: 0.60 to 0.93) Median PFS: 16.0 months (CI: 14.2 to 17.8) vs. 10.5 months (CI: 9.3 to 12.0)	(Confidence [GRADE]: LOW)	(CI: 0.63 to 0.97) Median OSI: 39.7 months (CI: 36.0 to 44.2) vs. 30.2 months (CI: 27.0 to 34.3)	(Confidence [GRADE]: LOW)			€82000/ QALY.	
Second-line									
Overall population (patients with recurrent epithelial ovarian, primary peritoneal, or fallopian-tube cancer)									
Pooled results		Hazard Ratio 0.48 (CI: 0.41 - 0.57)	Significant effect on PFS (Confidence [GRADE]: MODERATE)	Hazard Ratio 0.93 (CI: 0.77 - 1.12)	No significant effect on OS. NOTE: Both trials (OCEANS trial and AURELIA trial) reported overall survival as a secondary outcome, and were not powered individually to detect a significant difference (Confidence [GRADE]: MODERATE)	No results		/	No results
Subgroupen									
Platinum-sensitive (OCEANS)	First recurrence, in combination with carboplatin and gemcitabine, during 6 to 10 cycles and then in monotherapy until disease progression).	Hazard Ratio 0.48 (CI: 0.39 to 0.61) Median PFS: 12.4 months (CI: 11.4 to 12.7) vs. 8.4 months (CI: 8.3 to 9.7)	Significant effect on PFS	Hazard Ratio 1.03 (CI: 0.79 to 1.33) Median OS: 33.3 months (CI: 29.8 to 35.5) vs. 35.2 months (CI: 29.9 to 40.3)	No significant effect on OS .	No results		On average €587000 / QALY.	No results
Platinum-resistant (AURELIA)	Second-line treatment, in combination with	Hazard Ratio 0.48 (CI: 0.38 to 0.60)	Significant effect on PFS	Hazard Ratio 0.85 (CI: 0.66 to 1.08)	No significant effect on OS .	EORTC QLQ-OV28, proportion	Increased proportion of patients achieving a 15% improvement	On average	No results

| paclitaxel, topotecan or pegylated liposomal doxorubican until disease progression or unacceptable toxicity). | Median PFS: 6.7 months (CI: 5.7 to 7.9) vs. 3.4 months (CI: 2.2 to 3.7) | Median OS: 16.6 months (CI: 13.7 to 19.0) vs. 13.3 months (CI: 11.9 to 16.4) | with ≥15% improvement

8/9 weeks: Difference 12.7% (CI: 4.4 to 20.9%)

16/18 weeks: Difference 9.9% (CI: 2.9 to 17.0%) | in patient-reported abdominal / gastrointestinal symptoms (measured with EORTC QLQ-OV28) during chemotherapy, in patients with recurrent platinum-resistant cancer.
This treatment effect extends until 30 weeks.

No differences in quality of life found with other instruments (FOSI and EORTC QLQ-C30)
(Confidence [GRADE]: VERY LOW) | €172000 / QALY. |

4. COST-EFFECTIVENESS

4.1. Is bevacizumab cost-effective in a Belgian context?

From a health economic point of view, the calculated ICERs (see textbox) **in the first-line setting** are relatively high, for both the GOG-0218 or ICON7 trials, with ICERs of on average 158 000/QALY and 443 000/QALY, respectively (Table 1). The most optimistic results are based on the stage IV subgroup of the GOG-0218 trial. However, even in this subgroup analyses, average ICERs amount to €52 000/QALY in a rather optimistic scenario.[I] Scenarios including the quality of life assumptions according to the manufacturer's submissions to NICE do not have a major impact on our results. Results are most sensitive to the price of bevacizumab and the extrapolation period.

In this most optimistic scenario, a price discount of about 25% is needed to reach an ICER of about €40 000/QALY and needs to be more than 50% to reach an average ICER of about €27 000/QALY.

For the **second-line bevacizumab treatment** the ICERs are also relatively high: the average ICER based on the OCEANS and AURELIA trials amount to €587 000/QALY and €172 000/QALY, respectively. Even a price discount of 90% would still result in an ICER of about €90 000/QALY in case of the OCEANS trial and about €26000/QALY for the AURELIA trial.

Box 4 – How is cost effectiveness calculated? About ICERs and QALYs

A cost effectiveness analysis expresses the benefits of a treatment in 'life years gained' or in 'life years gained adjusted for quality of life' (QALY – Quality-Adjusted Life-Year) for patients. When a treatment costs less and provides more benefits for patients than the current standard practice, the decision is obvious. But often a treatment improves health, but also costs more than the standard treatment. In that case the ratio between the extra cost of the intervention and the number of gained life years (adjusted for quality of life or not) is calculated. This ratio is the so-called ICER (incremental cost-effectiveness ratio).

4.2. What do other economic evaluations say?

Based on the 11 identified economic evaluations, 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 in the manufacturer's submission file to NICE, the ICER was by far higher than NICE's threshold of £20 000 to £30 000 per QALY, both in first and second line, and at the licensed doses. In these files of the manufacturer, the probabilistic ICER was on average £145 000 per QALY based on the GOG-0218 study (first line) and £222 000 per QALY based on the OCEANS study (second line).

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-first line) or if the most up-to-date results would have been taken into account (TA285-second line).

[I]   An optimistic scenario including no decrease in quality of life, extrapolation of results to a lifetime time horizon with constant mortality, and not including all costs for side effects.

The best results were obtained for a subgroup from the ICON7 trial. The manufacturer's report mentions an average ICER of £33 000 per QALY. Since in this study an unregistered (i.e. half) dose was used, these results were not further considered by NICE. In our study, the results for the stage IV subgroup were better than for the ICON7 high-risk subgroup. The stage IV subgroup analysis has not yet been modeled in any previous study.

The studies confirmed that the price of bevacizumab is one of the most influential variables.

4.3. Overall quality of life

No good quality of life estimates for both the control arm and bevacizumab treatment arm were identified 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. Some authors assumed that there was a decrease in quality of life due to more side effects, others modeled an improvement thanks to an improved progression-free survival. In the identified RCTs, no values were published for the overall quality of life per treatment arm that were useful for the economic evaluations. The values used in the economic evaluations are either based on expert opinion or on studies with similar populations, which causes uncertainty.

To avoid such assumptions, the EUnetHTA Guideline for Health-Related Quality of Life (HRQoL) recommends to use, in addition to disease-specific instruments, a standard tool (e.g. EQ-5D) for measuring overall quality of life, in which the results are expressed on a scale of 0 (= dead) to 1 (= perfect health). In that way, life years can be transformed into QALY's.

In our basic scenario, we have not modeled any improvement or deterioration in quality of life. Scenario analyses show that the integration of values for quality of life, as shown in the NICE file of the manufacturer, does not cause a strong change in ICER values. A short-term decline in quality of life, as established in the first-line studies with bevacizumab, would certainly not have a positive impact on our results. Therefore, our modeled results are quite conservative.

4.4. Economic evaluations as part of the reimbursement request

The files submitted by the manufacturer to NIHDI to request reimbursement for bevacizumab in ovarian cancer did not include an economic evaluation. Even the results of the economic evaluation submitted by the manufacturer to NICE was not included in the document. This is because an economic evaluation is only requested for class I drugs (i.e. for which the manufacturer claims an added value) in the first indication for which reimbursement is requested. Bevacizumab was already used for other indications, such as for breast and colon cancer. Nevertheless, the cost-effectiveness of the same drug in another indication can be very different due to differences in efficacy/effectiveness, adverse events, impact on QoL, average treatment duration, etc. Also for an extension of reimbursement to other indications, economic evaluations have an important added value to support rational policy decisions.

4.5. Focus on stage IV subgroup in first line

When the overall results in trials are not convincingly positive, it might be tempting to focus on a specific subgroup. However, the danger of such analyses is that they present a form of 'data dredging', rather than a methodologically legitimate approach. Therefore a number of criteria were drawn up on an international level, to define when subgroup analyses are reasonable and how they should be performed and reported. The GOG-0218-study meets a number of these criteria: the factors that define the subgroups and the reason for the analysis are specified in the protocol beforehand, and the factors that define the subgroups were looked at before randomization. However, results of subgroup analyses always have to be interpreted with caution.

According to NICE, the results of the stage IV subgroup analysis were not sufficient to justify a review of its guideline.

Currently, bevacizumab is reimbursed in first line for this stage IV subgroup. For that reason, and despite the danger of such analyses, we decided to perform an economic evaluation for this subgroup (see section 4.1). As mentioned by NICE, confirmatory studies are required to support the conclusion of this subgroup analysis. At this moment, at least three studies

are ongoing in first line that include stage IV patients. We recommend to follow up on the long term results of the already published and new 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.

For this subgroup, the budget impact was estimated at € 6 million, assuming a cost of €40 000 per patient and 150 patients a year (Table 1) (see the scientific report for further information). This figure does not account for any confidentially negotiated price discounts.

4.6. Confidential contracts and changing reimbursement conditions

The reimbursement of bevacizumab for the treatment of ovarian cancer is based on a contract between the Minister and the manufacturer (article 81 of the Royal Decree of 21 December 2001). 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. Additional scientific information in the public part of these contracts was delivered by the RIZIV to the research team.

However, we have no access to the confidential appendices and do not know whether the contract only contains e.g. price-volume agreements. As a consequence, we were unable to make models based on the real cost for the authorities, but only based on the official market price. To tackle this problem, we performed sensitivity analyses with price discounts between 0% and 100%. The results were transparently presented per study in a figure (for details, see scientific report).

Changing the conditions of the reimbursement of a product (e.g. when a contract expires) is from a clinical viewpoint often difficult to accept. At least, the changed reimbursement conditions should be explained to all parties concerned, such as patients, physicians and the manufacturer. Obviously, changed reimbursement conditions should not cause the interruption of treatments with bevacizumab that have already started.

■RECOMMENDATIONSᵐ

To the Minister of Public Health and the competent bodies at NIHDI (RIZIV – INAMI)

- **KCE recommends to take into account the different clinical and health-economic findings, as summarized in Table 1, in the decision-making process on the (further) reimbursement of bevacizumab.**

- **For stage IV patients, the results of the ongoing studies should be followed up.**

- **Currently, no economic evaluations are requested for the reimbursement request for an extension of indications of class 1 drugs. Because the cost-effectiveness of the same drug in a different indication may be very different, we recommend to also request an economic evaluation for the extension to other indications.**

To the manufacturers of drugs and medical devices

- **In the design of future clinical studies, from the beginning, we recommend to incorporate overall survival and quality of life as endpoints, in addition to progression-free survival.**

- **According to the EUnetHTA guidelines on measuring health-related quality of life, disease-specific and generic utility instruments (such as EQ-5D) should both be included in the research protocols. We recommend to follow these guidelines and to report the results in a transparent way.**

ᵐ   The KCE has sole responsibility for the recommendations.

Layout:	Ine Verhulst, Joyce Grijseels

Domain:	Health Technology Assessment (HTA)
MeSH:	Ovarian Neoplasms; Bevacizumab; Cost-Benefit Analysis
NLM Classification:	WP 322
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2017/10.273/23
ISSN:	2466-6459